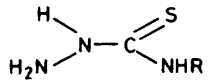
Effect of Chlorine Substitution on the Structure and Activity of 4-Phenylthiosemicarbazide: Crystal and Molecular Structure of 4-(4-Chlorophenyl)thiosemicarbazide

Asok Kumar Nandi, Siddhartha Chaudhuri, and Sunil Kumar Mazumdar
Crystallography and Molecular Biology Division, Saha Institute of Nuclear Physics, Calcutta 700 009, India
Saktiprosad Ghosh*
Department of Inorganic Chemistry, Indian Association for the Cultivation of Science, Calcutta 700 032, India

The crystal structure of 4-(4-chlorophenyl)thiosemicarbazide has been determined by direct methods. This *p*-chloro-substituted 4-phenylthiosemicarbazide, with greater antibacterial activity than its unsubstituted precursor, crystallises in the space group $P2_1/c$ with $a = 14.594(4)$, $b = 10.495(5)$, $c = 12.384(4)$ Å, $\beta = 104.73(2)°$, $Z = 8$, $D_c = 1.469$ g cm^{-3}, and μ(Mo-K_α) = 5.83 cm^{-1}. The structure has been refined using 1 967 reflections with $I \geqslant 3\sigma(I)$. The antibacterial activity of both the present compound and its precursor has been attributed to electron delocalisation in the thiosemicarbazide moiety enhancing both its donor and reductive capacities.

With the recognition of the fact that many functionally important biomolecules contain S–N donor sites in suitable positions and the discovery of the antibacterial, antiviral, and antitumour properties of various thiosemicarbazides, thiosemicarbazones, and their metal complexes,[1] interest in the study of the chemical, biochemical, and structural aspects of these compounds and their derivatives is growing. The biological activity is, in general, believed to originate from metal-complexing[2] and reductive[3] capacities of these organic ligands. Thiosemicarbazides, containing both hard (N) and soft (S) donors[4] in positions suitable for chelating metal ions, have been shown to act as versatile complexing agents for various metal ions in different oxidation states. It has also been found that the antibacterial activities *in vitro* of different substituted phenylthiosemicarbazides and their metal complexes vary with the nature of the substituent in the phenyl ring.[5] It is to be expected that the *para*-substitution of a chlorine atom, having a +*R* effect, in the phenyl ring of 4-phenylthiosemicarbazide will make the thiosemicarbazide chain more electron rich in comparison with the corresponding chain in 4-phenylthiosemicarbazide (**2**). The crystal structure of 4-(4-chlorophenyl)thiosemicarbazide (**1**) was determined with the aim of correlating its structure and that of the previously reported[6] 4-phenylthiosemicarbazide (**2**) with their biological activities and to account for the greater activity of the chlorine-substituted compound (**1**).



(**1**) R = *p*-ClC$_6$H$_4$
(**2**) R = Ph

Experimental

The compound, obtained in powder form, was recrystallised from ethanol.

Crystal Data.—$C_7H_8ClN_3S$, $M = 201.68$, $a = 14.594(4)$, $b = 10.495(5)$, $c = 12.384(4)$ Å, $\beta = 104.73(2)°$, $V = 1\,834(2)$ Å^3, $D_c = 1.46$ g cm^{-3}, $F(000) = 832$, μ(Mo-K_α) = 5.83 cm^{-1}, space group $P2_1/c$, $Z = 8$ (two molecules in the asymmetric unit).

The data were collected on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated radiation in the range $2° \leqslant \theta \leqslant 25°$. 1 967 out of the 3 422 unique reflections measured were considered to be observed [$I \geqslant 3\sigma(I)$]. The intensities were corrected for Lorentz and polarisation effects but not for absorption.

