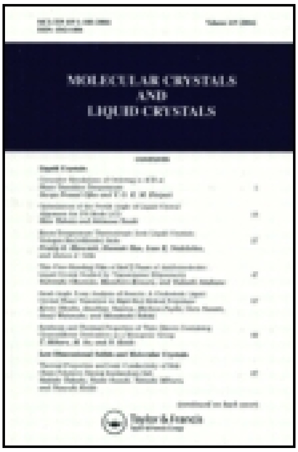

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Crystal Structure and Conformation Study of 4-N,N-Dimethylamine Benzaldehyde Thiosemicarbazone Derivative

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Crystal Structure and Conformation Study of 4-N,N-Dimethylamine Benzaldehyde Thiosemicarbazone Derivative

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Thiosemicarbazones are N-N-S donor ligands having the ability to bind metal ions and inhibit ribonucleoside reductase, an enzyme important for DNA synthesis of all the mammalian cells. One of the important phenyl thiosemicarbazones, the title compound, has been synthesized and its stereo projection was analyzed by crystallographic methods. The X-ray data of DABT are $C_{10}H_{14}N_4S$; *M.W* = *222.31, monoclinic, space group* $P2_1/n$, $a = 5.677(7)$ Å, $b = 8.951(2)$ Å, $c = 22.773(4)$ Å, $\beta = 93.51(5)°$; $V = 1155.1(1)$ Å^3, $Z = 4$, $D_{cal} = 1.278$ Mg/m^3, λ (Cu K_α) = 1.54184 Å, *final* R_1 *and* wR_2 *are 0.0563 and 0.1407, respectively. The molecular packing can be viewed as a dimer held together by two N-H···S type intermolecular hydrogen bonds. In addition to van der Waals forces, C-H···N, N-H···S, C-H···S, and N-H···N types of inter- and intramolecular hydrogen bonds facilitate the molecules in crystal packing.*

Keywords Conformation; heterocyclic; hydrogen bond; space group; thiosemicarbazone

Introduction

The relationship between the metal ions and cancer are interesting and controversial. French and Freedlander [1] suggested that some antitumor agents possess the ability to function as chelating agents. So, French and Blanz [2] prepared many thiosemicarbazone (TSC) derivatives and found that all the tumor inhibitors potentially act as N-N-S type donor ligands. The biological activities of TSC*s* depend on the parent aldehydes or ketones [3]. Pyridine-2-carbaldehyde thiosemicarbazone was the first heterocyclic compound (HFoTsc) reported to have carcinostatic properties [4]. The mechanism of action of HFoTsc is due to its ability to inhibit the biosynthesis of DNA, possibly by blocking the enzyme ribonucleoside reductase (RNR) or blocking base replication; creation of lesions in DNA strands by oxidative rupture [4,5].

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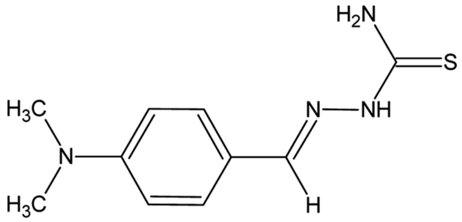


Scheme 1. Chemical diagram of **DABT** molecule.

Thiosemicarbazone is a versatile tridentant ligand, which combines with aldehydes or ketones to generate the TSC derivatives. These types of derivatives have a wide range of biological activities such as antitumor [6], antimalarial [7], antileukemic [8], antiviral [9], antibacterial [10], and antifertility [11] properties because of their reduction capabilities. The TSC moiety is planar and adopts an extended (E) conformation due to the extensive π-electron delocalization throughout the moiety. In general, the N, S donor ligands of TSCs are attributed to their ability to form metal chelates [12] and non linear optical properties [13] due to their reductive capacities [14].

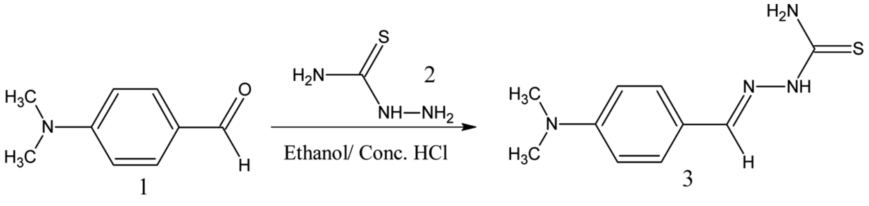
The electrons are smearing on the sulfur and hydrazinic N atoms due to electron delocalization, which helps in complexation with positively charged metal ions. Both these S and N atoms chelate to metal ions of the biological molecule and are believed to possess the pharmaceutical activity of this molecule. In addition to the biological properties, the TSCs possess second-order nonlinear optical (NLO) properties, which have broad applications in opto-electronics, such as optical frequency conversion [15,16] and optical parameter oscillator (OPO).

