

Competing intramolecular N—H···O=C hydrogen bonds and extended intermolecular network in 1-(4-chlorobenzoyl)-3-(2-methyl-4-oxopentan-2-yl) thiourea analyzed by experimental and theoretical methods



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ARTICLE INFO

Article history:

Received 27 November 2013

In final form 19 January 2014

Available online 25 January 2014

Keywords:

Thiourea

Crystal structure

FTIR spectroscopy

Raman spectroscopy

Hydrogen bond

NBO

Topological analysis

ABSTRACT

The synthesis of a novel 1-acyl-thiourea species (C₁₄H₁₇N₂O₂SCl), has been tailored in such a way that two distinct N—H···O=C intramolecular competing hydrogen bonds are feasible. The X-ray structure analysis as well as the vibrational (FT-IR and FT-Raman) data reveal that the *S* conformation is preferred, with the C=O and C=S bonds of the acyl-thiourea group pointing in opposite directions. The preference for the intramolecular N—H···O=C hydrogen bond within the —C(O)NHC(S)NH— core is confirmed. The Natural Bond Orbital and the Atom in Molecule approaches demonstrate that a strong hyperconjugative lpO → σ*(N—H) remote interaction between the acyl and the thioamide N—H groups is responsible for the stabilization of the *S* conformation. Intermolecular interactions have been characterized in the periodic system electron density and the topological analysis reveals the presence of an extended intermolecular network in the crystal, including a Cl···N interaction playing a relevant role in crystal packing.

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1. Introduction

It is well-known that compounds containing the >N—C(S)—N< functionality are identified as thioureas [1,2]. The 1-(acyl/aroil)-substitution implies the presence of a carbonyl group bonded to the thiourea core [3]. Substitutions can occur also in the second nitrogen atom, giving 1-(acyl/aroil)-3-(mono-substituted) and 1-(acyl/aroil)-3,3-(di-substituted) thioureas, with general formula R¹C(O)NHC(S)NR²R³, where R may be an alkyl, aryl, aralkyl or heterocyclyl substituent [4–6]. Several conformations are feasible for this kind of compounds, depending on the dihedral values around the acyl-N bond and the adjacent N—C bond [7]. Following Woldu and Dillen [8], the four main forms can be denoted as *S*, *M*, *Z* and *U*, where the capital letters reflect the position of the C=O and C=S double bonds relative to the vertically drawn N—H bond (see Scheme 1).

For 1-(acyl/aroil)-3-(mono-substituted) thiourea derivatives, with R²=H, a local planar structure of the central —C(O)—NH—C(S)—NH— moiety is preferred, with opposite orientation between the C=O and C=S double bonds (“*S*-shape”) [9]. In this conformation the C=O and H—N groups form a pseudo 6-membered ring, favoring an intramolecular hydrogen bond, as is shown in Scheme 2. On the other hand, when the formation of a suitable hydrogen bond is prevented, as in 1-(acyl/aroil)-3,3-(di-substituted) thiourea derivatives (R², R³ ≠ H), the *anticlinal* geometry (*U* form) is preferred [10,11].

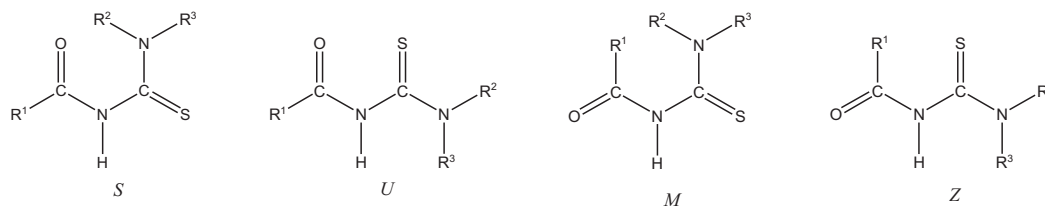
Surprisingly, the occurrence of a 1-(acyl/aroil)-3-(mono-substituted) thiourea having a *U* form was recently reported. In fact, as independently demonstrated by Arslan et al. [12] and Yusof et al. [13], nitrogen substitution with a 2-pyridyl group (R²=H, R³=2-pyridyl) changes the expected conformational preference. In the crystal, an N—H···N intramolecular hydrogen bond involving the 2-pyridyl group prevails, leading to a *synperiplanar* conformation between the C=S and C=O groups. This conformation forces the two amide and thioamide hydrogen atoms to opposite direction.

Prompted by this finding, we became interested in the synthesis of substituted 1-(acyl)-thioureas which can display unusual

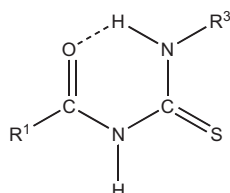
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Scheme 1. Main conformations around the $-C(O)NHC(S)N-$ moiety of 1-(acyl/aryl)-3-(substituted) thioureas.



Scheme 2. Representation of the *S* conformer in 1-(acyl/aryl)-3-(mono-substituted) thioureas ($R^2=H$), showing the intramolecular $C=O \cdots H-N$ hydrogen bond.

conformational properties. In the frame of our ongoing project devoted to the study of 1-(acyl/aryl)-3-(mono-substituted) thioureas [14,15], in this article we present a structural study on the novel species 1-(4-chlorobenzoyl)-3-(2-methyl-4-oxopentan-2-yl) thiourea. In this compound a second $C=O$ bond is introduced in such a position that the *U* form (Scheme 3, right) is eventually favored due to the formation of a six membered ring with the $N-H$ bond over the usual *S* form (Scheme 3, left). One of the aims of this work is to elucidate whether the ketene-like $C=O$ group is able to compete with the 1-acyl group in the formation of a pseudo-six membered $C=O \cdots H-N$ hydrogen bond and how the conformation of the acylthiourea moiety is affected by this intramolecular interactions.

