Published in: Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy: 112; 2013; 84-89.

Reinvestigation of growth of urea thiosemicarbazone monohydrate crystal

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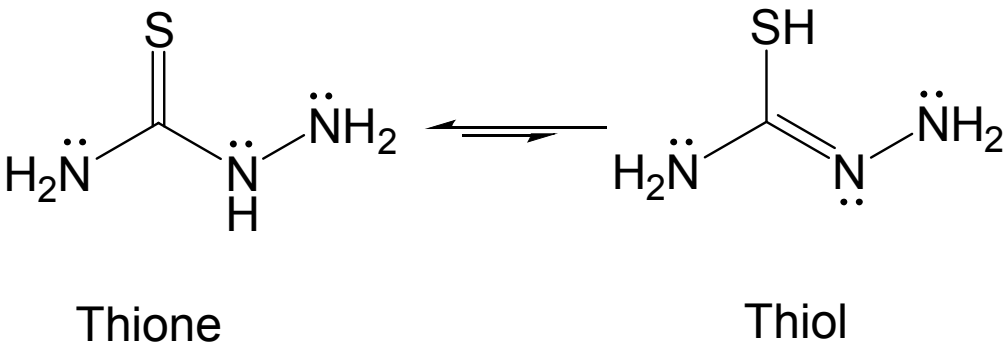
Graphical Abstract

Reinvestigation of the reaction of urea with thiosemicarbzide **1** reported in Spectrochim. Acta A91 (2012) 345-351, reveals that the crystal obtained is the starting material namely thiosemicarbzide. Compound **1** exhibits thione-thiol tautomerism in solution.



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Highlights

- Reaction of urea with thiosemicarbazide is reinvestigated.
- Urea being an amide does not form any thiosemicarbazone product.
- Thiosemicarbazide crystallizes in the triclinic $P1^{-}$ space group.
- Thiosemicarbazide exhibits thione-thiol tautomerism in solution.
- Thiosemicarbazide exists as the thione tautomer in solid state.

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Abstract

The reaction of urea with thiosemicarbazide in 1:1 mole ratio in aqueous solution does not result in the formation of urea thiosemicarbazone monohydrate crystal, as reported by Hanumantharao, Kalainathan and Bhagavannarayana [Spectrochim. Acta A91 (2012) 345-351]. A reinvestigation of the reported reaction reveals that the crystal obtained is the starting material namely thiosemicarbazide, which has been unambiguously confirmed with the aid of infrared and ^{1}H NMR spectra and single crystal X-ray structure determination. Analysis of ^{1}H NMR spectrum reveals that thiosemicarbazide exhibits thione-thiol tautomerism in solution. In contrast, thiosemicarbazide exists as the thione tautomer in the solid state.

Keywords: urea; thiosemicarbazide; urea thiosemicarbazone monohydrate; ^{1}H NMR; X-ray structure; thione-thiol tautomerism.

Introduction

Urea is the chief nitrogen-containing end product of protein metabolism and is thus an important biochemical. It is synthesized on a large scale for use as a fertilizer and as a raw material for the manufacture of urea-formaldehyde plastics and drugs. The chemistry of urea has been well studied since its first laboratory synthesis was reported by Wöhler in 1828 [1] and is described in standard organic chemistry text books [2]. Urea crystallizes in

the non-centrosymmetric space group $P4\bar{2}_1m$ [3]. In nonlinear optical (NLO) materials research, the ready availability of high pure urea, has made it as an useful reference compound for reporting (as well as comparing) second harmonic generation (SHG) efficiency of non-centrosymmetric compounds [4, 5].

Urea is a carbodiimide as its structure consists of a central carbonyl moiety (>C=O) flanked by two $-NH_2$ (amine) groups on either side. Unlike its hydrolysis to ammonia (or ammonium) and carbon dioxide under alkaline (or acidic) conditions or by the enzyme urease, where the >C=O group is converted to CO_2, formation of urea-formaldehyde plastics, barbituric acid etc. are reactions in which the carbonyl group remains in tact. While substitution reactions at the amino functionalities are known to result in products retaining the original >C=O moiety, transformations of urea involving the carbonyl group, which are typical of aldehyde or ketone are seldom known.

