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STRUCTURE DETERMINATION AND TAUTOMERIC TRANSITION OF 3-AMINO-1{[BIS(BENZYLSULFANYL)METHYLIDENE]AMINO}UREA

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The single crystal X-ray analysis of 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea shows that the compound crystallizes in the triclinic system with the space group *P*-1 and *Z* = 4. The asymmetric unit contains two independent molecules of 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea. Both bis(benzylsulfanyl)methylidene groups are in a *trans* configuration with respect to the C16/O1/N3/N4 and C32/O2/N7/N8 fragments, respectively. The tautomeric transition energies of the three tautomeric forms are calculated at the generalized gradient approximation (GGA) level by the BLYP/DND method to estimate the kinetic and thermodynamic barriers. The keto form has a lower energy than the other two forms. Relatively lower values of kinetic barriers (about 58 kcal/mol for the transition between (a) and (b) forms) are found.

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K e y w o r d s: carbohydrazide, urea derivatives, sulfur based molecule, hydrogen interaction, tautomeric transition.

Urea and its substituted derivatives are of interest to researchers due to their potential biological activities [1, 2]. On the contrary, sulfur-based compounds, e.g. dithiocarbazates, dithiocarbamates and thioureas, are well known to possess various biological properties [3, 4]. It would be an added advantage to combine these two classes of molecules to give interesting molecular structures and the potential biological properties. Our main focus was to synthesize the titled compound with good yield.

Materials and methods. Carbon disulphide (6.04 ml, 0.1 mol) was added dropwise to a 90 % ethanolic solution of carbohydrazide (9.01 g, 0.1 mol) and potassium hydroxide (5.61 g, 0.1 mol) at a temperature below 5 °C. Upon completion of the addition of carbon disulphide, benzyl chloride (11.51 ml, 0.1 mol) was added to the solution with vigorous stirring to give a white precipitate. The precipitate formed was filtered, washed with cold ethanol and dried under silica gel and recrystallized in ethanol. Crystals were obtained by slow evaporation from ethanol. Yield: 65 %, m.p. 93.7—95.1 °C. Anal. Calc. for $C_{16}H_{18}N_4OS_2$: C 55.5, H 5.2, N 16.2; found C 55.0, H 5.8, N 16.7.

Physical and spectroscopic measurements. The melting point was determined in an open capillary using a Melting Point Apparatus SMP3 (Stuart Scientific). The IR spectrum was recorded in the range 400—4000 cm^{-1} with a KBr pellet on a Perkin Elmer (Spectrum GX) infrared spectrophotometer.

Crystal structure determination and refinement. A single crystal of the titled compound was selected and mounted on a glass fiber using perfluoropolyether oil and cooled rapidly to 100 K in a stream of cold N_2. Diffraction data were measured using a Bruker Kappa APEXII diffractometer with

Table 1

Selected bond lengths (Å), *bond angles* (deg.), *and the hydrogen bond geometry for* 3-*amino*-1[(*bis-benzylsulfanylmethylidene*)*amino*]*urea*

Selected bond length				Selected bond angle			
S1—C1	1.757(4)	N1—C1	1.276(5)	C1—S1—C2	100.84(19)	S1—C1—S2	113.8(2)
S1—C2	1.818(4)	N1—N2	1.375(4)	C1—S2—C9	98.80(19)	C3—C2—S1	108.1(3)
S2—C1	1.778(4)	N2—C16	1.386(5)	C17—S4—C18	102.89(19)	O1—C16—N3	123.8(4)
S2—C9	1.825(4)	N3—C16	1.346(5)	C17—S3—C25	103.38(18)	O1—C16—N2	120.8(4)
S4—C17	1.779(4)	N3—N4	1.432(5)	C1—N1—N2	118.1(3)	N3—C16—N2	115.4(4)
S4—C18	1.833(4)	N5—C17	1.271(5)	N1—N2—C16	118.4(3)	N5—C17—S3	121.5(3)
S3—C17	1.751(4)	N5—N6	1.384(4)	C16—N3—N4	119.7(4)	N5—C17—S4	129.1(3)
S3—C25	1.820(4)	N6—C32	1.369(5)	C17—N5—N6	118.3(3)	S3—C17—S4	109.3(2)
O1—C16	1.227(4)	N7—C32	1.355(5)	C32—N6—N5	118.3(3)	O2—C32—N7	123.3(4)
O2—C32	1.233(4)	N7—N8	1.423(5)	C32—N7—N8	120.5(3)	O2—C32—N6	120.5(4)
				N1—C1—S1	119.7(3)	N7—C32—N6	116.2(4)
				N1—C1—S2	126.5(3)		

