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Understanding the conformational changes and molecular structure of furoyl thioureas upon substitution

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ABSTRACT

1-Acyl thioureas [$R^1C(O)NHC(S)NR^2R^3$] are shown to display conformational flexibility depending on the degree of substitution at the nitrogen atom. The conformational landscape and structural features for two closely related thioureas having R^1 = 2-furoyl have been studied. The un-substituted 2-furoyl thiourea (**I**) and its dimethyl analogue, i.e. 1-(2-furoyl)-3,3-dimethyl thiourea (**II**), have been synthesized and fully characterized by spectroscopic (FT-IR, ^{1}H and ^{13}C NMR) and elemental analysis. According to single crystal X-ray diffraction analysis, compounds **I** and **II** crystallize in the monoclinic space group P21/c. In the compound **I**, the *trans–cis* geometry of the almost planar thiourea unit is stabilized by intramolecular N—H···O═C hydrogen bond between the H atom of the *cis* thioamide and the carbonyl O atom. In compound **II**, however, the acyl thiourea group is non-planar, in good agreement with the potential energy curve computed at the B3LYP/6-31 + G(d,p) level of approximation. Centrosymmetric dimers generated by intermolecular N—H···S═C hydrogen bond forming $R_2^2(8)$ motif are present in the crystals. Intermolecular interactions have been rationalized in terms of topological partitions of the electron distributions and Hirshfeld surface analysis, which showed the occurrence of S···H, O···H and H···H contacts that display an important role to crystal packing stabilization of both thiourea derivatives.
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1. Introduction

1-Acyl thiourea derivatives, with general formula $R^1C(O)NHC(S)NR^2R^3$, are versatile compounds that have attracted much attention in many fields, such as chemical intermediates in synthesis, biological and pharmaceutical chemistry, and as promising new materials in environmental applications. Comprehensive review articles can be found in the recent literature covering the chemistry, structure and applications of these compounds [1–4].

It has been determined that desired properties depend on the structure and conformation adopted by the central 1-acyl thiourea group. The interplay between intermolecular and intramolecular hydrogen bonding greatly affects the chemical properties of these compounds, including their use as ligand in metal complexes [1], as reagents in cyclization reactions [4], biological activities and other useful applications. In particular, a ligand-based structural optimization methodology for the preparation of a series of 1-(acyl)-3-(mono) and 1-(acyl)-3,3-(di) substituted thioureas has been developed, with potent smoothened antagonist [5]. Interestingly, a series of analogous acylureas or acylguanidines compounds displayed similar biological activities [6,7]. From this similitude, the existence of common hydrogen-bonding interactions between the ligands and the receptor pocket was proposed [6]. Similarly, the hydrogen-bonding ability of 1-(acyl)-3-(mono) substituted thioureas make these molecules candidates for anion receptors [8–10].

Hydrogen bonds also influence the conformational equilibria around the 1-acyl thiourea core. In effect, several conformations are possible for these compounds, depending on the orientations adopted by the C═O and C═S double bonds with respect to the C—N bonds [11–13]. Following Woldu and Dillen [14], the two main forms are denote as *S* and *U* (the letter reflects the position of the C═O and C═S double bonds relative to the vertically drawn N—H bond, as shown in Scheme 1). As

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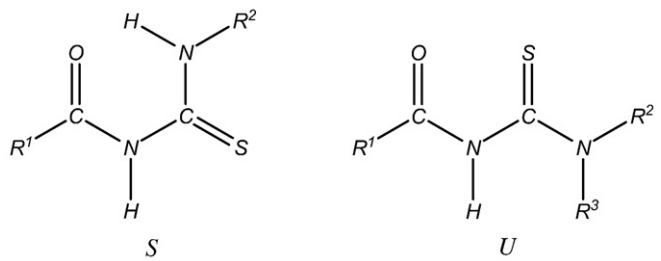


Scheme 1. Main conformations observed for 3-mono (*S* form) and 3,3-di substituted (*U* form) 1-acyl thioureas.

reported by Becker and coworkers [15], the *S* form prevails for 1-(acyl/aroyl)-3-(mono-substituted) thiourea derivatives with $R^2 = H$, because the formation of intramolecular C═O···H—N hydrogen bond strongly stabilize this conformation [16–18]. On the other hand, 1-(acyl/aroyl)-3,3-(di-substituted) thioureas tend to adopt the *U* form since in this case R^2 and $R^3 \neq H$ and thus, the formation of a intramolecular hydrogen bond is disallowed [19].

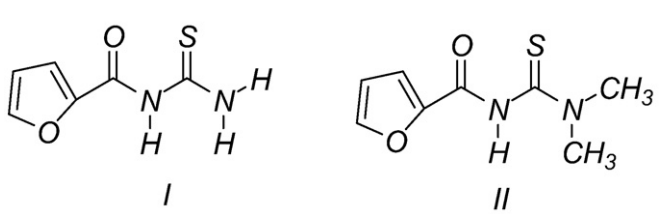
Thiourea derivatives containing the 2-furoyl group were synthesized [20–24] and the complexation ability of these ligands toward various metal ions was investigated [25–28], with salient analytical applications [29]. In particular, 1-(2-furoyl)-3-substituted thioureas were probed as useful intermediates used in environmental control and as ionophores in ion selective electrodes [26,30]. Recently, mesoporous silica hybrid materials functionalized with 1-(2-furoyl) thioureas exhibited good ability to remove Hg(II) from aqueous solutions [31].

In this article the effect of substitution at the 2-furoyl thiourea core is analyzed by studying two closely related species, i.e. the "parent" and the novel 3,3-dimethylated thioureas (compounds **I** and **II** in Scheme 2, respectively). Structural characterization includes experimental spectroscopic (FT-IR and Raman) and X-ray diffraction studies, complemented with a detailed analysis of intermolecular interactions by Hirshfeld surfaces and Atom in Molecule (AIM) topological analysis of the electron charge density.