Besides the fundamental interest, the understanding of conformational properties, especially the role of hydrogen bonding interactions of ureas and thioureas, has relevance in applied fields. In particular, Fabbrizzi et al. reported that substituted-phenyl urea compounds interact through hydrogen bonding with a variety of oxoanions to give bright colored complexes [16,17]. A variety of receptors containing the urea and the thiourea groups have been designed for anion recognition [18,19]. These are promising potential compounds for developing novel chemosensors for selective and sensitive naked-eye recognition for anions [20,21]. Moreover, important new developments on biological [22] and pharmaceutical [23-25] applications of 1-acyl thioureas rely in the formation of proper hydrogen bonds with particular receptors [26].

Here, the synthesis of 1-(4-chlorobenzoyl)-3-(2-methyl-4-oxopentan-2-yl) thiourea has been specially tailored and the molecular and crystal structures have been determined by X-ray diffraction analysis. Moreover, the vibrational properties are studied by using infrared and Raman spectroscopies in conjunction

with quantum chemical calculations. In order to characterize the intermolecular interactions at play, the topology of the electron density obtained from a periodic quantum calculation was analyzed within the context of the Bader's theory of atoms in molecules (AIM) [27]. In addition, Natural Bonding Orbital (NBO) [28-30] population analysis has been performed with the primary aim to deepen the understanding of how electronic interactions affect the conformational behavior.

2. Results and discussion

2.1. Synthesis and characterization

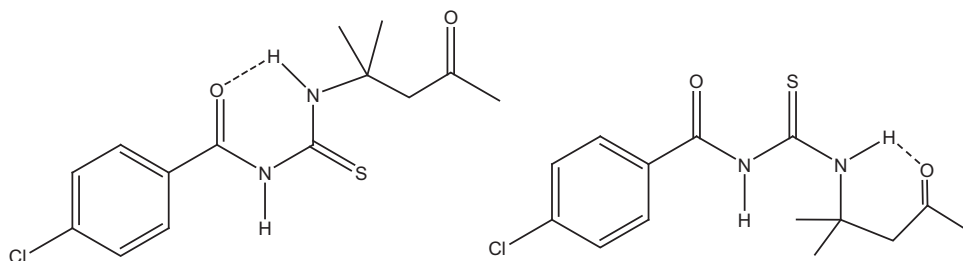
The 4-amino-4-methylpentan-2-one, an important precursor to the target compound was freshly prepared by the amination of 4-methylpent-3-en-2-one using aqueous ammonia. A solution of 4-chlorobenzoyl chloride in dry acetone was treated with an equimolar quantity of potassium thiocyanate in dry acetone to afford the 4-chlorobenzoyl isothiocyanate as intermediate. Treatment of the latter with an equimolar quantity of 4-amino-4-methylpentan-2-one in acetone furnished the title thiourea derivative as showed in Scheme 4 [31].

The 1H -NMR data displayed characteristic singlets at 3.44 (2H, CH_2-), 2.18 (3H, CH_3) and 1.64 (6H, $(CH_3)_2$). In addition, singlets at δ 8.71 and 11.0 ppm were observed for $HN(1)$ and $HN(2)$ respectively. The ^{13}C -NMR data displayed signals at δ 206.3, 177.4 and 165.6 ppm for the ketonic carbonyl, thiocarbonyl and amide carbonyl carbons, respectively. The mass spectral and elemental data was consistent with the reported structure.

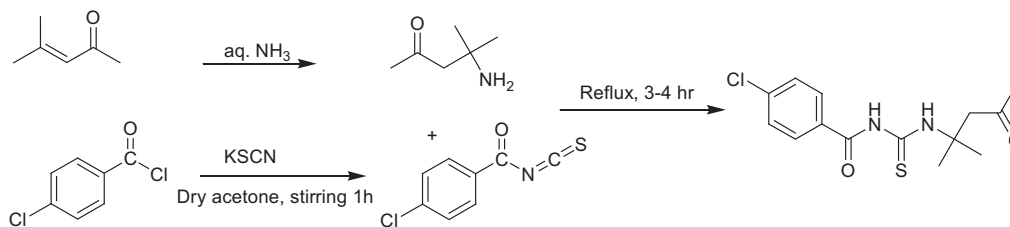
2.2. Vibrational analysis

The FTIR and FT-Raman spectra for the title compound in the solid phase are shown in Fig. 1. The observed wavenumbers and those calculated at the B3LYP/6-311++G(d,p) level for the *S* form of the isolated molecule are reported in Table S1 of the Supplementary data, together with a tentative assignment of the bands. The assignment has been carried out by comparison with theoretical wavenumbers as well as on comparison with the reported data for related molecules [32-39].

The close analysis of the $1800-1500\text{ cm}^{-1}$ region is especially important for understanding the structural features of the title



Scheme 3. Representation of the *S* (left) and *U* (right) conformers for the title compound stabilized by different $C=O \cdots H-N$ intramolecular hydrogen bonds in competition.