Thiosemicarbazone is a crystalline derivative of thiosemicarbazide and is usually prepared by reacting it with an aldehyde (or ketone) [6-8]. The formation of thiosemicarbazone is an addition reaction wherein the N atom of $-NH_2$ group (nucleophile) of thiosemicarbazide adds on to the carbon centre of the >C=O functionality of the aldehyde (or ketone) resulting in an imine (-C=N-) compound with the elimination of a water molecule. In a recent report (title paper hereinafter), Hanumantharao *et al* [9] have claimed growth of urea thiosemicarbazone monohydrate ($C_2H_9N_5OS$) crystals by reacting urea with thiosemicarbazide and reported that the reaction mechanism is similar to that of benzaldehyde thiosemicarbazone monohydrate.

Urea being an amide is not expected to behave like an aldehyde (or ketone). If the >C=O group of urea can couple with the $-NH_2$ functionality of thiosemicarbazide in a facile manner just by mixing aqueous solutions of urea and thiosemicarbazide, as claimed by the authors of [9], to give an imine namely urea thiosemicarbazone, then it should also be

possible that the $-NH_2$ group of one urea molecule couples with a neighboring molecule to form an urea dimer or alternatively one can expect the formation of a trimeric compound in view of the fact that the carbonyl group is flanked by $-NH_2$ on either side. However, there is no literature report on the formation of any self condensation product of urea from an aqueous solution. In view of this, the reported crystal growth of urea thiosemicarbazone monohydrate appeared quite unusual. The inconsistencies in the reported spectral data [9] for the characterization of the grown crystal, for example assignment of the $DMSO_6$-*d* signal (NMR solvent) for the compound, assignment of a signal at m/z = 133 (Formula weight of $C_2H_9N_5OS$ = 151.04) as the molecular ion peak, reporting a higher carbon weight % (42.92) and a lower weight % of N (29.30) for the formula $C_2H_9N_5OS$ (for elemental composition see Table S1), raised serious doubts about the correctness of the reported molecular formula. Since spectral data were inconsistent for $C_2H_9N_5OS$, the possibility that the crystal was incorrectly formulated could not be ruled out. The urea thiosemicarbazone crystal is a nitrogen rich compound containing five N atoms in $C_2H_9N_5OS$. In order to establish the correct identity of the crystal in view of the possible applications of a nitrogen rich compound, we have reinvestigated the reaction of urea with thiosemicarbazide reported by Hanumantharao *et al* [9] and have characterized the crystals obtained with the aid of infrared and ^1H NMR spectra and single crystal X-ray structure. The results of this reinvestigation are described in this report.

Materials and Methods

Reagent grade urea and thiosemicarbazide were purchased from commercial sources and were used as received without any further purification in this study. Infrared spectra of the samples diluted in KBr were recorded in the region 4000 – 400 cm^{-1} using a Shimadzu (IR Prestige-21) FT-IR Spectrometer, at a resolution of 4 cm^{-1}. ^1H NMR spectra were recorded

in DMSO-d_6 using a Bruker 400 MHz (Avance) FT-NMR spectrometer. X-ray intensity data were collected at room temperature using Oxford X Calibur, Gemini diffractometer equipped with EOS CCD detector. Monochromatic Mo-K_α radiation (λ = 0.71073 Å) was used for the measurements. Data were collected and reduced by using the ‗CrysAlispro‘‘ program [10]. An empirical absorption correction using spherical harmonics was implemented in ‗SCALE3 ABSPACK‘‘ scaling algorithm. The structure was solved by direct methods using SHELXS97 [11] and refinement was carried out by full-matrix least-squares technique using SHELXL97 [11]. Anisotropic displacement parameters were calculated for all non-hydrogen atoms. H atoms attached to the N atoms were located in a difference fourier map and refined isotropically. Technical details of data acquisition and selected refinement results are listed in Table 1.

Reaction of urea with thiosemicarbazide

A mixture of urea (0.300 g, 5 mmol) and thiosemicarbazide (0.455 g, 5 mmol) was taken in distilled water (~40 ml). The mixture was stirred well for ~15 min to get a clear solution. The reaction mixture was filtered and the clear filtrate was left undisturbed at room temperature. Slow evaporation of the solvent resulted in the separation of transparent crystals after three to four days. The crystals were isolated by filtration, washed with a little ice-cold water and dried in air to yield 0.231 g of crystalline product.