2. Experimental

2.1. Material and Measurements

Thin layer chromatography (TLC) was performed on 0.25 mm silica gel pre-coated plastic sheets (40/80 mm) (Polygram SIL G/UV254, Macherey & Nagel, Düren, Germany) using benzene/methanol (9/1) as eluent. The IR spectra were recorded on a FT-IR Bomem-Michelson 102 spectrometer, in KBr pellets with a resolution of 2 cm^{-1} in the 4000–400 cm^{-1} range. Raman spectra for compounds **I** and **II** were recorded using a Horiba Jobin Yvon T64000 Raman spectrometer equipped with a liquid N_2-cooled back-thinned CCD detector. Spectra were recorded as the co-addition of up to 16 individual spectra with CCD exposure times of 10–20 s each. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 MHz, internally referenced to TMS, chemical shift (δ), multiplicity (m), spin–spin coupling constant (J), integral (I) are given. $CDCl_3$ was used as solvent. Partial elemental analyses were carried out in an instrument of CHNS staff EA 1108 of the FISONS. Thermal analyses were performed with Shimadzu TGA-50 unit, between room temperature and 750 °C, at a heating rate of 5 °C/min and nitrogen flow of 50 mL/min.



Scheme 2. 1-(2-furoyl) thioureas **I** and **II** studied in this work.

2.2. Quantum Chemical Calculations

Optimization of molecular geometries was accomplished within the frame work of the density functional theory [32,33] as implemented in the Gaussian 03 package [34]. Contracted Gaussian basis sets of triple-zeta quality plus polarized and diffuse functions 6-311++G(d,p) for all atoms were used throughout the present work [35]. The corresponding vibrational analyses were performed for the optimized geometries (Cartesian coordinates are given in Tables S1 and S2 in the Supporting information) to verify whether they are local minima or saddle points on the potential energy surface of the molecule. Calculated normal modes were also used as an aid in the assignment of experimental frequencies. Natural Bond Orbital (NBO) population analysis were performed and the energy of the donor–acceptor interactions estimated by the second order perturbation theory [36].

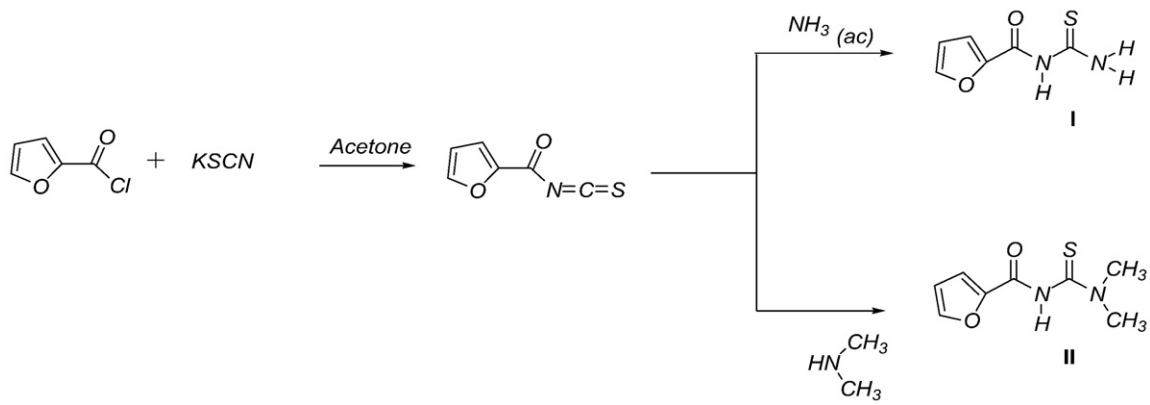
Periodic calculations were performed at the B3LYP/6-31G(d,p) level with Crystal14 code [37]. Using the experimental estimations as the starting point, the coordinates of the hydrogen atoms in the crystal were optimized to minimize the crystal energy with heavy atom coordinates and cell parameters fixed at their experimental values. The topology of the resulting electron density was then analyzed using the TOPOND14 code [38,39].

2.3. Synthesis of 2-Furoyl Thioureas

Detailed descriptions of syntheses and characterization of related furoyl thioureas have been previously reported [13]. A solution of an appropriately acyl chloride (30 mmol) in acetone (50 mL) was added drop wise to a suspension of KSCN (30 mmol) in acetone (30 mL). The mixture was stirred until a precipitate appeared (KCl), indicating the formation of 2-furoyl isothiocyanate. Ammonia [31] or dimethyl amine (30 mmol), dissolved in acetone was slowly added with constant stirring of the resulting solution (Scheme 3). The solution was cooled in an ice-water bath and the stirring was continued at room temperature during 2–9 h, until the reaction was completed (the reaction progress was monitored by TLC). The reaction mixture was then poured into 600 mL of cold water. The solid thioureas were collected by filtration and finally purified by re-crystallization from acetone:water mixture. The identity of the products was confirmed by the analysis of the ^1H and ^{13}C NMR spectra (given in Figs. S1–S4 of the Supplementary information) in comparison to similar compounds previously reported in the literature [13].

2-Furoyl thiourea (**I**): yield 79%, mp 146–147 °C. FT-IR [ATR (solid), $\nu \cdot cm^{-1}$]: 3336, 3320, 3302, 3000, 1679, 1606, 1529, 1350, 1178, 883, 756. ^1H NMR (400 MHz, DMSO-d_6): 10.92 (s, 1H, NH, D_2O exchangeable); 9.58 (s, 1H, NH, D_2O exchangeable); 8.02 (dd, 2H, $J = 2.6$ Hz Ar), 7.79 (dd), 6.73 (dd,). ^{13}C NMR (400 MHz, DMSO-d_6): 181.5 (C═S); 157.1 (C═O), 148.1, 144.7, 118.2 and 112.5. Anal. Calc. for $C_6H_6N_2O_2S$ (170.01): C, 42.34; H, 3.55; N, 6.46; S, 8.84%; Found: C, 42.00; H, 3.50; N, 5.90; S, 8.90%.

1-(2-furoyl)-3,3-dimethyl thiourea (**II**): yield 82%, mp 146–147 °C. FT-IR [ATR (solid), $\nu \cdot cm^{-1}$]: 3161, 2923, 1697, 1571, 1473, 1263, 1178, 929, 761. ^1H NMR (400 MHz, $CDCl_3$): 8.63 (s, ^1H, NH, D_2O exchangeable); 7.56 (dd), 7.27 (dd), 6.58 (dd), 3.40(s, CH_3) and 3.28 (s, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): 179.0 (C═S); 153.4 (C═O), 146.1, 145.5, 117.3, 112.8. Anal. Calc. for $C_8H_{10}N_2O_2S$ (198.05): C, 48.47; H, 5.08; N, 4.13; S, 8.17%; Found: C, 48.00; H, 5.30; N, 4.50; S, 8.50%.



Scheme 3. Synthesis of 2-furoyl thioureas **I** and **II**.