Hydrogen bond geometry				
D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (deg.)
N2—H1···N8	0.91(4)	2.27(5)	3.107(5)	152(4)
N4—H3···O1	0.93(6)	2.11(6)	3.033(5)	173(5)
N7—H6···O1	0.88(4)	2.26(4)	3.021(4)	145(4)
N3—H2···O2	0.84(5)	2.17(6)	2.940(5)	152(5)
N6—H5···N4	0.89(4)	2.26(5)	3.069(5)	152(4)
N8—H8···S4	0.96(6)	2.83(7)	3.773(5)	168(5)

monochromatic MoK_α radiation, $\lambda = 0.71073$ Å. Data reduction were performed using SAINT [5]; the structure was solved using SHELX S97 [6], and the refinement was carried out using the SHELXL-97 program(s) [6]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. All the hydrogen atoms were located from difference Fourier maps, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93—0.98, N—H in the range 0.86—0.89 and U_{iso}(H) (in the range 1.2—1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints. CIF file containing complete information on the studied structure was deposited with CCDC, deposition number 902682, and is freely available upon request from the following web site: www.ccdc.cam.ac.uk/data_request/cif. Crystallographic data, experimental details, and refinement results: $C_{16}H_{18}N_4OS_2$, $M_r = 346.46$, monoclinic, space group P-1, $a =$ $= 9.8441(15)$, $b = 12.1825(19)$, $c = 14.646(2)$ Å, $\alpha = 74.149(3)$, $\beta = 88.803(3)$, $\gamma = 88.071(3)°$, $V =$ $= 1688.6(5)$ Å^3, $Z = 4$, $D_x = 1.363$ mg/m^{-3}, $\mu = 0.325$ mm^{-1}, colorless crystal, block, size 0.04×0.04× ×0.03 mm, 16370 reflections measured, 7705 independent ($R_{int} = 0.0935$), 4121 observed ($I > 2.0\sigma(I)$), $\theta_{max} = 27.5°$, index ranges $-12 \le h \le 11$, $-15 \le k \le 15$, $-19 \le l \le 19$, 447 parameters, $R = 0.0609$, $wR =$ $= 0.1248$, $\Delta\rho_{min}$ / $\Delta\rho_{max} = 0.001$ / 0.034 e/Å^3. Selected bond lengths, bond angles, and the hydrogen bond geometry are given in Table 1.

Tautomeric transition study. The initial X-ray structure of 3-amino-1-[(bis-benzylsulfanylmethylidene)amino]urea was in the keto form (*trans* form) as in Fig. 2, *a*. The other two amide forms as in Fig. 2, *b* and *c* were modeled from the X-ray structure of the *trans* form. All the three forms were further optimized using density functional theory with the B3LYP basis set. Then transition path calculations of each tautomeric form were carried out with linear synchronous transit (LST) under Dmol3 module in Material Studio 4.3 for the structure optimization and path calculations [7, 8]. All calculations were performed at the Generalized Gradient Approximation (GGA) level, with the BLYP/DND

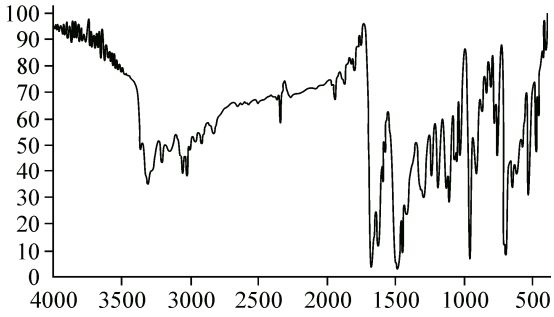

Fig. 1. IR spectrum of 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea

method to estimate the kinetic and thermodynamic barriers. The size of the DND basis is comparable to Gaussian 6-31G* basis sets.