Results and discussion

Synthetic aspects and infrared characterization

The recently reported reaction of urea and thiosemicarbazide has been reinvestigated to unambiguously characterize the crystalline product. The crystalline material obtained from the reaction is referred to as compound **1** and investigated for its infrared and ^{1}H NMR spectral characteristics. The IR spectrum of **1** was compared with that of the starting

materials namely urea and thiosemicarbazide. The comparison revealed that the IR spectrum of **1** is identical to that of pure thiosemicarbazide (Fig. S1). In order to confirm this unambiguously, more batches of crystals of **1** were checked and in all cases the IR spectrum of **1** was always the same as that of thiosemicarbazide indicating that no urea thiosemicarbazone compound (Fig. 1) is formed. This observation can be easily explained due to the fractional crystallization of thiosemicarbazide. Both reactants are water soluble (Table S1) but the less soluble (85 g / L) thiosemicarbazide crystallizes first, with the more soluble urea (824 g / L) remaining in solution. The yield of isolated crystals amounted to ~50% of reagent taken. In view of the isolation of only starting material, no efforts were taken to isolate more product. Since the assignment of bands in the IR spectrum of thiosemicarbazide is well documented in the literature [12] and IR spectroscopy has been used as a characterization tool to infer if a new product is formed, no discussion of the IR spectrum and the assignment of bands is presented.

*NMR spectral characterization of **1***

The residual protons and water present in the deutrated solvents used for recording NMR spectra exhibit characteristic chemical shifts which are listed in standard spectroscopy text books [13]. For DMSO-d_6 these signals appear at δ = 2.49 ppm (residual proton signal) and δ = 3.35 ppm (DMSO water). The authors of the title paper have not taken this aspect into consideration and have assigned the solvent signal for compound and vice versa and hence their NMR assignments are incorrect. The proton NMR spectrum of **1** in DMSO-d_6 (Fig. 2) was not only identical with that of the spectrum of pure thiosemicarbazide but also with that of the reported spectrum for the alleged compound urea thiosemicarbazone monohydrate [9]. More interestingly the spectra recorded by us showed a one to one correspondence in terms of the number, position and integration of the signals with the

reported spectrum clearly indicating that the crystals labeled as compound **1** by us in this work and the crystals reported in the title paper [9] are nothing but thiosemicarbazide. In order to confirm this unambiguously, we have recorded the NMR spectra of crystals of **1** obtained from three different reactions and in all these cases the spectra were identical and exhibited four signals excluding the DMSO solvent and water signal. Analysis of the ^{1}H NMR spectrum of **1** reveals that thiosemicarbazide exhibits thione-thiol tautomerism in solution. The thione and thiol forms of thiosemicarbazide alongwith the assignment of chemical shifts are depicted in Fig. 3. If thiosemicarbazide exists exclusively in the thione form it is expected to show only three signals in the intensity ratio of 1:2:2 in addition to the signals of DMSO and water. For the thiol form four signals in the intensity ratio 1:1:1:2 are expected, all of which are observed in the NMR spectrum (Fig. 1) and also in the NMR spectrum reported in the title paper ruling out the formation of urea thiosemicarbazone hydrate.

In our opinion, ^{13}C NMR could have been a more appropriate technique to confirm the formation of a compound of formula $C_2H_9N_5OS$ containing two non-equivalent C atoms, as such a compound (if at all it exists) is expected to give two distinct ^{13}C resonances, and thus can be distinguished from urea or thiosemicarbazide, which exhibit a single signal in their ^{13}C NMR spectra.

Single crystal X-ray crystallography

The unit cell parameters of the crystals (compound **1**) obtained by us in this work are not only in excellent agreement with those reported in the title paper [9] for the crystal formulated as urea thiosemicarbazone monohydrate but also with that of thiosemicarbazide (Table 2) whose crystal structure was reported by Domiano *et al* [14]. Although, the Domiano cell (column 4 of Table 2) appears different, the cell is still the

same as the one obtained by us in the present work (column 1) as can be evidenced by the parameters of the reduced cell (last column of table 2). It is to be noted that the Domiano cell (column 4) can be transformed to the all-acute 'reduced cell' (column 5) using the transformation matrix $1\bar{}00/001/01\bar{}1\bar{}$. It is interesting to note that for crystal structure determination of thiosemicarbazide, Domiano *et al* [14] used X-ray intensity data, obtained from integrated Weissenberg photographs using the multiple film technique and Ni-filtered Cu-Kα radiation, while a CCD diffractometer and Mo-Kα radiation was used in the present work. The above is only a testimony to the well-known fact that for a given solid crystalline material, the unit cell data are very characteristic.