2.4. Crystal Structure Determination

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of $CHCl_3$:*n*-hexane (3:1) solutions of the furoyl thioureas **I** and **II**. Diffraction data were collected on an Enraf-Nonius Kappa-CCD diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The final unit cell parameters were based on all reflections. Data collections were performed using the COLLECT program [40], integration and scaling of the reflections were performed with the HKL Denzo–Scalepack system of programs [41]. Absorption corrections were carried out using the Gaussian method [42]. The structures were solved by direct methods with SHELXS-97 [43]. The models were refined by full-matrix least-squares on F^2 by means of SHELXL-97. The projection views of the structures were prepared using ORTEP-3 for Windows [44]. Hydrogen atoms were stereochemically positioned and refined with the riding model. The crystal and refinement data for title compounds are listed in Table 1 with the CCDC deposit numbers for supplementary crystallographic data.

Table 1
Crystal data and refinement parameters for compounds **I** and **II**.

Compound	I	II
Empirical formula	$C_6H_6N_2O_2S$	$C_8H_{10}N_2O_2S$
Formula weight	170.19	198.24
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Unit cell dimensions (Å; °)		
a (Å)	9.3851(6)	4.97290(10)
b (Å)	7.3711(5)	10.7065(5)
c (Å)	10.6129(5)	17.7566(7)
β (°)	95.038(4)	94.568(2)
Volume (Å^3)	731.35(8)	942.40(6)
Z	4	4
Density calc (mg/m^3)	1.546	1.397
Absorption coefficient (mm^{-1})	2.998	0.312
F(000)	352	416
θ range for data collection (°)	3.37 to 25.97	2.986 to 25.996
Index ranges	$-11 \le h \le 11$	$-6 \le h \le 5$
	$-8 \le k \le 9$	$-13 \le k \le 12$
	$-13 \le l \le 12$	$-21 \le l \le 19$
Reflections collected	4544	6464
Independent reflections (R_{int})	1419	1835
	[R(int) = 0.0351]	[R(int) = 0.0414]
Goodness-of-fit on F^2	1.071	1.313
R1 [I > 2σ (I)]	R1 = 0.0411	R1 = 0.0336
wR2 [I > 2σ (I)]	wR2 = 0.1064	wR2 = 0.0734
Largest diff. peak and hole (eÅ^{-3})	0.251 and −0.309	0.294 and −0.326
CCDC deposit number	931,558	1,502,060

3. Results and Discussion

3.1. Synthesis and Characterization

2-Furoyl thioureas **I** and **II** were synthesized according to the general method early reported by Douglass and Dains [45] and further optimized for 2-furoyl substitutions [13,31]. The one-pot procedure involves the in situ reaction between 2-furoyl chloride and KSCN and the reaction of the intermediate 2-furoyl isothiocyanate with the appropriated amine. The reaction proceeds via a nucleophilic addition of the amine to the isothiocyanate with good yields (79 and 82%, for **I** and **II**, respectively). The synthesized compounds were purified by recrystallization from an acetone:water mixture (1:2) and characterized by elemental analysis, ^{1}H NMR, ^{13}CNMR, and FT-IR spectroscopy. In ^{1}H NMR, the compounds exhibited broad signals in the range of 10.92, 9.58 and 8.63 ppm, which were assigned to the N—H protons. ^{13}C NMR spectrum showed the peaks at about δ 181.5 and 179.0 for C═S (thioamide) and 157.1 and 153.4 for C═O (amide), respectively. The elemental analyses closely corresponded to calculated values.

3.2. Vibrational Spectra

Infrared and Raman spectroscopies have shown to be very useful for analyzing the conformational properties, as well as intermolecular and intramolecular hydrogen bond interactions involving N—H donors of acyl thioureas [11,46–54]. As early noted by Reguera et al. [21] the joint analysis of both infrared and Raman spectroscopy are required for study the effect on the substitution for a series of mono- and disubstituted thioureas. Recently, we have shown the complementarily of both techniques for the analysis of 1-(adamantane-1-carbonyl)-3-(mono)- and 3,3-(di) substituted thioureas [55]. The 3N − 6 = 45 normal modes of vibration for compound **I** can be classified as 31 A′ in-plane modes and 14 A″ out-of-plane modes in the C_S symmetry group.

In particular, the 1720–1050 cm^{-1} region of the Raman spectrum of compounds **I** and **II** is shown in Fig. 1. The close examination of the ν(C═O) stretching mode region reveals a strong absorption at 1679 cm^{-1}, with a counterpart in the Raman spectrum at 1680 cm^{-1} for compound **I**, whereas this mode appears shifted toward higher frequencies for compound **II**, with values at 1697 cm^{-1} (IR) and 1693 cm^{-1} (Raman), as shown in Fig. 1. These values are in good agreement with those previously reported for related acyl thioureas and 1-acyl-3,3-di-substituted thioureas [56]. The experimental values are well-reproduced by the quantum chemical calculations, with computed ν(C═O) frequency values of 1735 and 1760 cm^{-1} for **I** (A′ symmetry species) and **II**, respectively. The lower force constant of the ν(C═O) stretching found for compound **I** is associated with the intramolecular N—H···O═C hydrogen bond.

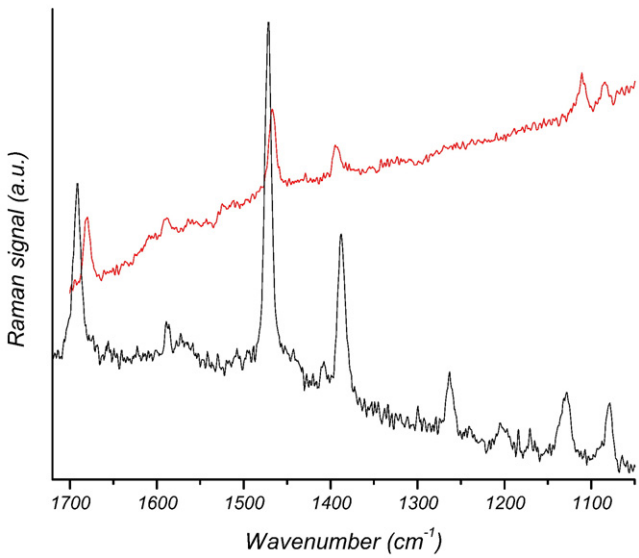


Fig. 1. Selected region of the Raman spectra for the solid phase of compounds **I** and **II**.

