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Semicarbazones and Thiosemicarbazones, XII [1]: Crystal Structure of Salicylaldehyde Semicarbazone

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Summary. The crystal and molecular structure of salicylaldehyde semicarbazone was obtained by single crystal X-ray diffraction. The O atom of the semicarbazone fragment is *anti* to the N atom of the hydrazinic group. The distribution of bond lengths in the semicarbazone fragment indicates delocalization of the π-electrons. The crystal structure is stabilized by intra- and intermolecular hydrogen bonds.

Keywords. Salicylaldehyde semicarbazone; Semicarbazone; Crystal structure.

Semicarbazone und Thiosemicarbazone, 12. Mitt.: Die Kristallstruktur des Salicylaldehyd-Semicarbazons

Zusammenfassung. Die Kristallstruktur und die molekulare Struktur des Salicylaldehyd-Semicarbazons wurde über Einkristall-Röntgenstreuung ermittelt. Das O-Atom des Semicarbazonteils steht *anti* zum N-Atom der Hydrazin-Gruppierung. Die Bindungslängen in der Semicarbazoneinheit zeigen eine Delokalisierung der π-Elektronen an. Die Geometrie der Verbindung wird durch stabilisierende intra- und intermolekulare Wasserstoffbrückenbindungen bestimmt.

Introduction

Thiosemicarbazones (*TSC*) have a wide range of biological activities including antitumor activity [2]. In constrast, the majority of semicarbazones (*SC*) are void of any useful biological activity.

The anti tumor activity of *TSC* is attributed to their ability to form metal complexes [2]. It has been proposed that the planar, mononegative, tridentate nature of active *TSC* is an essential feature for their pharmacological activity [3]. When the metal derivatives obtained with different salicylaldehyde semicarbazones or thiosemicarbazones, all of them mono negative (or binegative), planar, tridentate ligands, are compared, the most clear difference between them is the stabilization of certain oxidation states by the *TSC* compounds. For example, when Fe(II) and Co(II) are made to react with salicylaldehyde semicarbazones the *M*(II) compounds are obtained [1, 4, 5], while when the corresponding salicylaldehyde thiosemicarbazones are used, the *M*(III) derivatives are the air stable compounds [6–8]. With copper it is possible to isolate the Cu(II) [9–11] and Cu(I) [10, 11] *TSC* derivatives, but with *SC* only the Cu(II) compounds are obtained [1, 4, 5, 12]. If, as suggested, the biological activity of *TSC* is centered around the S atom, the redox properties of this atom towards the *TSC*, as well as the extensive electron delocalization observed in this compounds (and its possible influence in the redox properties of the ligands), might be important features in their biological activity.

As part of our studies of the chemistry of thiosemicarbazones and semicarbazones [1] we decided to study the molecular geometry of salicylaldehyde semicarbazone (*SASC*) and examine the structural differences of similar thiosemicarbazones, with the ultimate aim of understanding the differences in biological activity between *TSC* and *SC*.

Experimental

Salicylaldehyde semicarbazone was prepared by reacting salicylaldehyde with semicarbazide hydrochloride in water in the presence of a small amount of sodium acetate [13]. Crystals of *SASC* were obtained by recrystallization from ethanol.

Crystal Data

$C_8H_9N_3O_2$, $M = 179.18$; cell dimensions ca. $0.1 \times 0.2 \times 0.4$ mm, space group $C_{2/c}$, $a = 13.203$ (4), $b = 5.278$ (1), $c = 25.158$ (6) Å, $\beta = 106.57$ (2)°, $V = 1680$ (2) A^3, $D_{\mathrm{calc.}} = 1.42\,\mathrm{g\,cm^{-3}}$, $Z = 8$, μ (Cu – Kα) $8.40\,\mathrm{cm^{-1}}$, F (000) 752.