As a part of the ongoing study on thiosemicarbazone derivatives, four different *para-* substituted phenyl thiosemicarbazone derivatives have been synthesized and their antimicrobial activity has been tested against 10 different bacterial species and 2 *Candida* fungi (unpublished results). Among these, the compound 4-N,N-dimethylaminebenzaldehyde thiosemicarbazone **(DABT)** reduces the bacterial and fungal growth significantly. In order to analyze the stereochemistry and molecular geometry of DABT, it was synthesized and characterized by X-ray crystallography method. The chemical diagram of compound DABT is shown in Scheme 1.

Experiments

Synthesis of Phenyl Thiosemicarbazones

The respective benzaldehyde (1) (0.1 M) was taken in the medium of 100% ethanol along with a little higher quantity (0.12 M) of thiosemicarbazide (2) in the presence of a few drops of conc. HCl. This reaction mixture was allowed to react on a water bath for 4 h and the respective thiosemicarbazone (3) derivative was separated out as colorless solids and dried. The dried samples were crystallized using suitable organic solvents.



X-Ray Data Collection and Reduction

A single crystal of **DABT** was mounted on a glass fiber and used for data collection. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 reflections in an ENRAF–NONIUS CAD4 automatic diffractometer [17]. Data were collected at 293(2) K using Cu*Ka* radiation ($\lambda = 1.54184$ Å) (University of Madras, Chennai, India) and the data reduction was carried out by XCAD4 [18] program. Out of 3614 reflections collected, 3304 reflections with $I \geq 2\sigma(I)$ were used for structure solution and refinement. The intensity data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods using the program *SHELXS97* [19], which revealed the position of all non-hydrogen atoms, and refined on F^2 by a full-matrix least squares procedure using *SHELXL97* [19]. The non-hydrogen atoms were refined anisotropically and the positions of hydrogen atoms were derived from the difference Fourier map. The final cycle of refinement converged to $R_1 = 0.0563$ and $wR_2 = 0.1407$ for the observed reflections. The maximum and minimum heights in the final difference Fourier map were found to be 0.440 and −0.261 $e \cdot Å^{-3}$, respectively. Least-squares planes and asymmetry calculations were done using the program *PARST97* [20]. The thermal ellipsoid plot and packing were done respectively using *ORTEP* [21] and *PLATON* [22]. Non-bonded interaction graphics were created using the program *PLATON* [22]. The crystallographic data and methods of data collection, solution, and refinement are shown in Table 1 and the atomic coordinates of the non-hydrogen atoms with their equivalent thermal displacement parameters are presented in Table 2. All other information about **DABT** structure is included in the deposited material (**CCDC 744645**).

Result and Discussion

The synthesized phenyl thiosemicarbazone derivatives, namely DABT crystallized in monoclinic space group $P2_1/n$. The perspective view of DABT ORTEP diagram is shown in Fig. 1. The S atom and the hydrazinic N8 atom are *trans* with respect to C10-N9 bond. A similar type of *trans* configuration is noted in many structures of thiosemicarbazide [23], *N*-methyl-2,6-diphenyl-3-isopropyl piperidin-4-one thiosemicarbazone [24] and 3,4,5-trimethoxy benzaldehyde thiosemicarbazone monohydrate [25]. The torsion angles and mean plane calculations confirm that the whole TSC moiety adopts an extended conformation and almost lies in the same plane of the benzene ring. The corresponding torsion angles of TSC are as follows:

Conformational bonds	Angle (°) DABT
C7-N8-N9-C10	175.8 (2)
N8-N9-C10-N11	5.7 (3)
N8-N9-C10-S1	174.1 (1)

The bond length variation in C4-C7 of molecule DABT [1.441(3)Å] indicates the influence of conjugation between the phenyl ring and C7-N8 [1.277(2)Å for DABT]