The structure was solved by MULTAN[7] using 280 *E* values, up to $E_{min.} = 1.7$, 2 000 unique phase relationships, and three origin-defining and five other starting reflections. An *E* map computed with the phase set having the highest combined figure of merit, out of the total of 32 phase sets generated, revealed the positions of all the non-hydrogen atoms. Full-matrix least-squares refinement, with isotropic thermal parameters, of these atoms converged to a residual (*R*) of 0.145. Further refinement, with anisotropic thermal parameters, reduced *R* to 0.055. A difference electron density map computed at this stage enabled the location of all the 16 hydrogen atoms in the asymmetric unit. Further refinement, with isotropic thermal parameters assigned to the hydrogens, converged to the final residuals of $R = 0.035$ and $R_w = 0.040$ for the observed reflections. Thoughout the refinement the weights used were equal to $1/\sigma^2(|F_o|^2)$. The atomic scattering factors for the non-hydrogen atoms were taken from ref. 8 and those for the hydrogen atoms from ref. 9. The scattering factors for the non-hydrogen atoms were corrected for anomalous dispersion.[10] The final atomic parameters are listed in Table 1. The anisotropic thermal parameters and structure factors are listed in Supplementary Publication No. SUP 56018 (27 pp.).†

Evaluation of Antibacterial Activity.—The *in vitro* antibacterial activity of 4-(4-nitrophenyl)thiosemicarbazide, 4-phenylthiosemicarbazide, 4-(4-chlorophenyl)thiosemicarbazide, and 4-(3,4-dichlorophenyl)thiosemicarbazide against *E. coli* were evaluated by standard techniques, in a nutrient broth medium; their m.i.c. (μg ml^{-1}) values were found to be 80.0, 55.5, 26.3, and 27.2, respectively.

Results and Discussion

The atomic labelling scheme is shown in Figure 1. To avoid confusion in the text the atoms of the two molecules

† For details of Supplementary Publications see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.

Table 1. Positional and thermal parameters with their estimated standard deviations in parentheses

	Molecule A				Molecule B			
Atom	*x*	*y*	*z*	$B_{eq}/B(Å^2)$	*x*	*y*	*z*	$B_{eq}/B(Å^2)$
N(1)	0.940 1(2)	0.095 8(3)	0.757 6(2)	4.48	0.232 7(2)	0.096 8(3)	0.110 4(2)	4.33
N(2)	0.955 2(2)	0.211 1(3)	0.707 4(2)	3.77	0.180 1(2)	0.145 7(3)	0.182 4(2)	3.38
C(3)	0.923 9(2)	0.228 3(3)	0.598 1(2)	3.01	0.217 2(2)	0.145 8(3)	0.292 3(2)	2.91
N(4)	0.874 3(2)	0.130 0(2)	0.541 1(2)	3.43	0.307 1(2)	0.108 7(3)	0.327 1(2)	4.32
C(5)	0.830 3(2)	0.124 3(3)	0.424 9(2)	2.92	0.359 5(2)	0.104 2(3)	0.440 8(2)	3.59
C(6)	0.840 3(2)	0.015 9(3)	0.366 6(2)	3.92	0.370 9(2)	−0.011 4(4)	0.497 2(3)	4.09
C(7)	0.793 0(3)	0.002 2(3)	0.256 1(2)	4.31	0.420 9(2)	−0.017 2(4)	0.606 9(3)	4.10
C(8)	0.735 6(2)	0.099 2(3)	0.204 1(2)	3.33	0.459 3(2)	0.928(4)	0.659 6(2)	3.96
C(9)	0.725 7(2)	0.208 9(3)	0.259 2(2)	3.46	0.449 5(2)	0.206 0(4)	0.605 2(3)	4.69
C(10)	0.772 5(2)	0.221 3(3)	0.371 0(2)	3.28	0.399 1(2)	0.211 6(3)	0.495 1(3)	4.59
Cl	0.671 45(7)	0.081 0(1)	0.065 04(6)	5.24	0.523 59(7)	0.085 2(1)	0.799 64(7)	6.46
S	0.950 38(6)	0.364 84(9)	0.540 83(6)	4.02	0.152 37(6)	0.190 86(8)	0.381 29(6)	3.32
H1(N1)	0.925(2)	0.107(3)	0.810(2)	5.1(8)	0.191(2)	0.038(3)	0.070(2)	5.1(8)
H2(N1)	1.002(2)	0.059(3)	0.782(2)	5.0(8)	0.233(2)	0.151(3)	0.070(2)	5.3(8)
H(N2)	0.993(2)	0.273(3)	0.747(2)	3.5(6)	0.120(2)	0.151(3)	0.158(2)	3.7(7)
H(N4)	0.874(2)	0.062(2)	0.575(2)	2.6(6)	0.332(2)	0.085(3)	0.278(2)	3.1(6)
H(C6)	0.886(2)	−0.046(3)	0.402(2)	4.3(7)	0.341(2)	−0.075(3)	0.463(2)	3.9(7)
H(C7)	0.797(2)	−0.067(3)	0.219(2)	5.4(8)	0.428(2)	−0.090(3)	0.645(2)	3.7(7)
H(C9)	0.689(2)	0.277(3)	0.226(2)	3.3(6)	0.473(2)	0.270(3)	0.635(2)	4.6(7)
H(C10)	0.760(2)	0.293(3)	0.409(2)	2.9(6)	0.396(2)	0.286(3)	0.453(2)	4.6(7)