Intense absorptions in the 1500–1600 cm^{-1} region due to the δ(N—H) deformation modes are usually observed in the infrared and Raman spectra of thioureas [57], whereas only one δ(N—H) band is expected for the 3,3-disubstituted species. The infrared spectra show very strong and rather broad absorptions at around 1559 (1579 cm^{-1} Raman) and 1571 cm^{-1} (1587 cm^{-1} Raman) for **I** and **II**, respectively, in agreement with previous works [58].

The ν(C═S) stretching mode of 1-acyl thiourea compounds is sensitive to the presence of intermolecular interactions involving the C═S group [46] and it is found in the 600–800 cm^{-1} range [21,25,59,60]. In accordance with the computed vibrational data, we assigned this mode to the absorptions observed at 756 and 761 cm^{-1}, with counterparts in the Raman spectra at 753 and 755 cm^{-1}, for compounds **I** (A′ symmetry species) and **II**, respectively.

3.3. Thermal Analysis

In order to know the thermal stability of the two compounds, the thermogravimetric study (TG) was carried out. The analysis of TG curves indicates that both compounds point toward a similar thermal behavior over the temperature range of 100–750 °C, as shown in Fig. 2. Further it can be seen that nearly the total decomposition occur between the temperature range from 100 to 300 °C in both compounds. Compound **I** decomposes at slightly higher temperature than compound **II**. This thermal stability is in agreement with the nearly planar structure in **I,** favors in this way the donor → acceptor interactions through the intramolecular, N—H···O═C, hydrogen bonds, as will be discussed below. The first step observed in the TG curve for compound **I** with a loss mass of 88.54%, is consistent with the removal (fragmentation) of furoyl C(O)NC(S) moiety (calculated loss weight of 89.90%). The second step observed in the TG curve with a loss mass of 9.76%, is probably due to the formation of NH_3 as a result of a mechanisms simultaneous by a migrating of the NH hydrogen atoms and the cleavage (homolysis) of C—N bonds (loss of weight calculated 9.98%). This thermal fragmentation mechanism is in agreement with that suggested previously in the pyrolysis of related furoyl thioureas studied by mass spectrometry methods [61,62].

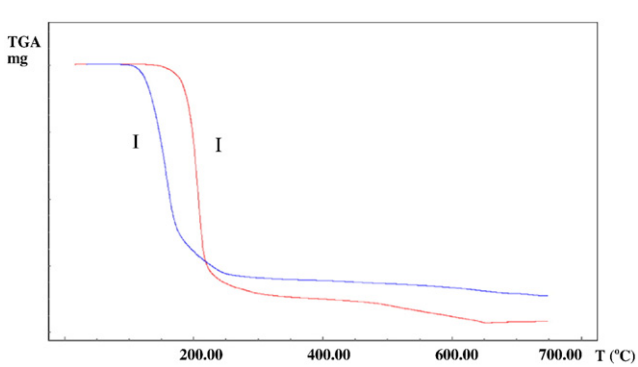


Fig. 2. TGs curves for compounds **I** (red) and **II** (blue).

3.4. Molecular Structure

3.4.1. Theoretical Conformational and Natural Bond Orbital Analysis

A rich conformational landscape can be anticipated for the studied compounds. In particular, several conformations can be adopted depending on the relative orientation of the C═O and C═S double bonds of the acyl thiourea core. Based on previous reports [11,12] the most relevant conformational changes are expected by differences in the relative orientations around the C—N bond joining the amide and thioamide groups [18]. The potential energy curve around the C—N bond for compounds **I** and **II** have been computed at the B3LYP/6-31 + G(d,p) level of approximation, allowing geometry optimizations with the δ(CN—CN) dihedral angle varying from 0 to 360° in steps of 20° (Fig. 3). For compound **I**, the most stable structure corresponds to the *S* form (see Scheme 1) with a dihedral angle of 0°. In this conformation the C2═O1 and H—N1 groups form a pseudo 6-membered ring, favoring an H-bond intramolecular interaction. For compound **II**, the minimum occurs at a dihedral angle ca. 60°, with mutual synclinal orientation of the C1—N1 and C6—N2 bonds (see Figs. 4 and 5 for atoms numbering).

The structures with δ(CN—CN) = 180° correspond in both cases to local maxima in the potential energy curve, the energy barriers being ca. 15 and 11 kcal/mol, higher for compound **I**. Two equivalent local minima are observed at δ(CN—CN) values of ca. 150 and 210°. These conformers are located higher in energy and correspond to structures with a nearly antiperiplanar orientation between the C—N and C—N bonds.

It is recognized that remote donor-acceptor orbital interactions can play a decisive role on the peptide backbone conformation [63]. In particular, it has been proposed that C═O···H—N hydrogen bonds [64] can

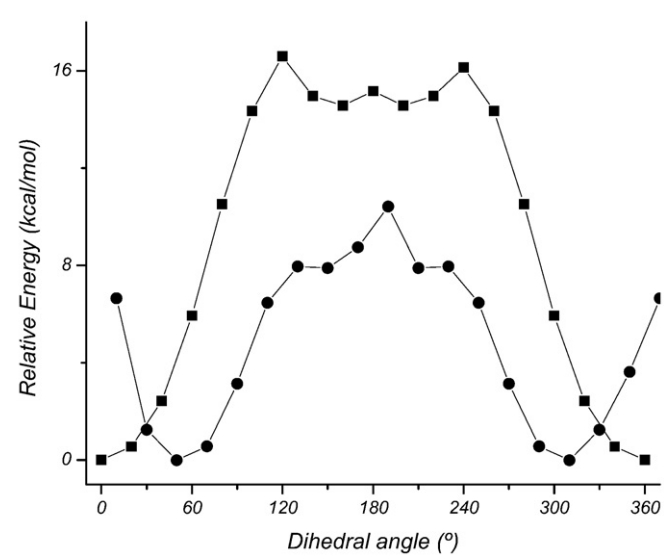


Fig. 3. Calculated [B3LYP/6-31 + G(d,p)] potential function for internal rotation around the δ(CN—CN) dihedral angle of thioureas **I** (–■–) and **II** (–●–).