Table 1. Crystal data and other relevant details for **DABT**

Parameters	DABT
CCDC	**CCDC 744645**
Empirical formula	$C_{10}H_{14}N_4S$
Formula weight	222.31
Temperature	293(2) K
Wavelength	0.71073 Å (Mo K_α)
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	
	$a = 5.677(7)$Å
	$b = 8.951(2)$Å
	$c = 22.773(4)$Å
	$\beta = 93.51(5)°$
Volume $Å^3$	1155.1(1)
Z, Calculated density	4, 1.278 Mg/m^3
Absorption coefficient	0.254 mm^{-1}
F(000)	472
Theta range for data collection	1.79 to 30.00°
Limiting indices	$0 \le h \le 7$
	$0 \le k \le 12$
	$-31 \le l \le 31$
Reflections collected/unique	3614/3304 [$R_{int} = 0.021$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3304/0/192
Goodness-of-fit on F^2	1.095
Final R-indices [$I > 2\sigma(I)$]	$R_1 = 0.0563$, $wR_2 = 0.1407$
R-indices (all data)	$R_1 = 0.0887$, $wR_2 = 0.1618$
Largest diff. peak and hole	0.440 and $-0.261\ e \cdot Å^{-3}$

imine double bonds. A similar effect is also noted in some other structures, 2,3-dihydroxybenzaldehyde thiosemicarbazone [26] and salicylaldehyde-4,4′-(hexane-1,6-diyl) thiosemicarbazone [27]. The bond lengths (Fig. 2a) in the thiosemicarbazone moiety show electron delocalization effect (Scheme 2) and this is extended even up to the imine nitrogen group. The TSC moiety and phenyl ring almost lie in the same plane, which is confirmed by the orientation angle of 15.5(1)°.

The bond angle of C2-C1-C6 [117.0(2)°] in DABT is comparatively much shorter than other reported structures having bond angle ranges from 120 to 121° [26,27]. This may be due to the effect of H···H short contacts between the atoms H14B···H6 = 2.02(4)Å and H2···H13B = 2.22(3)Å. These short contacts create electron–electron repulsion between the hydrogens, pushing the atoms C2 and C6 in opposite directions. The bond lengths of C1-C2, C1-C6, C3-C4, and C4-C5 in DABT molecule are 1.419(3), 1.399(3), 1.395(3), and 1.393(2)Å, respectively. These lengths are considerably higher than the normal value of 1.37 Å. These bond length variations are attributed to the resonance character of the dimethyl amine, phenyl ring and also that of imine nitrogen (Scheme 3).

In DABT, the whole molecule lies almost in the same plane. This happens due to the presence of hetero π-electron delocalization in the entire molecule (Scheme 3).

Table 2. Atomic coordinates ($\times 10^4$) and their equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for the non-hydrogen atoms of **DABT**

Atoms	x	y	z	$^*U_{eq}$
S1	7026(1)	3445(1)	574(1)	70(1)
C1	−2779(3)	3653(2)	3518(1)	50(1)
C2	−2787(3)	4491(2)	2989(1)	54(1)
C3	−1175(3)	4225(2)	2581(1)	51(1)
C4	557(3)	3130(2)	2669(1)	48(1)
C5	558(4)	2301(2)	3187(1)	57(1)
C6	−1059(4)	2541(2)	3599(1)	58(1)
C7	2381(4)	2861(2)	2269(1)	52(1)
N8	2455(3)	3534(2)	1776(1)	50(1)
N9	4365(3)	3189(2)	1459(1)	55(1)
C10	4559(3)	3751(2)	921(1)	48(1)
N11	2765(3)	4532(2)	690(1)	58(1)
N12	−4373(3)	3909(2)	3925(1)	63(1)
C13	−6017(4)	5142(3)	3859(1)	67(1)
C14	−4166(7)	3147(4)	4483(1)	90(1)

$^*U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a_i} \cdot \mathbf{a_j}$.

The corresponding torsion angles [C2-C1-N12-C13=] − 5.6(3)°, [C6-C1-N12-C13=] 174.8(2)°, [C2-C1-N12-C14=] − 173.6(2)°, and [C6-C1-N12-C14=] 6.9(3)° support this fact. The sum of the bond angles around the atom N12 is 358.7°, thus confirming that the atom N12 is in sp^2 hybridized state. The N,N-dimethyl group is oriented at an angle of 10.4(2)° to the phenyl ring. This deviation in planarity is attributed by the short contacts between the H13B $\cdots$ H2 and H14B $\cdots$ H6.