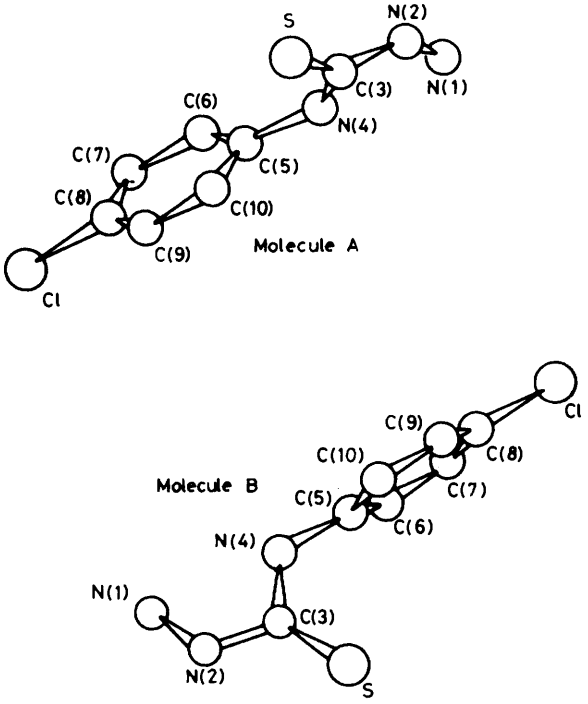


Figure 1. Perspective view of the molecules down the *b* axis with numbering scheme; hydrogen atoms have been omitted for clarity

constituting the asymmetric unit have been distinguished by the suffixes A and B. Figure 2 shows the packing of the molecules together with the hydrogen-bonding scheme. Bond distances and angles involving the non-hydrogen atoms are listed in Table 2.

As in the crystal structure of 4-phenylthiosemicarbazide,[6] the sulphur atom and the hydrazine NH_2 group assume a *trans*-configuration in both the molecules. This is the general configuration found in uncomplexed thiosemicarbazides.[3] The sulphur atom in both the molecules of (**1**) occurs in the thiocarbonyl (keto) form. The occurrence of this form is also indicated by the presence of a fairly strong band around 730 cm^{-1} in the i.r. spectrum.[11]

It is found that in (**1**) the two C(5)–N(4) bond lengths are significantly shorter than the corresponding bond length in (**2**). This cannot be a consequence of π-electron delocalisation with the phenyl ring as the dihedral angles between the rings and the C(5)–N(4)–C(3) groups differ widely (46.43 and 80.40°) between molecules A and B. The bond lengths C(5)–N(4) are however equal in A and B. The amount of delocalisation decreases with $\cos^2\theta$,[12] where θ is the above mentioned dihedral angle. The constancy of the C(5)–N(4) bond lengths in the two molecules of compound (**1**) and the shortening from that in compound (**2**) is, therefore, a consequence of chlorine substitution in the *para*-position. The observed C(3)–N(2) and C(3)–N(4) bond lengths in both (**1**) and (**2**) indicate extensive delocalisation of the π-electrons in these regions of the molecules.[13] Further shortening in the C(5)–N(4), C(3)–N(2), and N(2)–N(1) bond lengths in (**1**) compared with those, 1.44(5), 1.357(7), and 1.431(5) Å, in (**2**)[6] gives a direct evidence of enhanced electron delocalisation in the former. The C(3)–N(4) and C(3)–N(2) bond lengths in molecule A are greater than the corresponding bond lengths in molecule B, while the C(3)–S and N(1)–N(2) bond lengths are smaller in molecule A. Such differences in lengths of similar bonds may be ascribed to resonance similar to that in thiosemicarbazide[14] (Scheme). Extensive delocalisation in the thiosemicarbazide chains is also evidenced from the coplanarity of the atoms constituting these chains (Table 3).