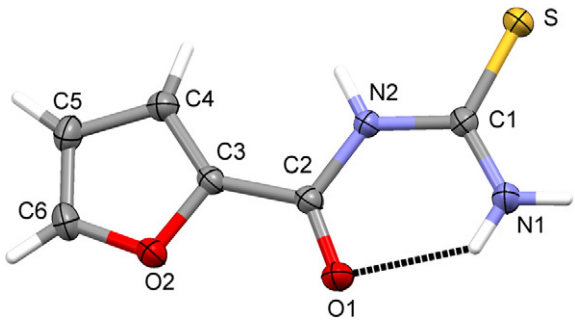


Fig. 4. The molecule structure of the compound **I** in the crystal. Ellipsoids represent 50% probability levels and dashed line indicates intramolecular hydrogen bond.

be analyzed 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 [65]. For benzenesulfonylamin acetamide, lpO → σ*(N—H) interaction values of ca. 9.5 kcal/mol were computed by using DFT methods [66].

We applied the Natural Bond Orbital population analysis for determining electron donations in the studied compounds. For the compound **I**, the second-order perturbation analysis of the Fock matrix [B3LYP/6-311++G(d,p) level of approximation] indicates a lpO1 → σ*(N1—H) remote interaction, amounting to 8.1 kcal/mol for the *S* form. The hyperconjugative interaction increases the electronic population of the σ*(N1—H) orbital (0.031 **e**), as compared with that of the second N—H group, i.e. σ*(N2—H), with 0.010 **e**. For compound **II**, without the possibility of forming intramolecular hydrogen bond, the σ*(N1—H), shows an electronic population of 0.016 **e**.

The NBO analysis for the most stable conformers for compounds **I** and **II**, respectively, indicates the presence of pure p-type [lp_p(N)] lone pair orbitals on both amide and thioamide nitrogen atoms. These orbitals display low electron occupancies (1.675 and 1.650 **e** and 1.703 and 1.597 **e** for the lp_p(N1) and lp_p(N2) of **I** and **II**, respectively) indicating their electron-donating capacity. The donor → acceptor interactions reveal that the lone pair orbital contributes to a strong resonance interactions with the carbonyl bond of the 2-furoyl group lp_p(N2) → π*(C2═O1), leading to the "amide resonance". The computed $E^{(2)}$ interaction values are 57.0 and 41.0 kcal/mol for **I** and **II**, respectively, in good agreement with reported values for other 1-acyl thioureas [67].

The resonant forms also can involve the thioamide group and can be evaluated within the donor → acceptor approach, being the acceptor the π*(C═S) and σ*(C═S) antibonding orbitals. For compound **I**, the lp_p(N) → π*(C1═S) interactions are computed to be 81.8 and 57.0 kcal/mol for the N1 and N2 nitrogen atoms, respectively. Lower values are obtained for **II**, amounting 75.3 and 41.0 kcal/mol, respectively, probably because the non-planar structure disfavors these interactions.

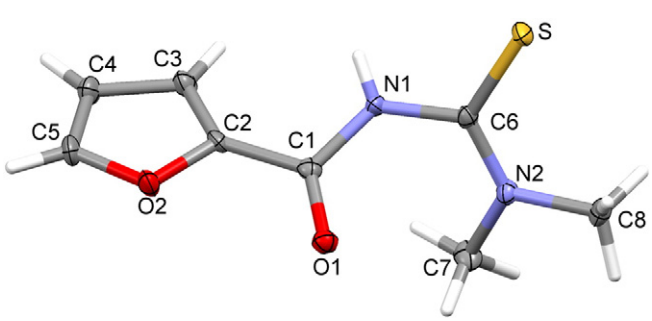


Fig. 5. Molecular structure of compound **II**. Displacement ellipsoids are drawn at the 50% probability level.

3.4.2. X-ray Molecular Structure

The molecular structure of crystalline 2-furoyl thiourea (**I**) is shown in Fig. 4. The compound **I** presents a nearly planar conformation, as a result, a pseudo six membered (O1—C2—N2—C1—N1—H1a) ring is formed, stabilizing an "*S*"-shaped conformation type. As a result the C═S and C═O groups are related to a maximum value of the O—S distance [68], two donor sites rich in electron density and the trans geometry of the thiourea unit is stabilized by intramolecular N1—H1a···O1 hydrogen bond, with N1···O1 distance of 2.676(2) Å and N1—H···O1 bond angle of 132°. The C1═S1 and O1—C1 bonds show a typical double bond character with bond lengths of 1.672(2) Å and 1.223(2) Å, respectively.

The Fig. 5 shows the molecular structure of the compound **II**. It is non planar forming a distorted -"S"-shaped conformation type, this conformation where the carbonyl and thiourea groups are non-planar with mutual anticlinal (O═C / C═S = 112.8°) orientation of the C═S and C═O double bonds (see Fig. S5 in the Supporting information) [68]. The C1═S1 and O1═C1 bonds show a typical double bond character with bond lengths of 1.687(2) Å and 1.221(2) Å, respectively.

The amidic (O)C—N2—H and thioamide N2H—C(S) and (S)C—N1 bonds for **I** and (O)C—N1—H and thioamide N1H—C(S) and (S)C—N2 for **II** are both shorter than a C—N single bond, typically ca. 1.472(5) Å. This fact indicates that these bonds have a pronounced double bond character. It is deduced that these thiourea derivatives make up a multi-electron conjugated *π* bond, in agreement with the NBO results discussed above. Other selected geometric parameters (Table 2) are between the ranges obtained for similar compounds [69].

3.5. Crystal Packing and Topology Analysis of the Electron Densities

Since many of the more relevant intra and intermolecular interactions involve hydrogen atoms, their positions in the crystal were optimized at the B3LYP/6-31G(d,p) level, keeping fixed at their crystallographic values the heavy atom positions and cell parameters. The electron density topology was analyzed and the values of the electron density and positive principal curvature of the Laplacian at the corresponding (3,−1) critical point were used as indicators of the interaction strength. Topological parameters of the predominant intermolecular interactions present in the crystal structures of **I** and **II** are reported in Tables 3 and 4, respectively.

In compound **I**, the basic crystal substructures are the centrosymmetric molecular pairs involving, each, a pair of N—H···S═C interactions with one of the hydrogen atom in the amino group as donor (I in Table 4), these being the most relevant from a topological view point. This pair can be classified as an $R_2^2(8)$ motif forming a pseudo eight-membered ring, as shown in Fig. S6 (Supporting information). In the structure of **I** the H1B···S is separated by 2.622 Å.