Scheme 4. Route of synthesis for the title compound.

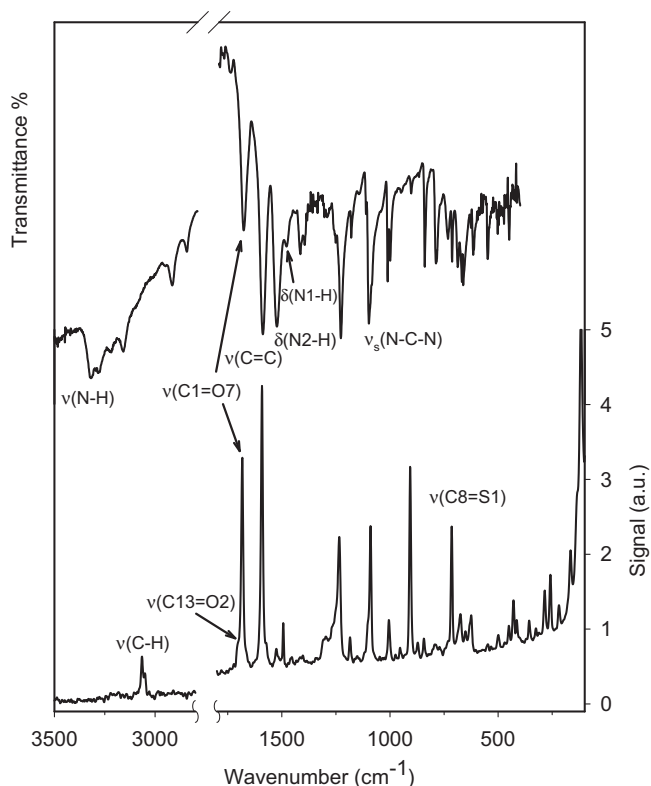


Fig. 1. Selected region of the IR (in KBr pellet) and Raman spectra for the solid phase of the title species.

molecule. It is expected that the ν (C=O) stretching and δ (N–H) deformation normal modes appear in this spectral window and these modes are very sensitive to conformational properties as well as to intra/inter molecular interactions [32,40].

The computed [B3LYP/6-311++G(d,p)] infrared spectra for the *S* form predicts the ν (C7=O1) stretching mode for the 1-acyl thiourea group as an intense absorption appearing at 1716 cm^{-1} , that is at lower wavenumbers than that for the carbonyl stretching mode of the ketene group [ν (C13=O2)] computed at 1779 cm^{-1} as a less intense absorption (see Fig. 3 for atom numbering). On the other hand, for the *U* conformer, both C=O stretchings are predicted to have very similar frequency values: 1770 and 1765 cm^{-1} for the ν (C7=O1) and ν (C13=O2), respectively. From this comparison, it is apparent that the N2–H...O1=C7 intramolecular interaction is responsible for the red-shift and high intensity of the ν (C=O) mode observed for the *S* form [11,40]. In the experimental infrared spectrum, a single broad absorption with strong intensity is observed centered at 1685 cm^{-1} . Such a low value is typical for 1-acyl-3-monosubstituted thiolactones with the C=O group involved in an intramolecular hydrogen bond interaction [41]. It is plausible that the broadening of the band toward the high

wavenumber side can account for the superposition with the ν (C13=O2) absorption. This description is well complemented by the analysis of the Raman spectrum, where a strong signal appears at 1683 cm^{-1} with a low intensity shoulder at higher wavenumbers (1703 cm^{-1}). It is well-known that due to the large dipole moment of the carbonyl group, C=O stretching vibrations are much stronger in the IR than in Raman. However, the stretching frequency and the intensity observed in the Raman spectrum can be affected by the formation of hydrogen bonds [42,43]. For the *S* conformer of the title molecule, quantum chemical calculations predict the 1716 cm^{-1} C=O stretching mode with strong Raman activity (207 $\text{\AA}^4/\text{amu}$) whereas the ν (C13=O2) for the ketene group at 1779 cm^{-1} displays a “normal” low activity (computed value: 8 $\text{\AA}^4/\text{amu}$).

The infrared spectrum shows two absorptions at 1531 and 1487 cm^{-1} , with very strong and medium intensities, respectively, which are tentatively assigned to the δ (N–H) deformation modes on the acyl thiourea group. Counterpart signals appear in the Raman spectrum at 1526 and 1493 cm^{-1} , respectively. For the δ (N–H) deformation modes, quantum chemical calculations for the *S* form confirms the presence of very intense absorptions at 1599 and 1557 cm^{-1} assigned to the δ (N2–H) and δ (N1–H), respectively. Both fundamentals appear at lower wavenumbers (around 1520 cm^{-1}) for the *U* form, a region in the spectrum that is congested by superposition with the δ (CH₃) modes. Finally, the ν (C8=S1) stretching is tentatively assigned to the medium intensity absorption observed at 737 cm^{-1} (733 cm^{-1} Raman), in good agreement with the computed value of 754 cm^{-1} [B3LYP/6-311++G(d,p)] and with reported data for species in the *S* form [11,33].

It is worth noticing that the joint analysis of the infrared and Raman spectra of the title compound, together with the vibrational results obtained from the quantum chemical calculations, gives rather conclusive evidences on the preference of the *S* form in the solid phase, after confirmed (see Section 2.4) by crystallographic results. Quantum chemical calculations are also in agreement with the preference of the *S* conformation, which is computed more stable than the *U* form by 11.8 kcal/mol for the molecule isolated in a vacuum (ΔE° value corrected by zero point energy at the B3LYP/6-311++G(d,p) level of approximation).

