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ORIGINAL PAPER

Crystal Structure and Conformation Study of 4-Chlorobenzaldehyde Thiosemicarbazone Derivative

N. Sampath · Rita Mathews · M. N. Ponnuswamy

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Abstract Thiosemicarbazones (TSCs) are very versatile tridentate ligands having the ability to bind transition metal ions by bonding through sulfur and hydrazinic terminal nitrogen atoms. TSC also inhibits ribonucleotide diphosphate reductase (RDR), the enzyme involved in the synthesis of DNA precursors in the mammalian cells. One of the important phenyl thiosemicarbazones, the title compound (*p*-CBT) has been synthesized and it was characterized by X-ray diffraction methods. The crystallographic data of *p*-CBT are: $C_8H_8ClN_3S$; M.W. = 213.68, Triclinic, space group, $P\bar{1}$, with cell parameters $a = 7.934(2)$ Å, $b = 11.242(3)$ Å, $c = 11.615(2)$ Å, $\alpha = 74.775(3)$, $\beta = 75.389(2)$, $\gamma = 83.448(2)$; $V = 966.0(4)$ Å^3, $Z = 4$, Dcal = 1.469 Mg/m^3, λ (Cu K_α) = 1.54184 Å. Molecular packing can be viewed as a dimer held together by two N–H…S type intermolecular hydrogen bonds. In addition, C–H…Cl and N–H…N types of inter and intra molecular hydrogen bonds also help the molecules in crystal packing.

Keywords Thiosemicarbazone · Heterocyclic · Conformation · Hydrogen bond · Space group

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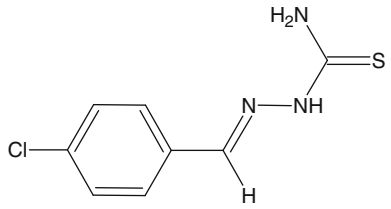
Introduction

Thiosemicarbazide is a tridentate ligand, which combines with aldehydes or ketones to generate the thiosemicarbazone (TSC) derivatives. These derivatives have a wide range of biological activities such as antitumour [1], antimalarial [2], antileukemic properties [3], antiviral activity [4], antibacterial [5] and antifertility property [6] because of their reduction capability. 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 thiosemicarbazones are attributed to their ability to form metal chelates [7], nonlinear optical properties [8] and reductive capacities [9].

The entire electron charges are smearing on the sulfur and hydrazinic N atoms due to electron delocalization which helps in complexation with positively charged metal ions. Both S and N atoms chelate the metal ions of the biological molecule and believed to be responsible for the pharmaceutical activity. In addition, TSCs also possess second-order nonlinear optical (NLO) properties which have broad applications in opto-electronics, such as optical frequency conversion [10, 11] and optical parameter oscillator (OPO).

The relationship between the metal ions and cancer are intriguing and controversial. French and Freedlander [12] suggested that some antitumour agents also possess the ability to function as chelating agents. French and Blanz [1] prepared many TSC derivatives and found that all tumor inhibitors potentially act as N–N–S type ligands. The biological activities of TSCs depend on the parent aldehydes or ketones [13]. Pyridine-2-carbaldehyde thiosemicarbazone was the first heterocyclic compound (HFoTsc) reported to have carcinostatic properties [14]. The mechanism of action of HFoTsc is due to its ability to inhibit the



Scheme 1 Chemical diagram of *p*-CBT

biosynthesis of DNA, possibly by blocking the enzyme ribonucleotide reductase (RNR) or blocking the base replication; creation of lesions in DNA strands by oxidative rupture [14, 15].

As part of the ongoing study on thiosemicarbazone derivatives, different *para* substituted phenyl thiosemicarbazone derivatives have been synthesized and their antimicrobial activity against 10 different bacterial species and 2 *Candida* fungi (unpublished result) were tested. One of the molecules, 4-chlorobenzaldehyde thiosemicarbazone (*p*-CBT) is found to have better activity against these bacteria and fungi compared to other compounds. So the title compound *p*-CBT was synthesized and its structural study has been done by X-ray crystallography method to establish the molecular geometry and stereochemistry. The chemical diagram of compound is shown in Scheme 1.

Experimental

Synthesis of Phenyl Thiosemicarbazones

The respective benzaldehydes (0.1 M) were taken in the medium of 100% pure ethanol with little more amounts (0.12 M) of thiosemicarbazide in presence of conc. HCl. This reaction mixture was allowed to react in a water bath for 4 h and the respective thiosemicarbazone derivative was separated out as colorless solids and dried. The dried sample was crystallized using acetonitrile as solvent.