The crystal structure of **I**, however, can be better described in terms of the infinite chains expanding in ***c*** axis direction (see Fig. 6a and Table 3), along which molecules are linked each other mainly through four interactions. The two strongest interactions link the carbonyl

Table 2
Selected bond distances (Å) for compounds **I** and **II**.

*Compound **I***			
S—C1	1.672(2)	O1—C2	1.223(2)
O2—C3	1.371(2)	O2—C6	1.352(2)
N1—C1	1.310(2)	N2—C1	1.390(2)
N2—C2	1.386(2)	C2—C3	1.455(2)
*Compound **II***			
S—C6	1.687(2)	O1—C1	1.221(2)
O2—C2	1.372(2)	O2—C5	1.365(2)
N1—C1	1.387(2)	N1—C6	1.404(2)
N2—C6	1.321(2)	N2—C7	1.467(2)
N2—C8	1.466(2)	C1—C2	1.464(2)

Table 3
Topological parameters (atomic units) of the close shell intermolecular (3,−1) critical points (electron density (ρ), Laplacian ($\nabla^2\rho$) and positive curvature (λ_3)) and geometrical parameters (Å and °) of the interactions used in the structure description of compound **I**.[a]

		ρ	$\nabla^2\rho$	λ_3	$d_{H\cdots O/S/N}$	$\theta_{D-H\cdots O/S/N}$
I	S···H_2N (i)	0.0175	0.0400	0.0755	2.461	164.8
II	C═O···H—N (ii)	0.0130	0.0444	0.0725	2.185	168.6
III	C═O···H_R (iii)	0.0126	0.0380	0.0642	2.339	151.1
IV	NH_2···S (iv)	0.0100	0.0332	0.0490	2.744	125.6
V	O_R···H_R (v)	0.0087	0.0312	0.0478	2.472	140.2
VI	H_R···S (vi)	0.0076	0.0268	0.0388	2.768	159.2

[a] Atom or group belonging to the reference molecule on the left of the interaction symbol. Between parenthesis symmetry operation generating the neighbor molecule (i: −1 − x,1 − y,−z; ii: x,1/2 − y,1/2 + z; iii: x,1/2 − y,1/2 + z; iv: −1 − x,1 − y,−z; v: x,1/2 − y,1/2 + z; vi: 1 − x,1/2 − y,1/2 + z).

Table 4
Topological parameters (atomic units) of the (3,−1) critical points (electron density (ρ), Laplacian ($\nabla^2\rho$) and positive curvature (λ_3)) and geometrical parameters (Å and °) of the intermolecular interactions used in the structure description of compound **II**.[a]

		ρ	$\nabla^2\rho$	λ_3	$d_{H\cdots O/S/N}$	$\theta_{D-H\cdots O/S/N}$
I	N—H···S (i)	0.0188	0.0427	0.0810	2.425	157.4
II	H_R···O ═C (ii)	0.0116	0.0440	0.0671	2.300	136.8
III	CH_3···O ═C (iii)	0.0104	0.0326	0.0534	2.431	150.5
IV	CH_3···O ═C (iv)	0.0095	0.0304	0.0494	2.463	157.79
V	H_R···S (v)	0.0085	0.0242	0.0378	2.850	159.7

[a] Atom or group belonging to the reference molecule on the left of the interaction symbol. Between parenthesis symmetry operation generating the neighbor molecule (i: 2 − x,−y,−z; ii: 2 − x,1/2 + y,1/2 − z; iii: 1 − x,−1/2 + y,1/2 − z; iv: 2 − x,−1/2 + y,1/2 − z; v: 1 − x,−y,−z).

oxygen atom with the amide hydrogen atom and with a hydrogen atom of the furoyl ring (II and III in Fig. 6 and Table 3). The other two interactions link an amino hydrogen atom with a sulfur atom (IV) and a hydrogen atom of the furoyl group with the oxygen atom also from a furoyl ring (V). Chains, in turn, are linked each other through the above mentioned N—H···S interactions and the H_R···S ones (VI). Alternation in the molecule orientation along a chain (see Fig. 6b) ensures the main three dimensional interaction network is thus completed.

In compound **II**, the basic substructures are the centrosymmetric molecular pairs involving, each, a pair of N—H···S interactions (I in Table 4 and Fig. 7). Linking of such pairs through C—H···O interactions (III) involving methyl groups and acting in almost perpendicular directions (see Fig. 7 a), give rise to molecular layers parallel to [1,0,2]. The main three dimensional interaction network is completed by three interactions that link layers with each other (see Table 4 and Fig. 7b). Two of them involve carbonyl hydrogen atoms, a ring hydrogen atom (II) and a methyl hydrogen atom (IV) of the reference molecule being the donors. The remaining one is a H···S interaction (V).

3.6. Hirshfeld Surface Analysis

Intermolecular contacts were also explored using both Hirshfeld surfaces and fingerprint plots. In recent years, many research groups have used Hirshfeld surfaces [70,71] and their two-dimensional fingerprints as an important tool to visualize and analyze structural properties in relation to packing patterns [72], including those observed in thiourea compounds [73,74]. The intermolecular interactions of **I** and **II** were analyzed using the Hirshfeld surface and the corresponding two-dimensional fingerprint plots [75] are shown in the Fig. 8.

The 3D d_{norm} Hirshfeld surfaces for **I** and **II** are represented in the Fig. 8A, in which the value of d_{norm} can be negative, positive or zero, when intermolecular contacts are shorter, longer or equal to van der Waals (vdW) radii, respectively. The d_{norm} values were mapped onto the Hirshfeld surface using a color gradient from blue to red indicates that region able to perform intermolecular interactions. Red regions represent closer contacts and a negative d_{norm} value, while blue regions represent longer contacts and a positive d_{norm} value. In the surface, white regions represent the distance of contacts equal to exactly the vdW separation with a d_{norm} value of zero. As can be seen in the Hirshfeld surfaces of the compounds **I** and **II** the most intense red

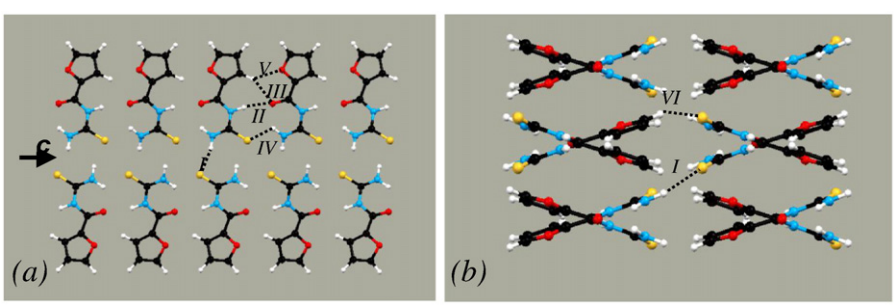


Fig. 6. (a) Two chains view along ***b*** axis direction, in the compound **I**. (b) Six chains view along ***c*** axis direction.