A compound (urea thiosemicarbazone monohydrate) whose molecular formula ($C_2H_9N_5OS$) differs greatly from that of thiosemicarbazide (CH_5N_3S) can never be expected to have the same unit cell as that of (CH_5N_3S). In view of a higher molecular weight the unit cell volume can be expected to be larger. Hence based on a comparison of the unit cell data of pure thiosemicarbazide [14] with those in the title paper one can easily confirm that the compound under study is thiosemicarbazide and not urea thiosemicarbazone monohydrate. However, the authors of the title paper have assigned the space group as non-centrosymmetric *P1* without either giving reasons for the choice of this space group or giving the Flack parameter [15] for this Sohncke space group. The authors of the title paper did not determine the crystal structure and they proposed the formula of their crystal as a new compound based only on unit cell data (without any esd‘s), which is an unacceptable practice in X-ray crystallography work [16]. It has been observed that such a practice leads to wrong conclusions and many such instances of erroneous reports in the literature in the area of NLO crystals, are given in [16-18].

In order to unambiguously prove that no urea thiosemicarbazone monohydrate is formed on reacting urea with thiosemicarbazide, we have isolated the crystals (compound **1**) from

such a reaction and have determined its single crystal X-ray structure. It can be evidenced from the single crystal structure that thiosemicarbazide exists exclusively as the thione tautomer in the solid state (Fig. 4) and both the tautomeric forms are observed only in solution, which has already been proved by its NMR spectrum recorded in DMSO-d_6. Examples of substituted thiosemicarbazide existing only in thione form in solid state are well documented [19-21]. We have determined the structure from the X-ray intensity data by standard procedures and have verified our cif file by using the IUCr Checkcif services (Checkcif report is given in Supplementray material) and thus have confirmed that our structure model is not only correct but more importantly in agreement with the reported work on thiosemicarbazide [14, 22]. Since the crystal structure [14] and the hydrogen bonding [22] in thiosemicarbazide are well documented in the literature and our present results are in agreement with reported data, no discussion pertaining to crystal structure of **1** is presented and the structure protocol and H-bonding table is provided as Supplementary material.

Other inconsistencies which disfavor urea thiosemicarbazone monohydrate formalism

Having established that no new product is formed in the aqueous reaction of urea with thiosemicarbazide based on IR and NMR spectra and single crystal X-ray data, the other inconsistencies in the title paper can be explained not only to rule out the formation of any new product but to prove that the product of the reaction is the starting material thiosemicarbazide. The melting point of thiosemicarbazide and urea are 180-183 and 132-135 ^{o}C respectively [23, 24]. The endothermic peak at 180 ^{o}C in the reported thermogram incorrectly assigned in the title paper for urea thiosemicarbazone monohydrate, can be now correctly confirmed as the melting point of thiosemicarbazide. The signal at ~130 ^{o}C assigned to a phase transition in the title paper can be reassigned for the melting point of urea and the very weak signal indicates that the amount of urea is very little (almost

traces) compared to that of thiosemicarbazide. A comparison of the X-ray powder pattern of thiosemicarbazide calculated from the single crystal data (theoretical pattern) with that of the pattern in the title paper (Fig. S2) reveals that the solid under study is not urea thiosemicarbazone monohydrate but thiosemicarbazide. We also note that in the reported X-ray powder pattern the reflection due to the (002) plane is shown as a very weak signal and no signal is assigned for the (200) diffracting planes [9]. However, it has been reported in the title paper that a high resolution X-ray diffraction analysis was performed using the (200) plane.