2.3. Natural bond orbital analysis

It has been proposed that the electrostatic character present in “classical” hydrogen bonds, like C=O...H–N [44], can be mainly explained on the basis of the hyperconjugative interaction involving the partial transfer of a lone pair of electrons of the oxygen atom to the N–H antibonding orbital [45]. In the frame of the Natural Bond Orbital (NBO) population analysis delocalization of electron density between occupied Lewis-type (bond or lone pair) NBO orbitals and formally unoccupied (antibond or Rydberg) non-Lewis NBO orbitals corresponds to a stabilizing interaction. The energy of these donor–acceptor interactions can be estimated by the second order perturbation theory [46]. Donor–acceptor interactions

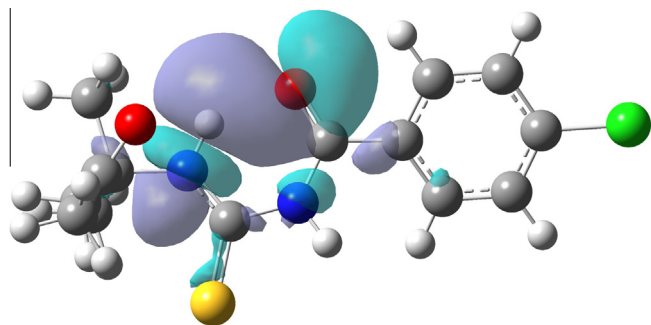


Fig. 2. 3D representation of the remote $lpO1 \rightarrow \sigma^*(N2-H)$ NBOs overlap for the *S* conformer.

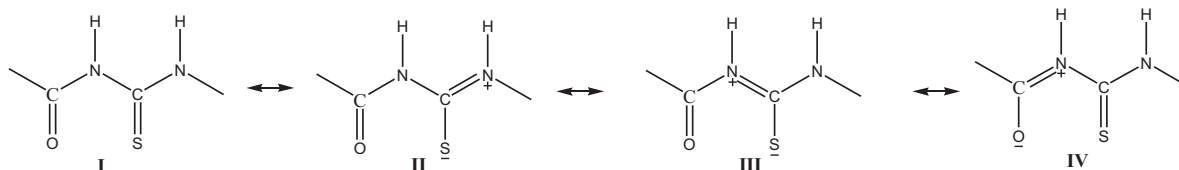
between remote orbitals deserve close inspections owing to the influence they can play on the backbone conformation [47]. For instance, the molecular structures of benzenesulfonylamino acetamide molecules are determined by the formation of a $C=O \cdots H-N$ hydrogen bond. Accordingly, $lpO \rightarrow \sigma^*(N-H)$ interaction values of ca. 9.5 kcal/mol were computed by using DFT methods [48].

For the title compound, the representation of the NBOs involving in the donor \rightarrow acceptor $lpO1 \rightarrow \sigma^*(N2-H)$ remote interaction is shown in Fig. 2. The second-order perturbation analysis of the Fock matrix indicates a strong donation, amounting 12.03 kcal/mol for the *S* form, whereas for the *U* form the corresponding value is below the threshold limit (less than 0.5 kcal/mol). The hyperconjugative interaction increases the electronic population of the $\sigma^*(N2-H)$ orbital (0.046 e) and produces an elongation of the $N2-H$ bond, which is computed to be 1.02 and 1.01 Å for the *S* and *U* forms, respectively.

Other interesting electronic properties of the central $-C(O)NHC(S)HN-$ moiety can be derived from the NBO analysis. In 1-acyl thiourea compounds, the resonance model of the amide and thioamide bonds leads to the conjugation of the nitrogen lone pairs with the $C7=O1$ and $C8=S1$ double bonds in terms of resonance structures showed in Scheme 5.

The NBO analysis for the *S* and *U* conformers of the title molecule indicates the presence of a pure p-type [$lp_p(N)$] lone pair orbital on both amide and thioamide nitrogen atoms. These orbitals display low electron occupancies (1.64 and 1.61 e and 1.70 and 1.66 e for the $lp_p(N1)$ and $lp_p(N2)$ of the *S* and *U* forms, respectively) indicating the electron-donating capacity for this orbital, especially for the *S* conformer. Delocalizing interactions evaluated by a second-order perturbation approach reveals that the lone pair orbital contributes to a strong resonance interactions with both carbonyl bonds $lp_p(N1) \rightarrow \pi^*(C7=O1)$, leading to the “amide resonance” (form IV in Scheme 5). The computed $E^{(2)}$ interaction values are 55.9 and 40.9 kcal/mol for the *S* and *U* conformations, respectively. For comparison, this interaction in the amide group of formamide [49] and imide [50] amounts 59.8 and 44.4 kcal/mol, respectively.

The resonant forms represented by the structures II and III in the Scheme 5 involve the thioamide group and can be also evaluated within the donor \rightarrow acceptor approach, the acceptor



Scheme 5. Main resonance structures for the 1-acyl thiourea moiety.

being the $\pi^*(C=S)$ antibonding orbital. For the *S* form, the $lp_p(N) \rightarrow \pi^*(C8=S1)$ interactions are computed to be 48.1 and 83.6 kcal/mol for the $N1$ and $N2$ nitrogen atoms, respectively. These electron donations into the $\pi^*(C7=O1)$ and $\pi^*(C8=S1)$ antibonding orbitals are reflected in the high population found for these “vacant” molecular orbitals, with an electronic occupancy of 0.30 and 0.48 e, respectively, as computed for the *S* form.