Considerable variations (1.687—1.706 Å) in the C–S distances are observed in the cases of the various thiosemicarbazides and thiosemicarbazones.[3] The C–S distance in (**1**) is comparable with that in (**2**). The slight lengthening of this distance in molecule B from that in molecule A may be attributed to the fact that S(B) accepts two hydrogen bonds while S(A) accepts only one. A longer C–S bond, 1.706(6) Å, is observed in 5-hydroxy-2-formylpyridine thiosemicarbazone where the sulphur accepts three hydrogen bonds.[3]

Some selected torsion angles have been listed in Table 4. Rotational flexibility about the C(5)–N(4) bond is indicated by the observed variation in the C(6)–C(5)–N(4)–C(4) and C(10)–C(5)–N(4)–C(3) torsion angles in compounds (**1**) and (**2**). Rotation about the C(3)–N(2) is apparently hindered owing to

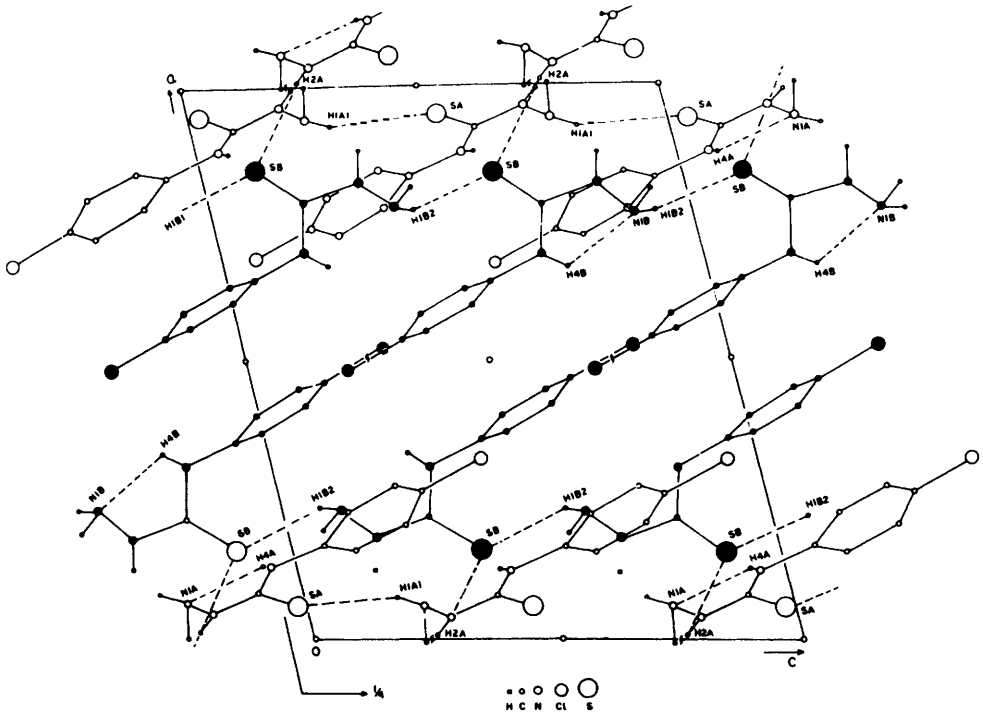


Figure 2. Projection of crystal structures of 4-(4-chlorophenyl)thiosemicarbazide on the *ac* plane; dashed lines showing the hydrogen bonds

Table 2. Bond lengths (Å) and angles (°) in 4-(4-chlorophenyl)-thiosemicarbazide involving non-hydrogen atoms

I Bond lengths (Å)