Based on a peak observed at m/z=133 in the mass spectrum, the authors of the title paper claimed that they could confirm the molecular mass of urea thiosemicarbazone monohydrate. However, the molecular mass for the alleged compound is actually 151.19 and hence the mass spectral result is also incorrect. The authors of the title paper claimed that SEM-EDS data was used to quantitatively determine the elements present in their sample. Contrary to this, the elemental % determined by using SEM-EDS was totally in disagreement for the proposed formula of ($C_2H_9N_5OS$). For this compound which has five N atoms in the formula, the % of N (46.32) is expected to be more than that of %C (15.89). The values reported by the authors were C, 42.92% and N, 29.30%. Neither are these values close to that of the actual compound thiosemicarbazide because the authors had coated their sample during sample preparation for SEM with carbon for the study and this carbon also contributed to the signal resulting in a large % C. It is strange to note that SEM-EDS method was used to study % of lighter elements especially carbon instead of elemental (C, H, N and S) analysis which could have easily settled the formula. It is to be noted that even though the %N of the starting materials urea (46.65%), thiosemicarbazide (46.11) and the incorrectly formulated ($C_2H_9N_5OS$) compound (46.32) does not vary much

(Table S1), the % C and S varies considerably, and thus a study of elemental analysis affords one more convenient method of characterizing the exact nature of product formed. Being a centrosymmetric solid, thiosemicarbazide is not expected to show any SHG signal [25]. Hence the claimed SHG signal in the alleged urea thiosemicarbazone monohydrate (which is actually thiosemicarbazide) can be attributed to the presence of impurities of urea which is a non-centrosymmetric solid. The presence of urea as impurity was also revealed by the TG data. It is pertinent to note that previous claims of centrosymmetric compounds showing SHG response have been convincingly proved to be due to the presence of impurities which are actually responsible for the SHG signal [26, 27].

Chemistry of the reaction of urea with thiosemicarbazide

Based on a reported reaction of benzaldehyde with thiosemicarbazide which results in the formation of benzaldehyde thiosemicarbazone monohydrate [28], the authors of the title paper have assumed that urea will react analogously with thiosemicarbazide forming urea thiosemicarbazone also as a monohydrate. The authors were perhaps unaware that an anhydrous benzaldehyde thiosemicarbazone is also reported [29], and did not take into consideration that even though both benzaldehyde and urea contain the >C=O group, both compounds are quite different in terms of their chemistry and reactivity. Urea is an amide (diamide to be more precise) while benzaldehyde is an aldehyde and formation of thiosemicarbazone is a characteristic reaction of aldehyde (or ketone) and not that of an amide [2].

In order to unambiguously identify the exact nature of product of the reaction of urea with thiosemicarbazide, the reported reaction was reinvestigated. We did note that in addition to an extremely unusual reaction scheme in terms of chemistry, the synthetic details reported in the title paper were also unusual with no quantities of reactants or solvent and

no yield of the final product given. The authors had reported under material synthesis *‗single crystals of urea thiosemicarbazone monohydrate were synthesized by mixing an aqueous solution of urea and thiosemicarbazide in the molar ratio 1:1'* giving an impression that the synthesis is a very facile process and the product can be isolated simply by mixing the reagents.

For the reinvestigation we have followed the same protocol of a 1:1 reaction stoichiometry (five millimole scale) in water at room temperature. We have also performed the same reaction at elevated temperatures (100 ^{o}C). Since it is well known that aqueous solutions of urea decompose on heating with evolution of ammonia, for reactions at elevated temperatures, an excess of urea was taken to compensate for urea loss. In addition, we performed the reaction of urea with thiosemicarbazide at room temperature by adding acetic acid and making the medium acidic. In all these different reactions, the only isolable product was thiosemicarbazide, indicating that no chemical reaction takes place and the less soluble of the two reactants namely thiosemicarbazide crystallizes first. The other starting material urea which is almost ten times more soluble than thiosemicarbazide remains in solution. Our results are on expected lines and in accordance with the well-known chemistry of urea which is an amide. We have unambiguously confirmed the formation of thiosemicarbazide as the only product by infrared and NMR spectral studies as described earlier. The authors of the title paper could have also recognised that the product of their reaction is thiosemicarbazide, if only they had analyzed their infrared spectrum carefully as it had the essential features of thiosemicarbazide. However, the spectrum being not of a very good quality, this clue was totally missed.