These results suggest a partial double bond character in the three $N-C$ bonds of the central moiety [55], similar to those observed for thiocarbamate compounds [51,52]. The computed second order perturbation energies agree with the tendency observed for $N1-C7$, $N1-C8$ and $N2-C8$ bonds, with experimental bond length values of 1.3798(16), 1.4024(15) and 1.3268(16) Å, respectively (see below). Higher $lp_p(N) \rightarrow \pi^*(C=O/S)$ interaction values are associated with shorter $C-N$ bond distances.

2.4. Molecular and crystal structure and topology of the electron densities

The title compound crystallizes in the $P21/c$ spatial group with an only nonequivalent molecule adopting the *S*-shaped conformation, as is shown in Fig. 3 (taken from Ortep [53]). This conformation is stabilized by an intramolecular $N2-H \cdots O1$ hydrogen bond [$d(N2 \cdots O1) = 2.6392(14)$ Å] which forms a pseudo-six-membered ring.

The topological analysis of the electron density showed that in addition to the $N2-H \cdots O1=C7$ interaction, the in-crystal molecule is also stabilized by three other weak hydrogen bonds (HBs) (see Fig. 4). In particular, the second $C13=O2$ group, forming the ketene moiety, weakly interacts with a methyl group. The most relevant topological parameters of all close shell intramolecular (3,−1) critical points (CPs) and the corresponding values obtained for the isolated molecule are reported in Table 1.

As regards molecular conformation, the carbonyl oxygen is twisted slightly away from the mean plane of the benzene ring, the $C5/C4/C7/O1$ torsion angle being $-152.59(13)^\circ$. Similar conformational features were reported for benzoyl thioureas [54]. Furthermore, the sulfur atom is twisted away from the carbonyl group even more with $C7/N1/C8/S1 = -161.65(10)^\circ$, $C5/C4/C7/N1 = 27.57(17)^\circ$ and $C8/N1/C7/C4 = 174.75(11)^\circ$, respectively, forming weak $C-H \cdots S$ intramolecular interactions. Bond lengths and angles are within normal ranges (see Tables S5 and S6 in the Supplementary data).

Crystal packing is schematically shown in Fig. 5, where short contacts are displayed. Those short contacts were confirmed to correspond to non bonding interactions by the electron density topological analysis. As expected for a crystal made of molecules with a large number of potential binding sites, the topological analysis revealed the existence of a rather complicated network of intermolecular interactions. In fact, thirty-one intermolecular (3,−1) critical points (CPs) were found. Relevant topological parameters of all of them are collected in Table S9 of the Supplementary data. For the dominant interactions – almost all involving a hydrogen atom –, topological parameters are also reported in Table 1. Main intermolecular bondpaths in the crystal are schematically shown in Fig. 6. On the basis of the ρ and λ_3 values [55] at the

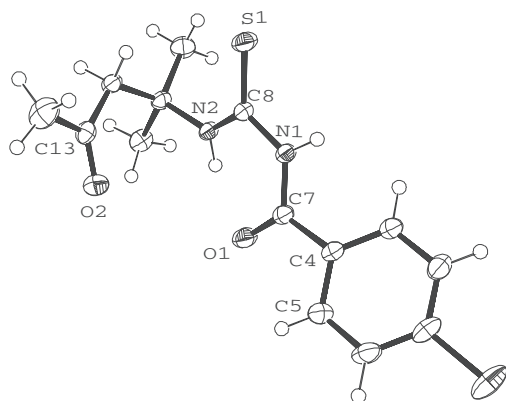


Fig. 3. Molecular structure of the title compound in a single crystal at 173 K (with the thermal ellipsoids shown at a 50% probability level). For simplicity, the labeling scheme is restricted to the atoms discussed in the text.

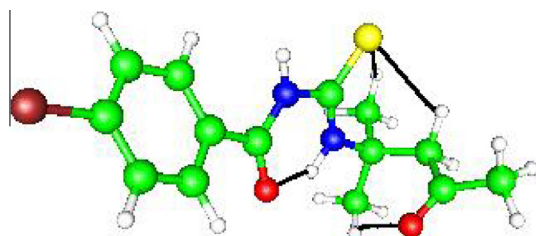


Fig. 4. Intramolecular bondpaths for the title molecule derived from the topological analysis.