	Molecule A	Molecule B
N(1)–N(2)	1.403(4)	1.414(4)
N(2)–C(3)	1.327(3)	1.330(3)
C(3)–S	1.687(3)	1.692(3)
C(3)–N(4)	1.351(3)	1.332(4)
N(4)–C(5)	1.420(3)	1.422(4)
C(5)–C(6)	1.374(4)	1.388(5)
C(6)–C(7)	1.375(4)	1.370(4)
C(7)–C(8)	1.371(4)	1.375(5)
C(8)–Cl	1.749(3)	1.751(3)
C(8)–C(9)	1.365(4)	1.355(5)
C(9)–C(10)	1.385(4)	1.376(5)
C(10)–C(5)	1.382(4)	1.364(5)

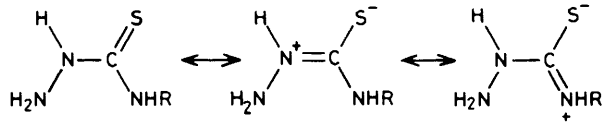
II Bond angles (°)

N(1)–N(2)–C(3)	121.1(3)	120.0(3)
N(2)–C(3)–S	119.2(2)	121.1(2)
N(2)–C(3)–N(4)	115.4(3)	116.2(3)
S–C(3)–N(4)	125.4(2)	122.6(2)
C(3)–N(4)–C(5)	127.2(3)	124.5(2)
N(4)–C(5)–C(6)	119.5(3)	119.5(3)
N(4)–C(5)–C(10)	121.4(3)	120.9(1)
C(10)–C(5)–C(6)	119.3(3)	119.5(3)
C(5)–C(6)–C(7)	121.1(3)	120.2(4)
C(6)–C(7)–C(8)	118.8(3)	118.9(4)
Cl–C(8)–C(7)	119.4(2)	118.9(3)
Cl–C(8)–C(9)	119.1(2)	119.7(3)
C(7)–C(8)–C(9)	121.4(3)	121.4(3)
C(8)–C(9)–C(10)	119.4(3)	119.6(4)
C(9)–C(10)–C(5)	119.9(3)	120.3(4)

Table 3. Deviations of the atoms (Å), with e.s.d.s in parentheses, from the least-squares planes defined by them. Atoms marked with asterisks have been excluded from the respective plane calculations

	Molecule A[a]	Molecule B[a]	Compound (2)[b]
Plane 1			
Atom			
C(5)	−0.003(3)	−0.003(2)	0.006(5)
C(6)	0.005(3)	0.003(3)	−0.010(7)
C(7)	−0.000(4)	0.002(3)	0.006(7)
C(8)	−0.007(3)	−0.004(3)	−0.002(6)
C(9)	0.009(3)	0.003(3)	0.001(6)
C(10)	−0.004(3)	0.001(3)	−0.004(6)
C(3)*	0.607(3)	−1.089(3)	0.949(5)
S*	1.870(1)	−2.631(1)	2.424(1)
N(1)*	−0.700(3)	0.372(3)	−0.572(5)
N(2)*	0.284(3)	−0.899(3)	0.686(5)
Plane 2			
N(1)	0.031(3)	−0.048(3)	−0.013(5)
N(2)	−0.033(3)	0.054(3)	0.018(4)
C(3)	−0.023(3)	0.021(3)	−0.013(5)
S	0.002(1)	−0.002(1)	−0.000(1)
N(4)	−0.000(3)	0.007(3)	0.007(4)
C(5)*	−0.029(3)	−0.007(3)	−0.008(5)
Plane 3			
N(2)	0.003(3)	−0.000(3)	0.004(4)
C(3)	−0.010(3)	0.000(3)	−0.018(5)
S	0.000(1)	−0.000(1)	0.000(1)
N(4)	0.003(3)	−0.000(3)	0.005(4)
C(5)*	−0.050(3)	0.020(3)	−0.001(5)
H(2)*	0.06(3)	−0.19(3)	−0.12(7)
H(4)*	0.14(3)	−0.04(3)	0.07(8)
Dihedral angles (°) between Planes			
1 and 2	48.70	80.80	67.60
1 and 3	49.05	81.07	67.51
2 and 3	1.03	1.46	0.36

[a] Present work. [b] Calculated from published co-ordinates in ref. 6.