Packing Features

The packing molecule of DABT viewed down the *b*-axis is shown in Fig. 3. The molecules are stabilized by N-H $\cdots$ N, N-H $\cdots$ S, C-H $\cdots$ S, and C-H $\cdots$ N types of

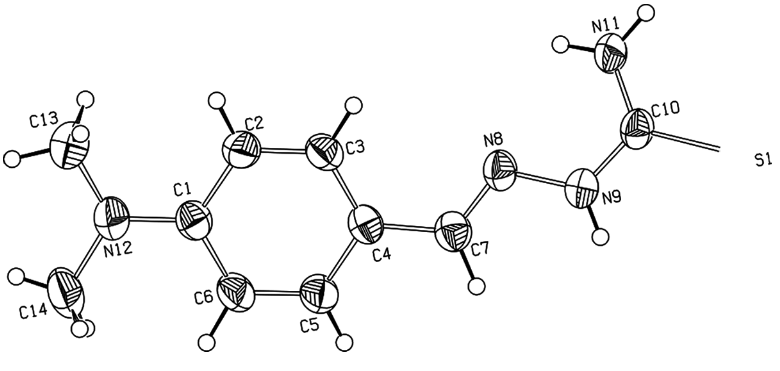


Figure 1. ORTEP diagram of the molecule **DABT** showing the thermal ellipsoids at 30% probability level.

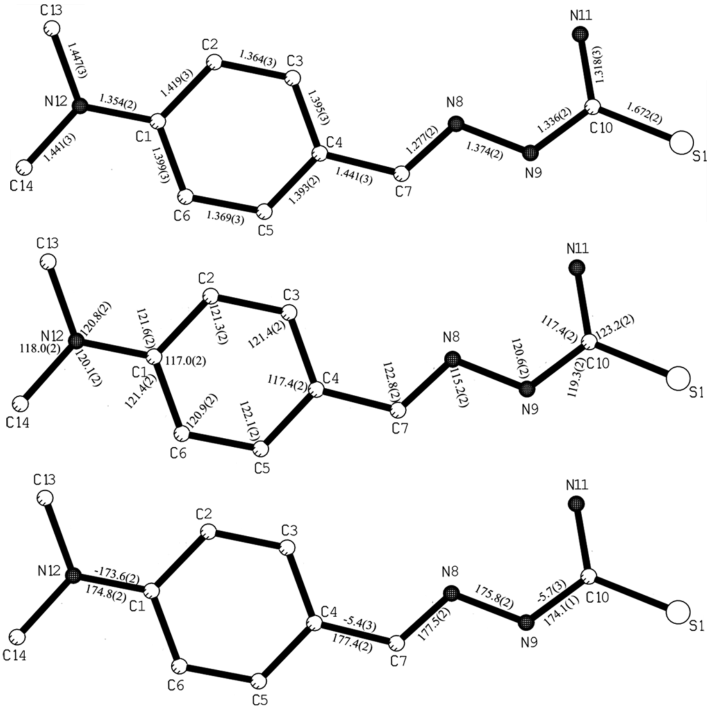
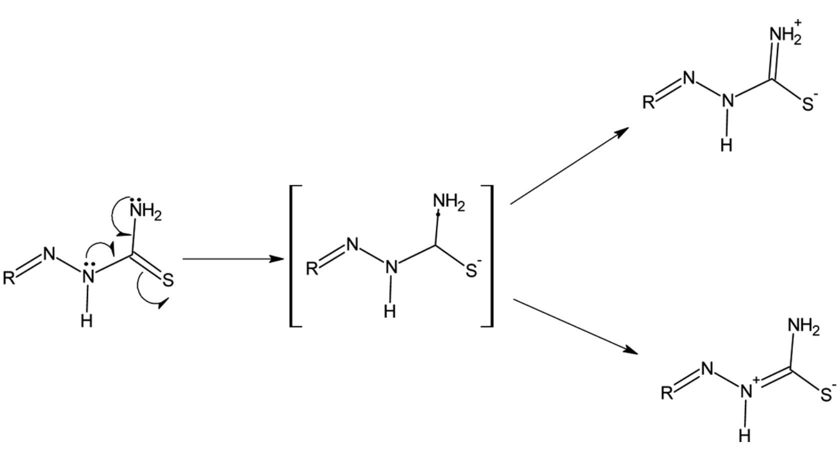
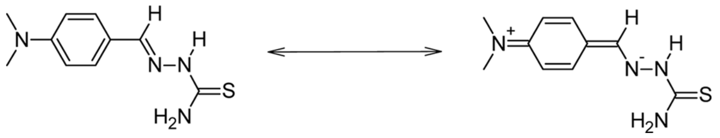