Results and discussion. Spectroscopic IR analyses (IR spectrum in Fig. 1) showed the presence of a band at 703 cm^{-1} assignable to υ(C—S) in 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea. It was observed that the υ(C=O) mode at 1639 cm^{-1} in carbohydrazide was shifted to a higher wave number (1685 cm^{-1}) in the titled compound. The same shifting pattern was also observed for the υ(N—H) mode, which was found at 3214 cm^{-1} as compared to the IR spectrum of carbohydrazide (3201 cm^{-1}). These shifts of the wavenumbers clearly indicate that 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea exists as a keto-amide tautomer with the nitrogen atom coordinated to the bis(benzylsulfanyl)methylene group as shown in Fig. 2, *a*.

The crystal structure of 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea shows that there are two independent molecules in the asymmetric unit, as shown in Fig. 3. The amide group in both asymmetric molecules are slightly twisted through the S_2C=N atoms with the —CNNC— torsion angles of 169.5(4)° and 174.5(5)°, respectively. The dihedral angles between the phenyl rings are 48.4(7)° and 49.5(1)°, respectively for the asymmetric molecules. It is found that the torsion angle along —CNNC— and the dihedral angles between the two planar bis(benzylsulfanyl)methylidene fragments is affected by different species of the substituent group attached along the S_2C=N atoms. The substituent groups would restrict the rotation and orientation that affect two planar bis(benzylsulfanyl)methylidene fragments.

The substituent group of isoniazid has a small —CNNC— torsion angle with large dihedral angles between the two planar bis(benzylsulfanyl)methylidene fragments (139.71(13)° and 76.42(9)°) [9], whereas the substituent group of 4-methoxybenzohydrazide gave a larger torsion angle with smaller dihedral angles between two planar bis(benzylsulfanyl)methylidene fragments (154.32(10)° and 57.5(2)°) [10].

The carbonyl C16—O1 and C32—O2 bonds are comparable to the literature values and show that they are of a double bond character [11]. The azomethine C1—N1 (1.276(5) Å) and C17—N5 (1.271(5) Å) bonds lying between typical C≡N and C=N show that there is extensive delocalization of the π electron density over the C1/N1/N2/C16 and C17/N5/N6/C32 linkages. This was further supported since both C16—N2 (1.386(5) Å) and C32—N6 (1.369(5) Å) were in between the typical C—N and C=N bonds [11].

In the crystal structure, the molecules are linked by several types of N—H···N, N—H···O, and N—H···S hydrogen bonds via all the N-donor atoms (except N1 and N5) with the carbonyl O acceptor and the thio S4 acceptor. There are hydrogen bonds across a centre of inversion, connecting the car-