Table 1

Topological parameters (atomic units) of the crystal and isolated molecule (3,−1) critical points: electron density (ρ), Laplacian ($\nabla^2\rho$) and positive curvature (λ_3).

| | ρ | $\nabla^2\rho$ | λ_3 |
|-------------------------------------|--------|----------------|-------------|
| INTRAMOLECULAR^{a,b} | | | |
| N2···H···O1 | 0.0401 | 0.1249 | 0.2421 |
| | 0.0399 | 0.1260 | 0.2429 |
| H _{met} ···O2 | 0.0145 | 0.0510 | 0.0748 |
| | 0.0135 | 0.0471 | 0.0719 |
| H _{met} ···S | 0.0147 | 0.0455 | 0.0697 |
| | 0.0146 | 0.0451 | 0.0690 |
| H _{et} ···S | 0.0122 | 0.0400 | 0.0584 |
| | 0.0125 | 0.0387 | 0.0575 |
| INTERMOLECULAR | | | |
| O2···H—N1 (v) | 0.0143 | 0.0448 | 0.0758 |
| H _{ar} ···O2 (viii) | 0.0096 | 0.0362 | 0.0531 |
| O2···H _{ar} (v) | 0.0099 | 0.0304 | 0.0505 |
| O2···H _{ar} (iv) | 0.0091 | 0.0317 | 0.0500 |
| Cl···N1 (viii) | 0.0089 | 0.0269 | 0.0386 |
| O1···H _{ar} (v) | 0.0079 | 0.0220 | 0.0374 |
| H _{met} ···N2 (vi) | 0.0066 | 0.0194 | 0.0304 |
| N2···H _{met} (vii) | 0.0052 | 0.0170 | 0.0258 |
| S···H _{et} (i) | 0.0057 | 0.0181 | 0.0234 |
| S···H _{met} (ii) | 0.0043 | 0.0150 | 0.0203 |
| S···H _{et} (ii) | 0.0045 | 0.0142 | 0.0191 |
| S···H _{met} (iii) | 0.0036 | 0.0094 | 0.0142 |

^a Crystal (first line) and isolated molecule in the crystal geometry.

^b Symmetry codes: i: $x, 1 + y, z$; ii: $1 - x, 1/2 + y, 1/2 - z$; iii: $x, 1.5 - y, 1/2 + z$; iv: $-x, -1/2 + y, 1/2 - z$; v: $x, -2 + y, z$; vi: $x, 1.5 - y, -1/2 + z$; vii: $x, 1.5 - y, 1/2 + z$; viii: $-x, 1/2 + y, 1/2 - z$.

corresponding critical points, the most relevant intermolecular interaction, comparable with the weakest intramolecular ones, is the N—H···O=C that can be characterized as hydrogen bond (HB) on geometrical grounds. On the same grounds, the remaining

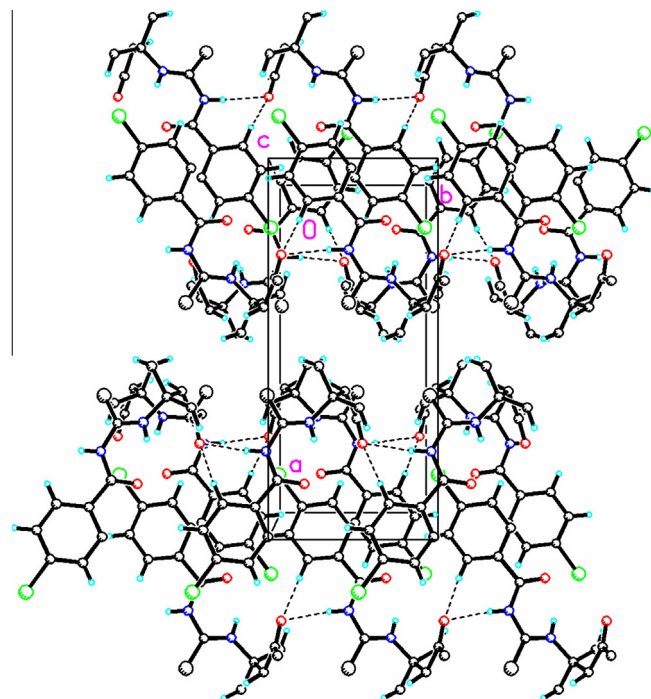


Fig. 5. Packing diagram of the title compound viewed along the c axis. N—H···O and C—H···O short contacts forming infinite 1-D chains along [010] are shown by dashed lines. H atoms not involved in hydrogen bonding have been deleted for clarity.

X—H···Y interactions can also be considered weak hydrogen bonds, their relevant geometrical parameters falling within the accepted ranges (see Table S8 in the Supplementary data). It is worth noticing, however, that if the third of the Koch and Popelier criteria [56] were considered strictly valid also for S as acceptor and B3LYP periodic calculations, interactions between methyl hydrogen atoms and sulfur could not be classified as hydrogen bonds (see Table 1). All intermolecular bond paths are nearly straight lines, as can be observed in Fig. 6.

Not surprisingly, intramolecular HBs are only marginally affected by crystal packing, this behavior being consistent with the

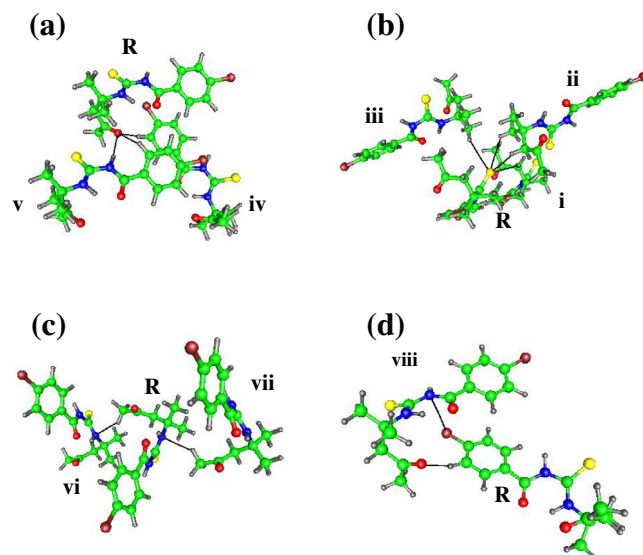


Fig. 6. Main intermolecular bondpaths in the crystal: (a) O···H interactions; (b) S···H interactions; (c) N···H and H···N interactions; (d) Cl···N and H···O interactions. R stands for the reference molecule. Each of the remaining molecules is labeled with the symmetry operation it is generated by (see Table 2).

fact that intermolecular interactions range from weak to very weak, as can be concluded from their topological characterization. As an indirect conclusion, it can be said that the ability of sulfur and oxygen atoms to behave as acceptors in intermolecular HBs is not affected by their roles in the rather strong intramolecular ones.