Scheme.

Table 4. Comparison of selected torsion angles

	Molecule A[a]	Molecule B[a]	Compound (2)[b]
C(10)–C(5)–N(4)–C(3)	−48.9(4)	−80.6(4)	−115.9(6)
C(6)–C(5)–N(4)–C(3)	135.6(3)	99.7(4)	67.8(7)
C(5)–N(4)–C(3)–S	−4.0(4)	−1.0(4)	2.5(7)
C(5)–N(4)–C(3)–N(2)	177.8(3)	179.0(3)	179.5(4)
N(4)–C(3)–N(2)–N(1)	2.4(4)	5.7(4)	3.9(7)
S–C(3)–N(2)–N(1)	−175.8(2)	−174.2(2)	−179.0(4)

[a] Present study. [b] Calculated from published data in ref. 6.

results are compared in Table 6. The two key atoms responsible for antibacterial activity are N(1) and the thiocarbonyl sulphur atom which actually take part in metal chelation. The electron density on N(1) is found to be significantly higher in the 4-chloro-substituted compound (**1**) and this may be attributed to electron drift towards the thiosemicarbazide side-chain which makes this substituted compound a better donor and a stronger reductant compared with the unsubstituted variety. Accumulation of negative charge on the thiocarbonyl sulphur is appreciable with no significant difference between the 4-chloro-substituted and unsubstituted compound.

The results of antibacterial study indicate that 4-(3,4-dichlorophenyl)thiosemicarbazide exhibits practically no significant enhancement of activity over the 4-chloro derivative. The 4-nitro derivative indicates a decrease in antimicrobial action compared with that of 4-phenylthiosemicarbazide molecule. This trend in variation of antimicrobial activity is supported by the structural data, like the variation in bond lengths of different reactive moieties. This is further supported

Table 5. Hydrogen bonds

D–H ··· A	Equivalent position of A	D–H (Å)	H ··· A (Å)	D ··· A (Å)	D–H ··· A (°)
N(1A)–H1(N1A) ··· S(A)	$x, \frac{1}{2}-y, \frac{1}{2}+z$	0.74(3)	2.81(3)	3.497(3)	155(3)
N(2A)–H(N2A) ··· S(B)	$1+x, \frac{1}{2}-y, \frac{1}{2}+z$	0.91(3)	2.52(3)	3.290(3)	142(2)
N(1B)–H2(N1B) ··· S(B)	$x, \frac{1}{2}-y, -\frac{1}{2}+z$	0.77(3)	2.86(4)	3.564(3)	154(3)
N(4A)–H(N4A) ··· N(1A)	x, y, z	0.82(3)	2.36(3)	2.64(3)	112(2)
N(4B)–H(N4B) ··· N(1B)	x, y, z	0.82(3)	2.21(3)	2.630(4)	112(2)

electron delocalisation in (**1**) and (**2**). This prevents the sulphur atoms from assuming the *cis*-configuration found in thiosemicarbazide hydrochloride[15] where the protonation of the hydrazine-NH_2 group prevents delocalisation and favours free rotation about the C(3)–N(2) (imino) bond.

Hydrogen Bonding.—The bond distances and angles involving the atoms taking part in hydrogen bonding have been listed in Table 5. All the nitrogens, excepting N(2B), in both the molecules take part in hydrogen bonding. The intramolecular hydrogen-bond geometries N(4)–H(4) ··· N(1), for both molecules A and B, are similar to the geometry, computed with the published atomic co-ordinates,[6] of an identical intramolecular contact in 4-phenylthiosemicarbazide. In all the cases the hydrogen, H(4), to acceptor, N(1), distances are less than the sum of the van der Waals radii for nitrogen and hydrogen (2.70 Å).[16] The N(1) atom in both the molecules acts simultaneously as an acceptor of an intramolecular hydrogen bond and as a donor of an intermolecular hydrogen bond. The lone pair of the hydrazine N(1) atom is responsible for the intramolecular hydrogen bond. A similar phenomenon has been observed in thiosemicarbazide.[16] The sulphur atoms in the two molecules A and B participate differently in hydrogen bonding. S(B) accepts two intermolecular hydrogen bonds while S(A) accepts only one. This causes the slight increase in the C–S distance in molecule B mentioned earlier.