X-Ray Data Collection and Reduction

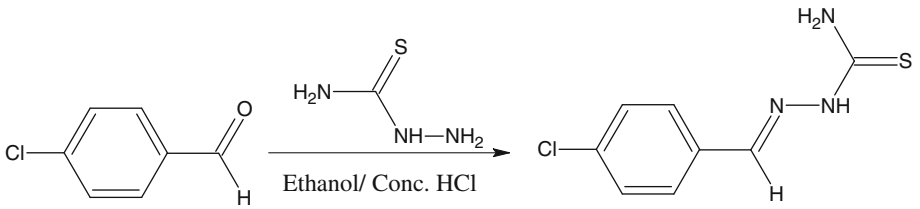
A single crystal of *p*-CBT was mounted on a glass fiber and used for data collection. Cell parameters and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 reflections in an ENRAF–NONIUS CAD4 automatic diffractometer [16]. Data were collected at 293(2) K using CuK_a radiation ($\lambda = 1.54184$ Å) and the data reduction was carried out by XCAD4 [17] program. Out of 3932 reflections collected, 3611 reflections with $I \geq 2\sigma(I)$ were used for structure solution and refinement. The intensity data were corrected for Lorentz and polarization absorption effects.

Structure Solution and Refinement

The structure was solved by direct-methods using the program *SHELXS97* [18], which revealed the position of all non-hydrogen atoms, and refined on F^2 by a full-matrix least squares procedure using *SHELXL97* [18]. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were allowed to ride over their parent atoms. The final cycle of refinement converged to $R_1 = 0.0721$ and w$R_2 = 0.2098$ for the observed reflections. The maximum and minimum heights in the final difference Fourier map were found to be 0.986 and -0.577 e Å^{-3}, respectively. Least-squares planes and asymmetry calculations were done using the program *PARST97* [19]. The thermal ellipsoid plot and packing were done, respectively, using *ORTEP* [20] and *PLATON* [21]. Non-bonded interaction graphics were created using the program *PLATON* [21]. The crystallographic data and methods of data collection, solution and refinement are shown in Table 1. All other information about *p*-CBT structure is included in the deposited material (CCDC 743746) as a complete list of bond distances and angles.

Result and Discussion

The synthesized 4-chlorobenzaldehyde thiosemicarbazone (*p*-CBT) crystallized in space group $P\bar{1}$, and it showed crystallographically two independent molecules in the asymmetric unit A and B. The perspective view of *p*-CBT *ORTEP* diagram is shown in Fig. 1. The bond lengths, bond angles and selected torsion angles of non-hydrogen atoms, respectively, are shown in Fig. 2a, b and c.



The S and hydrazinic N8 atoms are in *trans* position with respect to C10–N9 bond. Similar type of *trans* configuration is noted in many structures of thiosemicarbazide

Table 1 Crystal data and other relevant details for *p*-CBT

Parameters	*p*-CBT
CCDC	CCDC 743746
Empirical formula	$C_8H_8ClN_3S$
Formula weight	213.68
Temperature	293(2) K
Wavelength	1.54184Å (CuK_α)
Crystal system, space group	Triclinic, $P\bar{1}$
Unit cell dimensions	
	$a = 7.934(2)$ Å
	$b = 11.242(3)$ Å
	$c = 11.615(2)$ Å
	$\alpha = 74.775(3)°$
	$\beta = 75.389(2)°$
	$\gamma = 83.448(2)°$
Volume Å^3	966.0(4)
Z, Calculated density	4, 1.469 Mg/m^3
F(000)	440
Theta range for data collection	4.06° to 72.23°
Limiting indices	$-6 \le h \le 9$
	$-13 \le k \le 13$
	$-13 \le l \le 14$
Reflections collected/unique	3932/3611 [$R_{int} = 0.078$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3611/0/236
Goodness-of-fit on F^2	1.015
Final *R*-indices [$I > 2\sigma(I)$]	$R_1 = 0.0721$, w$R_2 = 0.2098$
R-indices (all data)	$R_1 = 0.0918$, w$R_2 = 0.2461$
Largest diff. peak and hole	0.986 and ≤ 0.577 e Å^{-3}

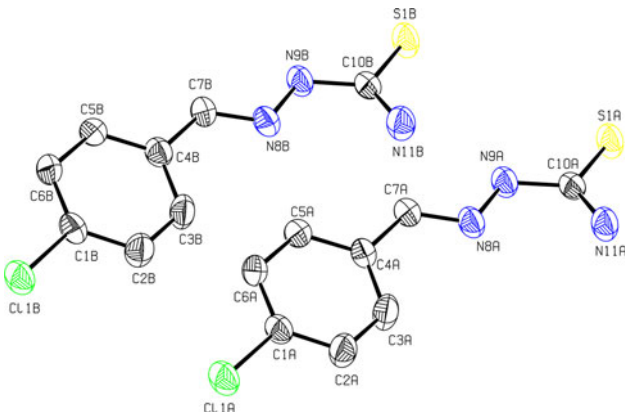


Fig. 1 ORTEP diagram of the molecule *p*-CBT (A and B) showing the thermal ellipsoids at 30% probability level. Hydrogen atoms were removed for clarity