There is one non HB intermolecular interaction that deserves particular attention. If the criterion based on ρ_c and λ_3 values is extrapolated to non HB interactions [57], the path linking the Cl atom of the reference molecule with one N atom of one of its first neighbors (see Fig. 6d) should contribute to crystal stability as much as the medium strength HBs. Interactions of this kind were thoroughly studied by Lommerse et al. [58], though some role in molecular packing had already been assigned to them still from before. But C—Cl...N interactions are also nowadays subject of study [57,59]. Accordingly to Lommerse et al. [58] geometrical parameters characterizing the interaction in the title compound are $\alpha = 109.0^\circ$ and $d = 3.316 \text{ \AA}$; and then $R3 = 1.015$ and $1 - \cos \theta = 0.67$. These values place the present case in a rather borderline position as regards the statistical results presented in Fig. 3 of reference [58]. Unfortunately we were not able to find more recent good quality statistical data and performing searches in the CSD database is beyond the scopes of the present paper. However, in the title compound the interaction is clearly far from head on, the Laplacian of the electron density was analyzed in several planes through the attractors, in order to find evidences of polar flattening in the electron density around the involved atoms. Though some polar flattening is observed (see Fig. S1 of the Supplementary data), local accumulations and depletions of electron density could hardly account for an attractive interaction [60]. It is worth noticing that in solid phase several intermolecular interactions are usually competing and departures from the “ideal” geometry are the rule. In order to elucidate to what extent crystal environment could be responsible for the behavior of the C—Cl...N interaction in the title compound crystal, the electron density topology of the corresponding isolated molecular pair was also analyzed, keep-

ing the in-crystal geometry intact, and, more importantly, after a full geometry optimization. The two main intermolecular links within the pair are the one under analysis and one C—H...O hydrogen bond, the two having similar strength other than in the crystal. When the geometry is optimized, however, the HB is reinforced and becomes dominant while the Cl...N becomes weaker, the Cl...N distance changing from 3.3 Å to 4.0 Å. This fact is a clear indication that C—Cl...N is favored by crystal packing, its geometry in the crystal being strongly conditioned for the remaining interactions. Some speculation can then be made on a little or no contribution of the interaction at the early stages of aggregation.

3. Conclusions

A novel 1-(4-chlorobenzoyl)-3-(2-methyl-4-oxopentan-2-yl) thiourea derivative was prepared by treating 4-chlorobenzoylthiocyanate (produced *in situ*) with 4-amino-4-methylpentan-2-one in good yield. This molecule was especially synthesized with the aim to investigate the effect exerted by competing intramolecular C=O...H—N hydrogen bonds in the molecular structure. The molecular and X-ray structure reveals that the 1-acyl thiourea group adopts a usual S form, stabilized by an intramolecular C=O...H—N hydrogen bond. The NBO analysis allowed to characterize the hyperconjugative $\text{lpO1} \rightarrow \sigma^*(\text{N2—H})$ remote interaction as an important factor of covalency for this bond. From a topological analysis of the corresponding electron densities four hydrogen bonds were characterized in the in-crystal and isolated molecules. The analysis in the crystal also revealed the existence of a network of weak intermolecular hydrogen bonds and a Cl...N interaction with a rather relevant role in the crystal packing.

4. Experimental

4.1. Synthesis and characterization of 1-(4-chlorobenzoyl)-3-(2-methyl-4-oxopentan-2-yl) thiourea

A freshly prepared solution of 4-chlorobenzoyl chloride (10 mmol) in dry acetone was added dropwise to a suspension of potassium thiocyanate (10 mmol) in acetone (30 ml) and the reaction mixture was refluxed for 30 min under nitrogen. After cooling to room temperature, a solution of 4-amino-4-methylpentan-2-one [61] (2.2 mL, 10 mmol) in acetone (10 mL) was added and the resulting mixture refluxed for 4 h. The reaction mixture was poured into cold water and the precipitate was recrystallized from ethanol and ethyl acetate as a yellow crystalline solid (2.7 gr, 8.8 mmol) with a yield of 88%. m.p: 167 °C; IR (KBr, ν/cm^{-1}): 3338, 3148, 3054, 2996, 2961, 1704, 1673, 1234; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 11.00 (s, CONH, 1H), 8.71 (s, CS-NH, 1H), 7.78 (d, $J = 8.4 \text{ Hz}$, Ar-H), 7.49 (d, $J = 8.1 \text{ Hz}$, Ar-H), 3.44 (s, 2H, —CH₂—), 2.18 (s, 3H, CH₃), 1.64 (s, 6H, —C(CH₃)₂); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): 206.3 (—CH₂—CO), 177.4 (C=S), 165.6 (—C=O), 130.3, 129.6, 129.4, 129.1, 128.8, 127.6, 55.2 (CH₂), 49.4 (CO—CH₃), 31.0 (—C(CH₃)₂), 27.0 (—C(CH₃)₂); GC—MS: 312 M⁺, 275, 262, 231, 216, 183 (100%), 135, 107, 91, 76, 51; Elemental analysis: Calcd. for C₁₄H₁₇ClN₂O₂S C 53.75, H 5.48, N 8.96, S 10.25. found C: 53.69%, H: 5.50%, N: 8.92%, S: 10.21%.