The chlorine atoms, Cl(A) (x, y, z) and Cl(B) $(x, y, 1+z)$, of the two molecules approach each other to a distance of 3.443(1) Å. The C(8)–Cl bond lengths, 1.749(3) Å in molecule A and 1.751(3) Å in molecule B, are in agreement with the mean value of the C–Cl distance, 1.740 4(11) Å, given in ref. 17*a*. The deviations of endocyclic angles in the phenyl rings from the ideal value, 120°, may be attributed to the effect of substitution.[17b]

The charge density distributions for compounds (**1**) and (**2**) have been calculated using the CNDO/2 method[18] and the

Table 6. CNDO results showing the net charges on the atoms in 4-(4-chlorophenyl)thiosemicarbazide and in 4-phenylthiosemicarbazide

	4-(4-Chlorophenyl)thiosemicarbazide		
Atom	Molecule A	Molecule B	4-Phenyl-thiosemicarbazide
N(1)	−0.1633	−0.1698	−0.1385
N(2)	−0.1010	−0.1170	−0.1212
C(3)	0.3110	0.3113	0.3111
N(4)	−0.1826	−0.1825	−0.1850
C(5)	0.1361	0.1365	0.1443
C(6)	−0.0300	−0.0315	−0.0362
C(7)	−0.0160	−0.0125	0.0098
C(8)	0.1300	0.1368	−0.0153
C(9)	−0.0110	−0.0232	0.0067
C(10)	−0.0218	−0.0145	−0.0193
Cl	−0.1835	−0.1831	
S	−0.4639	−0.4735	−0.4603
H1(N1)	0.1204	0.0942	0.1049
H2(N1)	0.0867	0.1170	0.0694
H(N2)	0.1367	0.1394	0.1333
H(N4)	0.1322	0.1360	0.1312
H(C6)	0.0161	0.0338	0.0117
H(C7)	0.0372	0.0342	0.0119
H(C8)			0.0162
H(C9)	0.0324	0.0457	0.0113
H(C10)	0.0345	0.0230	0.0141

by the fact that CNDO/2 calculations[18] on 4-phenylthiosemicarbazide and 4-(4-chlorophenyl)thiosemicarbazide indicate accumulation of significantly greater negative charge on N(1) in the latter compound which makes it a stronger chelating agent and a more powerful reductant.

Structure–Activity Relationship.—It has been reported that although some semicarbazones are toxic to certain insects, the majority of them are devoid of any useful biological activity.[13]

On the other hand, the presence of the sulphur atom in place of the oxygen in thiosemicarbazides and thiosemicarbazones render them biologically active. This activity is partly dependent on the parent aldehyde or ketone in the case of the thiosemicarbazones and on the substituent in the case of thiosemicarbazides. This dependence of biological activity of the thiosemicarbazides on the substituents has been corroborated by the study of antibacterial activity of 4-(4-chlorophenyl)thiosemicarbazide along with some other related compounds.

A comparison of the structure of the present ligand (**1**) with that of (**2**) reveals that the presence of the *o,p*-orientating chlorine atom situated *para* to the thiosemicarbazide moiety results in an electron enrichment in the thiosemicarbazide chain (+ *R* effect) which (i) enhances its donor capacity and (ii) makes it more reducing in comparison with 4-phenylthiosemicarbazide (**2**). The first effect makes this molecule a stronger complexing agent and hence a better scavenger of metal ions. The second effect makes it a better reactant for the reduction of Cu^{2+} to Cu^{+} and Fe^{3+} to Fe^{2+} and thereby enhances its capability for extracting both Cu^{2+} and Fe^{3+} from relevant metalloenzymes vital for the life processes of bacteria.

It has been reported by previous workers that these types of compounds, by their reductive capacities for metal ions, interfere in the process of enzymatic conversion of ribonucleotides into deoxyribonucleotides and thereby inhibit the biosynthesis of DNA. This may explain their antitumour activities.[19] These possibilities are supported by the observation that thiosemicarbazones cause urinary and fecal excretion of iron as a green iron(II) complex.[20] Thus, both compounds (**1**) and (**2**) hold the possibility of exhibiting antitumour activity. The increased electron delocalisation in (**1**) explains the observed greater activity *in vitro* towards *E. coli* compared with 4-phenyl thiosemicarbazide.