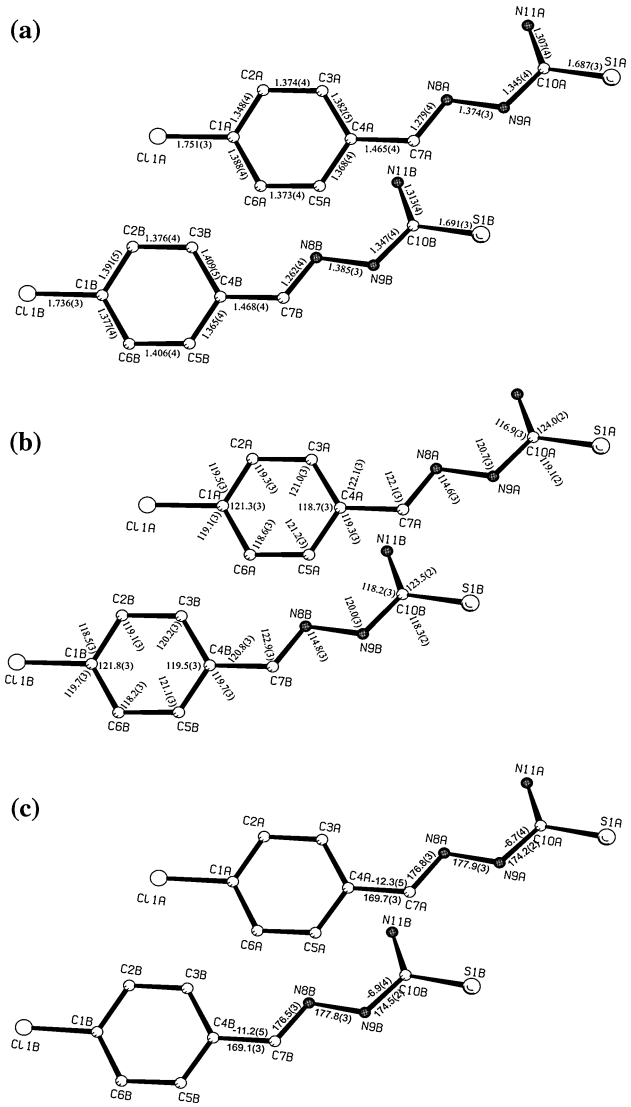
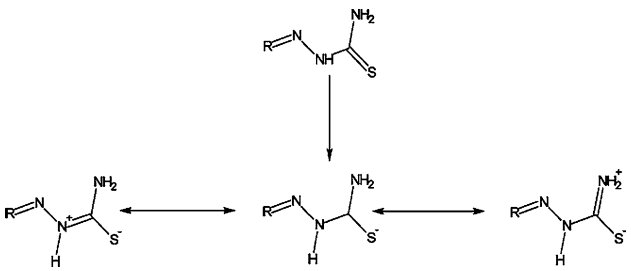


Fig. 2 **a** Bond lengths (Å) diagram of molecule *p*-CBT. **b** Bond angles (°) diagram of molecule *p*-CBT. **c** Selected torsion angles (°) of *p*-CBT. Hydrogen atoms are removed for clarity



Scheme 2 Resonance structures of thiosemicarbazone moiety

[22, 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 thiosemicarbazone moiety adopts an extended conformation and almost lie in the same plane of the benzene ring (Scheme 2). The corresponding torsion angles are as follows:

Conformational bonds	*p*-CBT angle (°)	
	Mol. A	Mol. B
C7–N8–N9–C10	177.9(3)	177.8(3)
N8–N9–C10–N11	−6.7(4)	−6.9(4)
N8–N9–C10–S1	174.2(2)	174.5(2)

The bond length variations in C4–C7 of molecules A and B of *p*-CBT [1.465(4) and 1.468(4) Å] indicate the influence of conjugation between the phenyl ring and C7–N8 [1.279(4) and 1.262(4) Å for A and B of *p*-CBT] imine double bonds (Fig. 2a). Similar effect is also noted in some other structures 2,3-Dihydroxybenzaldehyde thiosemicarbazone [26] and Salicylaldehyde-4,4′-(hexane-1,6-diyl) thiosemicarbazone [27]. In molecule *p*-CBT, C3–C4 bond lengths [1.382(5) Å for A and 1.409(5) Å for B] are not similar and this may be due to the influence of the chlorine atom substituted at the *para* position of phenyl ring. The bond lengths C1–Cl [1.751(3) Å for A and 1.736(3) Å for B] are also significantly different; this is due to the electron releasing capability of the chlorine to the benzene ring.