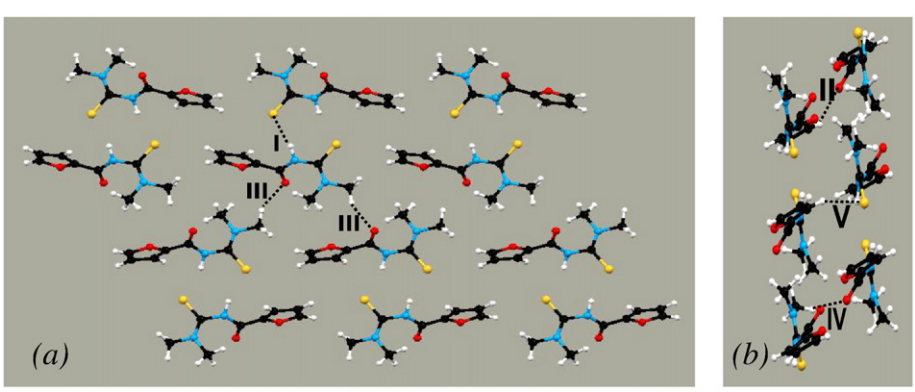


Fig. 7. (a) Layer view along a normal to [1,0,2]. (b) Two layers view along ***b*** axis direction in the compound **II**.

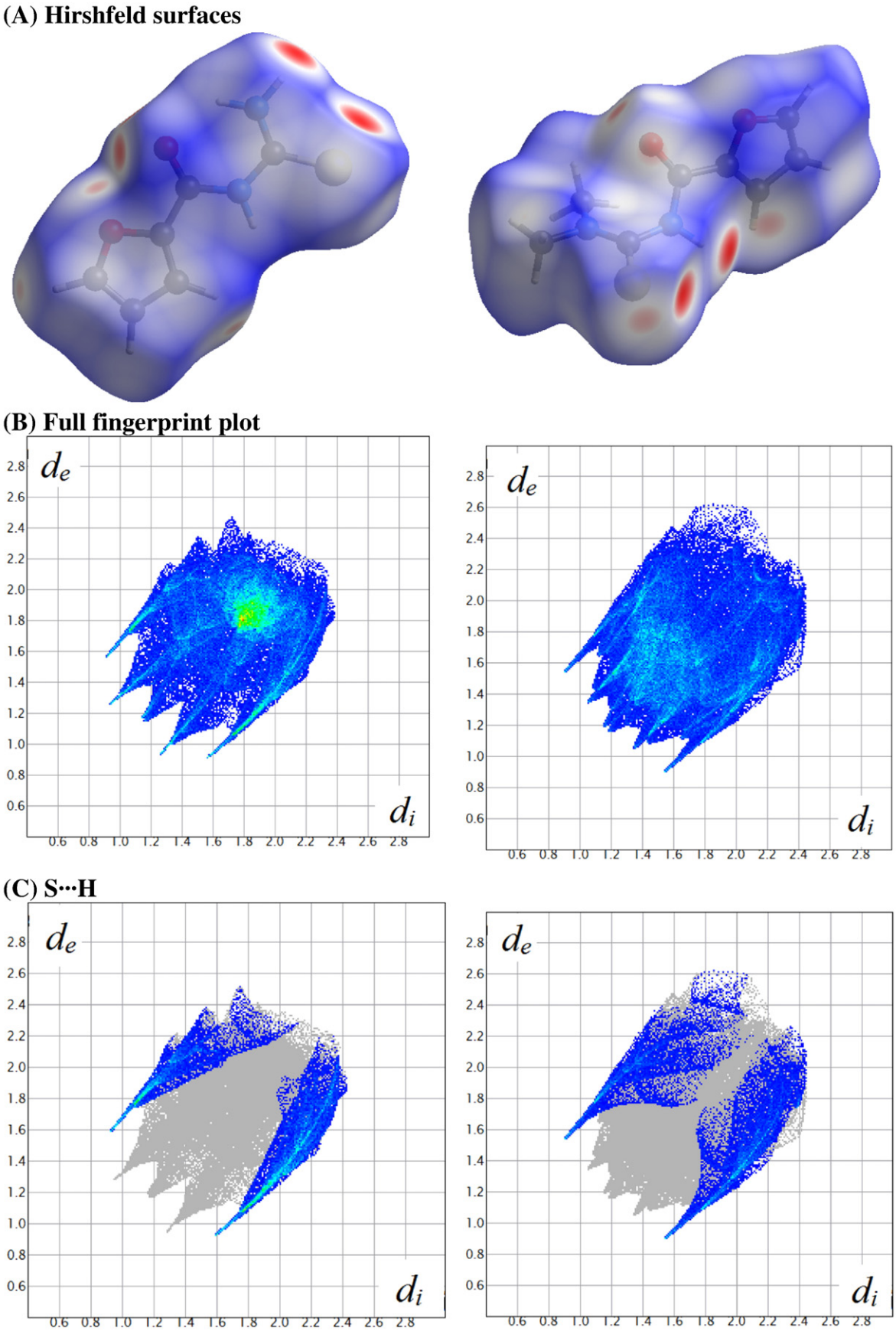


Fig. 8. Hirshfeld surfaces (A) and fingerprint plots (B-E) for compounds **I** (left) and **II** (right). The full fingerprint is represented in (B), and graphics C, D and E depict the S···H, O···H and H···H intermolecular contacts, respectively.