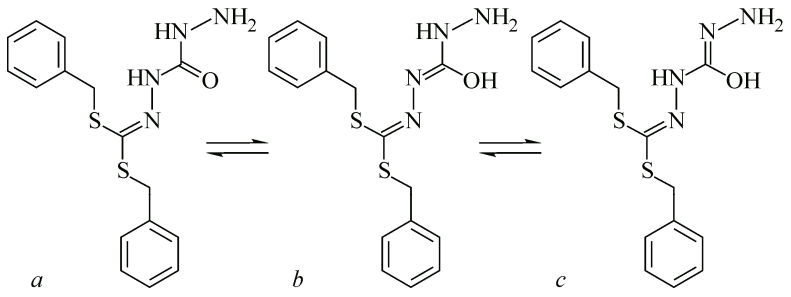

Fig. 2. Tautomeric forms of 3-amino-1-[(bis-benzylsulfanylmethylidene)amino]urea

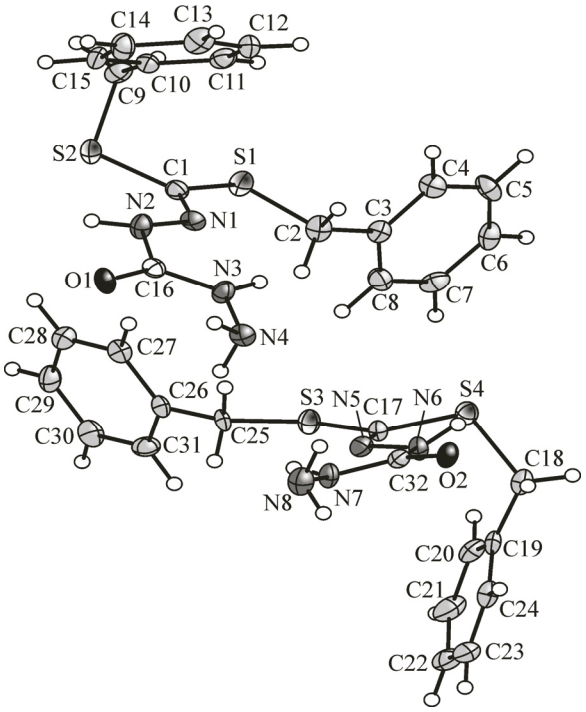

Fig. 3. Thermal ellipsoids drawn at a 50 % probability level of 3-amino-1[(bis-benzylsulfanylmethylidene)amino]urea. H atoms are shown as spheres of an arbitrary radius

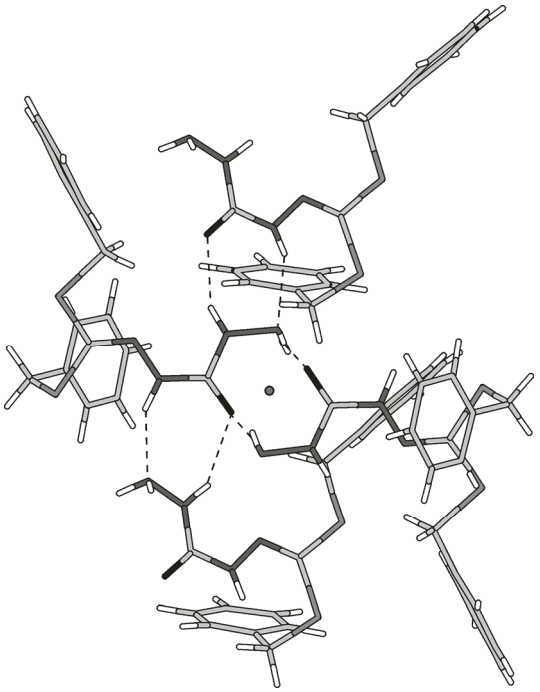

Fig. 4. Hydrogen bond environment in the structure

bonyl group from the first molecule to the primary amine of the second molecule and vice versa, as shown in Fig. 4. There are also hydrogen bonds formed between the same carbonyl group with its neighboring secondary amine connected to a primary and secondary amine of the second molecule respectively, as shown in Fig. 4. Both types of hydrogen bonds gave an $R_2^2(10)$ hydrogen bonding motif.

Following the tautomeric transitions in the 3D structure in Fig. 5 and the optimization, the energy path for the tautomeric transitions in transferring hydrogen between the keto and enol forms were shown in detail in Fig. 6. Two tautomeric forms differ from each other by the rearrangement positions of a hydrogen atom and a π bond. In most cases, the keto form is a more stable tautomer, which was determined by the relative stability, thus existing as the highest concentration as evidenced from the X-ray crystal structure. The equilibrium between the tautomers is usually rapid and often favors to wards one of the isomers. From our calculation for the tautomeric transition under investigation, the potential energy along the transition coordinate was plotted in accordance with the lowest energy structure (*a*) as obtained from single crystal X-ray structure. The amide forms (enol forms) have a

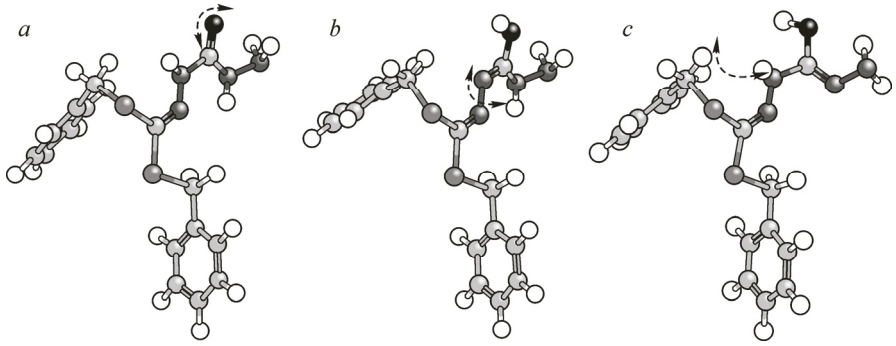

Fig. 5. 3D structure of the tautomeric form of 3-amino-1-[(bis-benzylsulfanylmethylidene)amino]urea