Conclusions

In this work, the reaction of urea with thiosemicarbazide has been reinvestigated to show how infrared and NMR spectra and single crystal X-ray diffraction can be effectively used for correct product identification. The main findings of this work are as follows:

i) Aqueous reaction of urea with thiosemicarbazide does not result in the formation of any new product, instead results in the fractional crystallization of thiosemicarbazide. ii) A correct interpretation of the ^{1}H NMR spectrum reveals that thiosemicarbazide exhibits thione-thiol tautomerism in solution. iii) The single crystal X-ray structure reveals that thiosemicarbazide exists as the thione tautomer in solid state.

Acknowledgments

The authors thank Miss Savitha Khandolkar and Miss Rita Jyai for helpful discussions. BRS and VSN acknowledge financial support under the Special Assistance Programme [F.540/25/DRS/2007/(SAP-I)] of University Grants Commission, New Delhi. The BRUKER 400 MHz FT-NMR instrument used in this study was procured out of DST-FIST grants sanctioned by the Department of Science & Technology (DST), New Delhi.

Appendix A. Supplementary data

Crystallographic data (excluding structure factors) for the structure of thiosemicarbazide **1** reported herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 918940. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK. (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk). Supplementary data (Table S1, Fig. S1 to S4, Checkcif report, Structure protocol) associated with this article can be found, in the online version, at *****

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Table 1

Crystal data and structure refinement for

Empirical formula	$C_2H_9N_5OS$
Formula weight	91.14
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic $P\bar{1}$
Unit cell dimensions	a = 4.9239(5) Å; α = 77.201(9) ^{o}
	b = 6.0118(6)Å; β = 77.043(9) ^{o}
	c = 7.3175(7)Å; γ = 83.737(8) ^{o}
Volume	205.45(4)Å^3
Z, Calculated density	2, 1.473 mg/m^3
Absorption coefficient	0.589 mm^{-1}
F(000)	96
Crystal size	0.38 x 0.32 x 0.28
θ range for data collection	2.92^o to 26.36^o
Limiting indices	$-6\leq h\leq 4$, $-6\leq k\leq 7$, $-7\leq l\leq 9$
Reflections collected /unique	1302 / 835 [R(int) = 0.0130]
Completeness θ = 25.00^o	100.0 %
Absorption correction	Multi scan
Refinement method	Full- matrix least-squares on F^2
Data / restraints / parameters	835 / 0 /46
Goodness –of-fit on F^2	1.038
Final R indices [I>2σ(I)]	R1 = 0.0331, wR2 = 0.0893
R indices (all data)	R1 = 0.0376, wR2 = 0.0930
Largest diff. peak and hole	0.313 and -0.171 e.A^{-3}

Table 2
Comparison of unit cell data for compound **1**, urea thiosemicarbazone monohydrate and Thiosemicarbazide

Unit cell data	Compound **1**	Urea thiosemicarbazone monohydrate	Thiosemicarbazide	Thiosemicarbazide (Buerger all-acute _reduced cell‘)
Molecular formula	CH_5N_3S	$C_2H_9N_5OS$	CH_5N_3S	CH_5N_3S
a (Å)	4.9239(5)	4.87	4.911(5)	4.91
b (Å)	6.0118(6)	5.95	7.127(7)	6.08
c (Å)	7.3175(7)	7.24	8.340(7)	7.13
α	77.201(9)°	77.41°	45°28′(3′)	77.9°
β	77.043(9)°	77.27°	83°50′(3′)	77.6°
γ	83.737(8)°	83.39°	77°34′(3′)	84.0°
V (Å^3)	205.45(4)	199	202.8	
Space group	*P1*¯	*P1*	*P1*¯	*P1*¯
Reference	This work	[9]	[14]	[14]
Comments	Space group from structure determination	i) No esd‘s reported; ii) Reason for choice of space group not given	i) Space group from structure determination; ii) Transformation matrix to get _reduced cell‘ 1¯00/001/01¯1¯	

Captions for figures:

Fig. 1. Aqueous reaction of urea with thiosemicarbazide

Fig. 2 ^{1}H NMR spectrum of compound **1**. The signals at 3.443 ppm and 2.506 ppm are due to DMSO water and the residual protons of DMSO respectively. For assignment of other signals see Fig. 3.