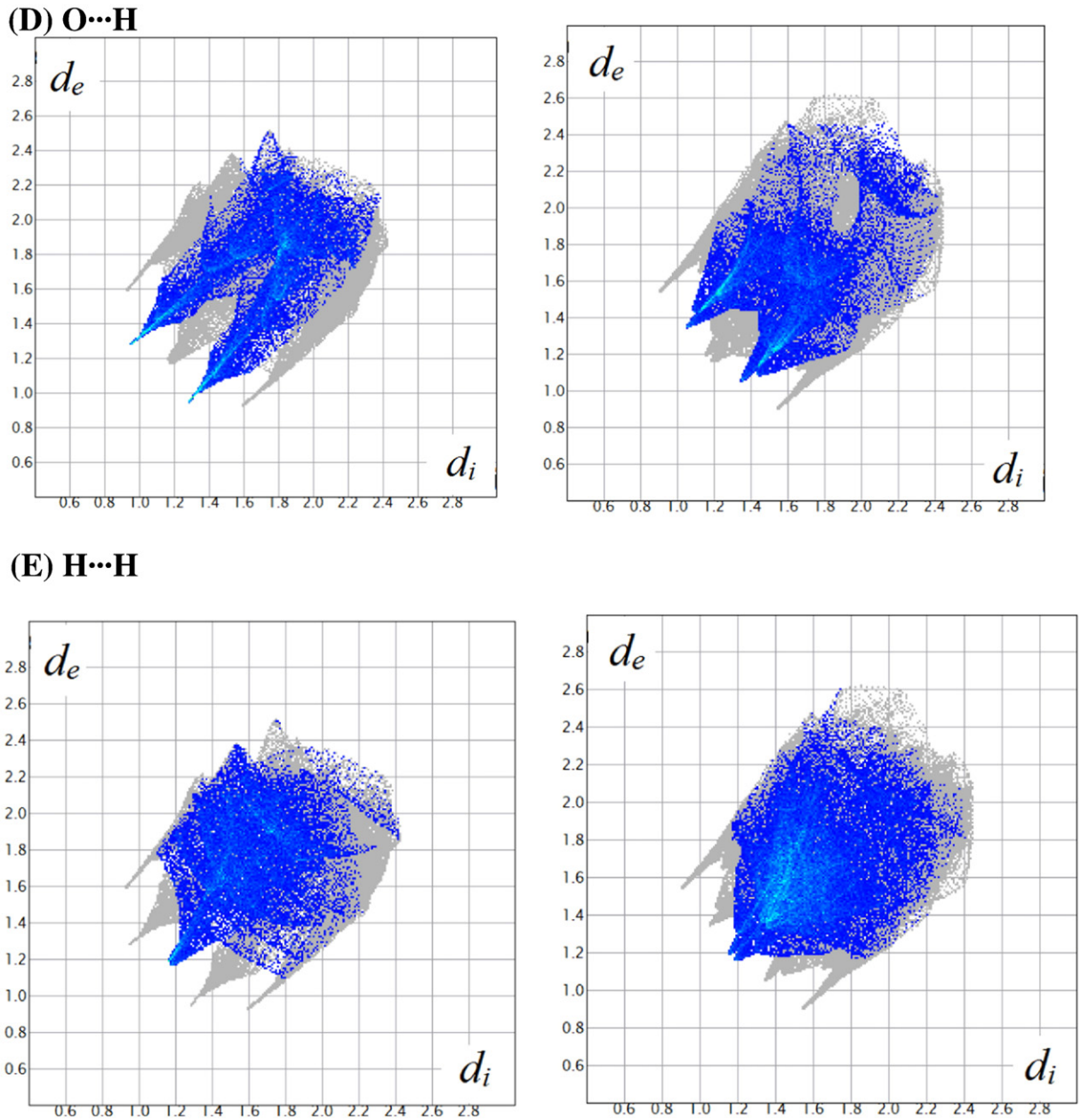


Fig. 8 (*continued*).

regions occur near to C═S and N—H groups, due to bifurcate N—H···S hydrogen bonds present in both structures (see Fig. S6 in the Supporting information). The compound **I** also exhibits red regions close to both oxygen atoms of carbonyl and furoyl groups, as a result of N—H···O and C—H···O hydrogen bonds, respectively, such as illustrated in the Fig. 6a and discussed in the crystal packing analysis. Differently, when we look at to Hirshfeld surface of the compound **II**, it is observed that the oxygen atom of the furoyl group is not involved in any close intermolecular contact, resulting in a white-to-blue gradient color in the Hirshfeld surface. Meanwhile the less intense red color gradient in **II** is observed on oxygen atom of the carbonyl, because this group is involved in a non-classical C—H···O hydrogen bond, such as represented in Table 4 and Fig. 7.

The fingerprint plots of the two molecules show the presence of S···H, O···H and H···H intermolecular contacts (Fig. 8B). The relative contribution of the main intermolecular contacts present in each compound is listed in the Table S3 (Supporting information). The biggest contribution includes hydrophobic intermolecular contacts (H···H, C···H and C···C). In addition, the hydrogen bonding (S···H and O···H) form well defined contacts as represented in the Fig. 8C–D, acting as driving forces to stabilize the crystal packing. Therefore, the hydrophobic intermolecular contacts together with the N—H···S hydrogen bonds provide forces for self-assembly in the compounds.

4. Conclusions

Two 2-furoyl thiourea derivatives (**I** and **II**) were prepared and their structural and spectroscopic properties have been determined. Our results clearly show that the conformation of the central acyl-thiourea [—C(O)NHC(S)N<] moiety depends on the substitution at the nitrogen atom. Thus, the simplest 2-furoyl thiourea (**I**) adopts a planar structure with the C═O and C═S double bonds mutually oriented in a pseudo-antiperiplanar arrange, favoring a strong C═O···H—N intramolecular hydrogen bond. The same conformation was very recently found in the crystal of the mono-substituted 3-phenyl thiourea [76]. However, di-methylation of the —NH_2 group leads to a different conformation

of the thiourea group: planarity is absent in compound **II** and anticlinal orientation of the C═S and C═O double bonds is observed. Inversion dimers with an $R_2^2(8)$ ring motif are observed for **I** and **II**, a supramolecular synthon that is assisted by strong N—H···S═C hydrogen bonds, as characterized by topological grounds and Hirshfeld surface analysis.

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Appendix A. Supplementary data

Cartesian coordinates of optimized structures [B3LYP/6-311++G(d,p)] for compounds **I** and **II** are given in Tables S1 and S2, respectively. In Table S3 the relative contribution to the Hirshfeld surfaces of the important intermolecular contacts present in each compound, **I** and **II** are given. ^{1}H and ^{13}C NMR spectra are given in Figs. S1–S4. Conformations of molecules of compound **I** are shown in Fig. S5 and centrosymmetric dimer the studied compounds are shown in Fig. S6. Supplementary data associated with this article can be found in the online version, at [10.1016/j.saa.2016.12.038].

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