4.2. Instrumentation

The melting points were recorded using conventional apparatus. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 at 300 MHz and 75 MHz, respectively. Elemental analyses were conducted using a standard analyzer.

Table 2
Crystal data and structure refinement for the title compound.

| | | |
|---------------------------------|---|-----------------------------|
| Empirical formula | C ₁₄ H ₁₇ N ₂ O ₂ S | |
| Formula weight | 312.81 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | monoclinic | |
| Space group | P 2 ₁ /c | |
| Unit cell dimensions | $a = 15.9805(3) \text{ \AA}$ | $\alpha = 90^\circ$ |
| | $b = 7.07622(15) \text{ \AA}$ | $\beta = 90.2566(15)^\circ$ |
| | $c = 13.4469(2) \text{ \AA}$ | $\gamma = 90^\circ$ |
| Volume | 1520.59(9) Å ³ | |
| Z | 4 | |
| Density (calculated) | 1.366 Mg/m ³ | |
| Absorption coefficient | 0.391 mm ⁻¹ | |
| F(000) | 656 | |
| Crystal size | 0.44 × 0.38 × 0.32 mm ³ | |
| Theta range for data collection | 3.03 to 32.35° | |
| Index ranges | −22 ≤ h ≤ 23, −10 ≤ k ≤ 10, −19 ≤ l ≤ 19 | |
| Reflections collected | 18955 | |
| Independent reflections | 5051 [R(int) = 0.0201] | |
| Completeness to theta = 25.00° | 99.9% | |
| Refinement method | Full-matrix least-squares on F ² | |
| Goodness-of-fit 1.072 | 1.072 | |
| Final R indexes [I >= 2 s(I)] | R1 = 0.419, wR2 = 0.0994 | |
| Final R indexes [all data] | R1 = 0.517, wR2 = 0.1049 | |

4.3. Vibrational Spectroscopy

Solid-phase (in KBr pellets) infrared spectra were recorded with a resolution of 2 cm^{-1} in the $4000\text{--}400\text{ cm}^{-1}$ range on a Bruker EQUINOX 55 FTIR spectrometer. The FT-Raman spectra of the powdered solid sample were recorded in the region $4000\text{--}100\text{ cm}^{-1}$ using a Bruker IFS 66v spectrometer equipped with Nd:YAG laser source operating at $1.064\text{ }\mu\text{m}$ line with 200 mW power of spectral width 2 cm^{-1} .

4.4. Computational details

Molecular quantum chemical calculations were performed with the GAUSSIAN 03 program package [62] at the B3LYP/6-311++G(d,p) level of approximation. The calculated vibrational properties corresponded in all cases to potential energy minima for which no imaginary frequency was found. Periodic calculations were performed at the B3LYP/6-31G(d,p) level with Crystal98 and Crystal09 [63,64] codes. Using the experimental estimations as the starting point, the coordinates of the hydrogen atoms in the crystal were optimized to minimize the B3LYP/6-31G(d,p) crystal energy with heavy atom coordinates and cell parameters fixed at their experimental values. The topology of the resulting electron density was then analyzed using the TOPOND98 [65] code. For consistency with the periodic results, molecular and supramolecular electron densities were also analyzed with TOPOND98 from calculations performed with Crystal98 using geometry optimized with Crystal09.

4.5. X-ray data collection and structure refinement

Crystallographic data for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2\text{SCl}$ are given in Table 2. The crystal was kept at $173(2)\text{ K}$ during data collection. Using Olex2 [66], the structure was solved with the Superflip [67] structure solution program using Charge Flipping and refined with the XL refinement package [68] using Least Squares minimization. All of the H atoms were placed in their calculated positions and then refined using the riding model with C—H lengths of $0.93\text{ }\text{\AA}$ (CH), $0.97\text{ }\text{\AA}$ (CH_2) or $0.96\text{ }\text{\AA}$ (CH_3) [69]. The isotropic displacement parameters for these atoms were set from 1.18 to 1.21 (CH, CH_2), or from 1.48 to 1.50 (CH_3), times U_{eq} of the parent atom.

Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC). Enquiries for data can be directed to: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK, CB2 1EZ or (e-mail) deposit@ccdc.cam.ac.uk or (fax) +44 (0) 1223 336033. Any request to the Cambridge Crystallographic Data Centre for this material should quote the full literature citation and the reference number CCDC 949912.

Acknowledgments

ACF and MFE are members of the Carrera del Investigador of CONICET (República Argentina). The Argentine authors thank the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the ANPCYT the Facultad de Ciencias Exactas, Universidad Nacional de La Plata for financial support. JPJ acknowledges the NSF-MRI Program (Grant No. CHE-1039027) for funds to purchase the X-ray diffractometer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.chemphys.2014.01.009>.

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