All these findings suggest that the electronic parameter is the major contributing factor towards antimicrobial activation due to substitution. However, other well recognised factors like log *p* and steric influence of the substituent may also have contributed to the enhanced activation.[21] But it has not been possible to make special studies to evaluate the relative importance of such factors and hence no specific comments in this line can be made with any confidence.

As evidenced from the crystal structure, all the nitrogens, excepting N(2B), and the sulphur atom in the both ligands (**1**) and (**2**) are involved in hydrogen bonding; this indicates that all these atoms are potential donors towards the majority of the metal ions present in biological systems and corroborates our previous observation.

Acknowledgements

We are thankful to Dr. P. K. Ray of I.A.C.S., Department of Inorganic Chemistry, for preparing compound (**1**).

References

1 N. N. Orlova, V. A. Aksenova, D. A. Selidovkin, N. S. Bogdanova, and G. N. Perskhin, *Russ. Pharmacol. Toxicol.*, 1968, 348; C. W. Johnson, J. W. Joyner, and R. P. Perry, *Antibiot. Chemother.*, 1952, **2**, 636; D. R. William, *Chem. Rev.*, 1972, **72**, 203; F. A. French and E. J. Blanz, *Cancer Res.*, 1965, **25**, 1454; *J. Med. Chem.*, 1966, **9**, 585.
2 S. Kirschner, Y. K. Wei, D. Francis, and J. G. Bergman, *J. Med. Chem.*, 1966, **9**, 369; E. Sirkin, W. Roth, and H. Erlenmeyer, *Helv. Chim. Acta*, 1952, **35**, 1736; F. A. French and B. L. Freedlander, *Cancer Res.*, 1958, **18**, 1290.
3 G. J. Palenik, D. F. Rendle, and W. S. Carter, *Acta Crystallogr., Sect. B*, 1974, **30**, 2390.
4 R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 581, 643; R. G. Pearson and R. S. Drago, *Chem. Br.*, 1967, **3**, 103, 516.
5 P. K. Ray, Ph.D. Dissertation, University of Calcutta, 1981.
6 A. Kálmán, G. Argay, and M. Czugler, *Cryst. Struct. Commun.*, 1972, **1**, 375.
7 P. Main, M. Woolfson, L. Lessenger, G. Germain, and J. P. Declereq, MULTAN 74, A System of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data, Universities of York and Louvain-la-Neuve.
8 D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, 1965, **18**, 104.
9 R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.
10 'International Tables for *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. 4, p. 149.
11 L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Chapman and Hall, London, 1975, p. 400.
12 G. G. Christoph and E. B. Fleischer, *Acta Crystallogr., Sect. B*, 1973, **29**, 121.
13 N. V. Dutta and G. J. Palenik, *Acta Crystallogr., Sect. B*, 1974, **30**, 2396.
14 P. Domiano, G. Fava Gaspari, M. Nardelli, and P. Sgarabotto, *Acta Crystallogr., Sect B*, 1969, **25**, 343.
15 L. Coghi, A. M. M. Lanfredi, and A. Tiripicchio, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1808.
16 G. D. Andreetti, P. Domiano, G. F. Gasparri, M. Nardelli, and P. Sgarabotto, *Acta Crystallogr., Sect B*, 1970, **26**, 1005.
17 A. Domenicano, A. Vaciago, and C. A. Coulson, *Acta Crystallogr., Sect B*, 1975, **31**, (*a*) 1630; (*b*) 221.
18 J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.
19 F. A. French, Jr., E. J. Blanz, S. C. Shaddix, and R. W. Brockman, *J. Med. Chem.*, 1974, **17**, 172.
20 F. A. French, A. E. Lewis, Jr., E. J. Blanz, and A. H. Sheena, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 1965, **24**, 402.
21 H. Konig, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 749.

Received 1*st August* 1983; *Paper* 3/1331