Fig. 3. The thione and thiol tautomers of thiosemicarbazide showing the assignment of chemical shifts.

Fig. 4. Crystal structure showing the thione form of thiosemicarbazide **1** in the solid state. Thermal ellipsoids are drawn at 50 % probability level excepting for H atoms, which are shown as circles of arbitrary radius.

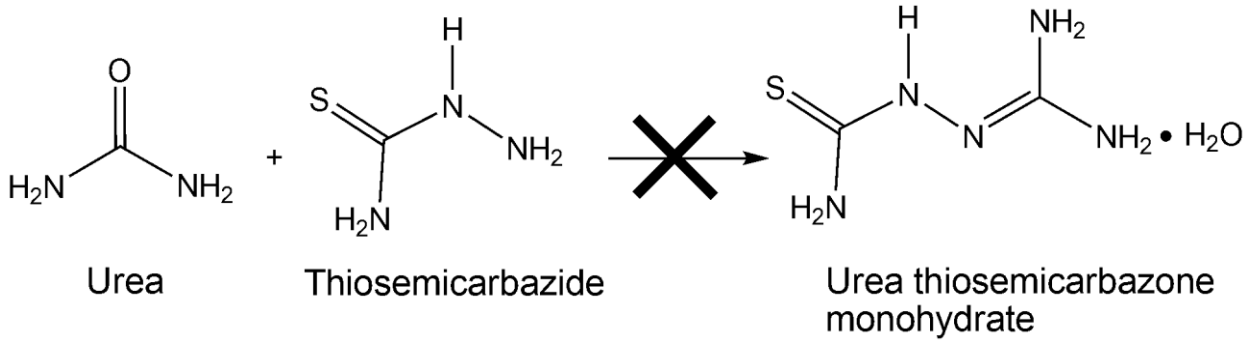

Fig. 1. Aqueous reaction of urea with thiosemicarbazide

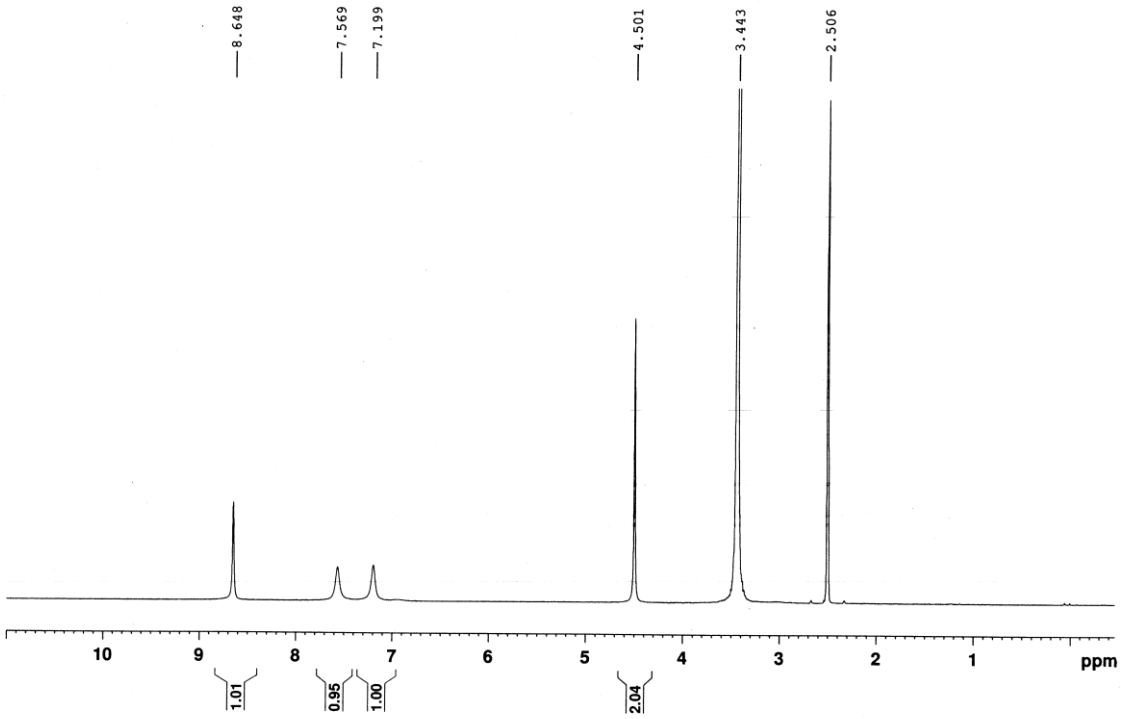