The bond lengths in the thiosemicarbazone moieties in both the molecular fragments show delocalization effect and this is extended even up to the imine nitrogen group. TSC moieties are oriented at angles 21.1(1)° and 21.3(1)° (A and B, respectively) to the phenyl rings of the molecule *p*-CBT. The bond angles C2–C1–C6 in the molecules A and B of *p*-CBT are 121.3(3)° and 121.9(3)°, respectively. This widening of bond angles in the *p*-CBT molecule is comparable with reported structures (*p*-substituted/unsubstituted thiosemicarbazones) have ranges of 119° to 121° [26, 27], but in *N*,*N*-dimethylaminebenzaldehyde thiosemicarbazone (DABT), the angle C2–C1–C6 [117.0(2)°] is shortened due to the H…H short contacts [28].

Packing Features

The packing of molecules viewed down *a*-axis is shown in Fig. 3. The *p*-CBT molecules are stabilized by N–H…N, N–H…S and C–H…N types of intra and intermolecular hydrogen bonds (Table 2). The N–H…N type intra molecular hydrogen bond forms a five-membered ring and this interaction is helping to the TSC extended conformation [29, 30]. The molecule *p*-CBT also has a weak π…π interaction [31] between the molecules A and B of benzene rings Cg1 [C1A through C6A] and Cg2 [C1B through C6B] forming a centroid–centroid distance of 3.75 Å. Pair of N11–H11…S hydrogen bonds across the centres of inversion results a dimer between the symmetry related molecules of *p*-CBT (Fig. 3). Such dimerization has also been observed in other similar structures [29, 30] and it is found to be a common feature of these moieties. These dimer interactions extend along the *c*-axis of unit cell packing.

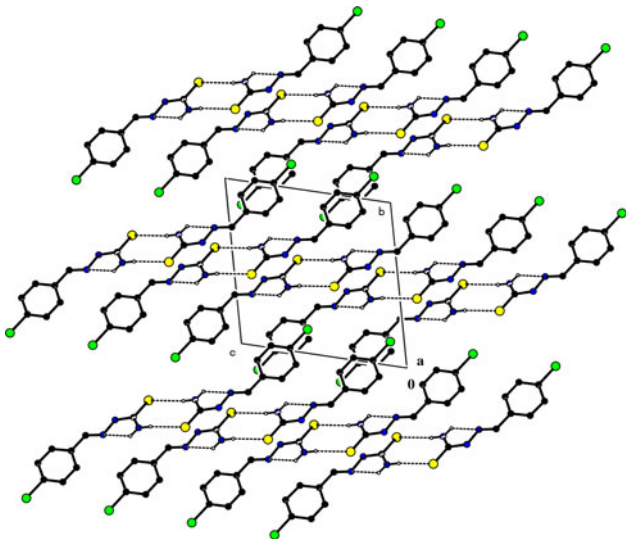


Fig. 3 Packing of the molecules *p*-CBT viewed down *a*-axis. *Dashed lines* represent hydrogen bonds

Table 2 Hydrogen bondings and the possible non-bonded interactions for *p*-CBT (°, Å)

D–H…A	d(D–H)	d(D…A)	d(H…A)	<D–H…A
N11A–H11A…N8A	860(3)	2.642(3)	2.288(2)	104.9(2)
N11B–H11C…N8B	0.860(3)	2.664(3)	2.319(2)	104.2(2)
N9A–H9A…S1B^{i}	0.860(2)	3.461(3)	2.773(1)	138.1(2)
N9B–H9B…S1A^{i}	0.860(2)	3.445(3)	2.755(1)	138.2(2)
C6B–H6B…Cl1B^{ii}	0.930(3)	3.827(3)	2.980(1)	152.1(2)
C6A–H6A…Cl1A^{iii}	0.930(3)	3.847(3)	2.993(1)	153.3(2)
N11B–H11D…S1B^{iv}	0.860(2)	3.509(3)	2.657(1)	171.2(2)

Equivalent positions

i. $-x + 1, -y-1, -z + 2$

ii. $-x + 1, -y, -z$

iii. $-x + 1, -y, -z + 1$

iv. $-x, -y-1, -z + 2$

Supplementary Material

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Database Centre as supplementary publication no. CCDC743746. 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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