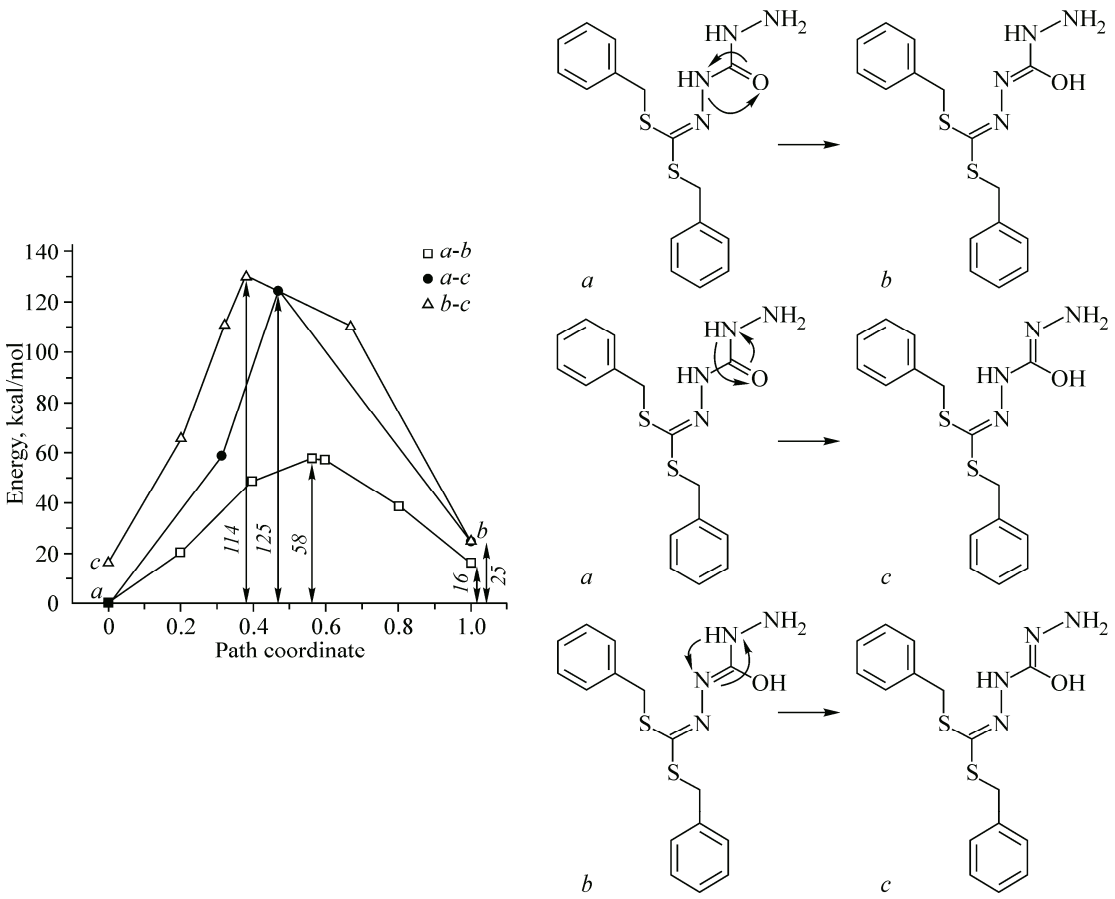

Fig. 6. Tautomeric transitions of three tautomeric forms (*a*), (*b*), and (*c*). The relative energy differences are labeled

higher energy of about 16 kcal/mol and 25 kcal/mol in (*b*) and (*c*) forms as labeled in Fig. 6 respectively in comparison to the keto form (*a*). Relatively lower values of kinetic barriers of about 58 kcal/mol for the transition between (*a*) and (*b*) forms were found. On the other hand, relatively higher values of the kinetic barriers of 114 kcal/mol and 125 kcal/mol were observed for the (*b*)—(*c*) and (*a*)—(*c*) tautomeric transitions respectively.

The titled compound 3-amino-1{[bis(benzylsulfanyl)methylidene]amino}urea crystallized in the keto amide tautomer, which was the most stable tautomeric form as was shown by different energy barriers existing in the other tautomeric forms.

CCDC 902682 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: Facsimile: (44) 01223 336033.

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