Fig. 2 ^{1}H NMR spectrum of compound **1** in DMSO-d_6 . The signals at 3.443 ppm and 2.506 ppm are due to DMSO water and the residual protons of DMSO-d_6 respectively. For assignment of other signals see Fig. 3.

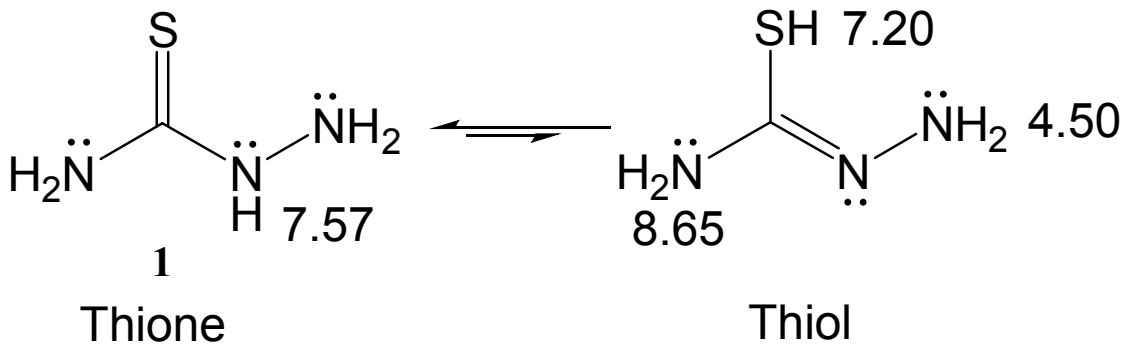

Fig. 3. The thione and thiol tautomers of thiosemicarbazide showing the assignment of chemical shifts.

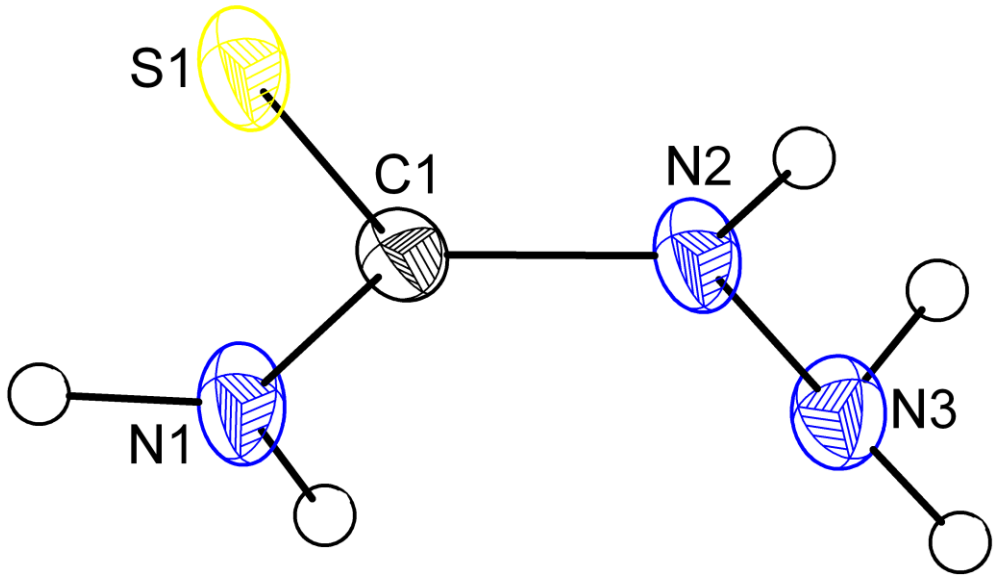

Fig. 4. Crystal structure showing the thione form of thiosemicarbazide **1** in the solid state. Thermal ellipsoids are drawn at 50 % probability level excepting for H atoms, which are shown as circles of arbitrary radius.