Figure 2. Geometrical diagram of the molecules of **DABT** (a) Bond lengths (Å); (b) bond angles (°); (c) selected torsion angles (°). Hydrogen atoms are removed for clarity.

intra- and intermolecular hydrogen bonds (Table 3). The N-H···N type intra molecular hydrogen bond forms a five-membered ring and this facilitates TSC moiety to form an extended conformation [28,29]. A pair of N11-H11···S hydrogen bonds across the centers of inversion result in a dimer between the symmetry related molecules of DABT. Such dimerization has also been observed in similar structures



Scheme 2. Resonance structures of thiosemicarbazone (TSC) moiety.



Scheme 3. Resonance character of the DABT structure.

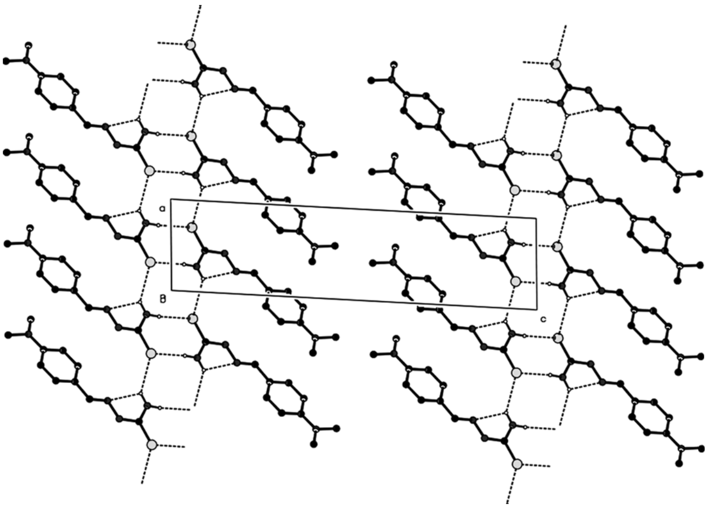


Figure 3. Packing of the molecules **DABT** viewed down the b-axis. Dashed lines represent hydrogen bonds.

Table 3. Hydrogen bondings and the possible non-bonded interactions for **DABT (°, Å)**

D-H···A	d(D-H)	d(D···A)	d(H···A)	<D-H···A
N11-H11A···N8	0.87(3)	2.645(2)	2.30(3)	105.9(2)
C5-H5···N8^{i}	0.94(2)	3.555(3)	2.72(2)	151.5(1)
C13-H13A···S1^{ii}	0.95(3)	3.896(3)	3.00(3)	160.2(3)
N11-H11A···S1^{iii}	0.87(3)	3.395(4)	2.75(3)	135.0(5)
N11-H11B···S1^{iv}	0.90(2)	3.409(2)	2.52(2)	174.6(1)
C13-H13B···Cg^{iii}	0.950	3.644	2.960	130.6

Equivalent positions:
i. $-x+1/2,\ y-1/2,\ -z+1/2$
ii. $-x+1/2,\ y+1/2,\ -z+1/2$
iii. $x-1,\ y,\ z$
iv. $-x+1,\ -y+1,\ -z$
Cg is the centroid of the benzene ring [Cg = C1 through C6].

like piperidine thiosemicarbazone derivatives [29] and it is found to be a common feature of these moieties. This dimer interaction extends along the *a*-axis and makes a catenation to help the crystal pack tightly. In addition to van der Waals forces, another weak C-H $\cdots \pi$ [Cg = C1 through C6] interaction [30] helps the molecules for crystal packing.

Supplementary Material

Crystallographic data (excluding structure factors) for the structure reported in this article have been deposited with the Cambridge Crystallographic Database Centre as supplementary publication no. **CCDC 744645**. Copies of available material can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223336033; e-mail: deposit@ccdc.cam.ac.uk).

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