Data Collection, Structure Solution and Refinement

The data were collected on a Nicolet R3m four-circle diffractometer, Ni-filtered Cu – Kα radiation (1.54178 Å) at 293°K. Lattice parameters were obtained from 25 machine-centered reflections with $7.31 < 2\theta < 27.82°$. Of the 1203 reflections from two octants, 881 had $I > 3.00\,\sigma(I)$ and were used in refinement. Index range $h\,0 \rightarrow 14$, $k\,0 \rightarrow 5$, $l \pm 25$, $2\theta:\theta$ scan mode, variable scan speed, scan width 1.0° (θ), $2\theta < 110°$. Two standard reflexions $(1, \bar{1}, \bar{2}; \bar{1}, \bar{1}, \bar{6})$ were monitored every 50 measurements and show no significant variation. Lp corrections were made. The structure was solved by direct methods using MITHRIL [14]. Full matrix least-square refinement with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were located from a difference Fourier map at an advanced stage of refinement and their coordinates were refined; all H atoms were assigned by fixed isotropic temperature factors, 1.2 times that of bearing atom. Final $R = 0.035$ and $R_w = 0.056$, $S = 1.07$, residual electron $\pm\,0.17\,\mathrm{e\AA^{-3}}$. Atomic scattering factors are from Ref. [15]. All calculations were performed on a VAX-STATION computer.

Results and Discussion

Structural Results

The molecular structure with the numbering scheme is illustrated in Fig. 1. Final positional parameters and equivalent isotropic temperature factors are given in Table 1. Bond lengths and angles for non-H atoms are listed in Table 2. Fig. 2 shows the packing arrangement of the molecules.

The O(2) atom is *anti* to the hydrazinic N(1) atom. A similar conformation was observed in semicarbazide hydrochloride [16], benzaldehyde semicarbazone (*BSC*) [17], salicylaldehyde thiosemicarbazone (*SATSC*) [18], 5-methoxy-salicyl-

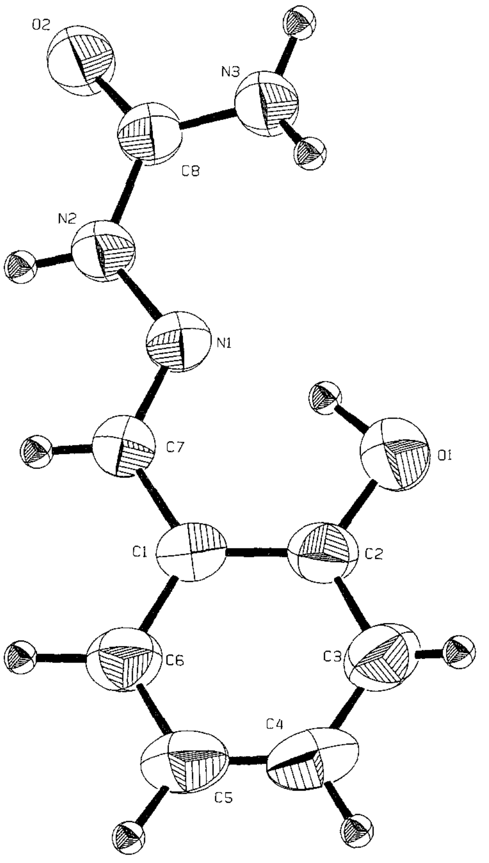

Fig. 1. The molecular structure of *SASC* with the numbering scheme

aldehyde 4-phenylthiosemicarbazone (*MeOPhTSC*) [19] and 2-hydroxyacetophenone thiosemicarbazone (*HAT*) [20]. In contrast, the acetone thiosemicarbazone (*ASC*) presents a *syn* conformation [17]. The configuration apparently depends on the hydrogen-bonding pattern observed in the crystal, *vide infra.*

The phenyl ring is almost planar, maximum deviations from the plane are 0.0109 (17) and −0.0119 (23) Å for C(1) and C(5), respectively, in contrast to the deviation observed in *HAT* [22]. The semicarbazone fragment is not all together planar, maximum deviations are −0.0595(15), 0.0435(17) and −0.0426(21) for N(1), N(2) and C(7) respectively. The semicarbazone fragment forms a dihedral angle of 14.78(5)° with the phenyl ring.

The distances in the semicarbazone fragment are tabulated in Table 3, together with the dimensions reported for other related compounds. When a comparison between the semicarbazones is made, the similarity in molecular dimensions is evident. However, the C−O distance of 1.243(3) Å is shorter than that found for urea [21], *ASC* [17] and *BSC* [17] semicarbazones.

The distribution of bond lengths in the ureide group indicates delocalization of the π electrones. This delocalization is clearly reflected in the theoretical calculation, see Table 4. When the N(2)−C(8) and C(8)−N(3) distances of *ASC* and *SASC* are compared with the corresponding distances in *ATSC* and *SATSC*, it is clear that in the sulphur compound there is an increase of the electron delo-

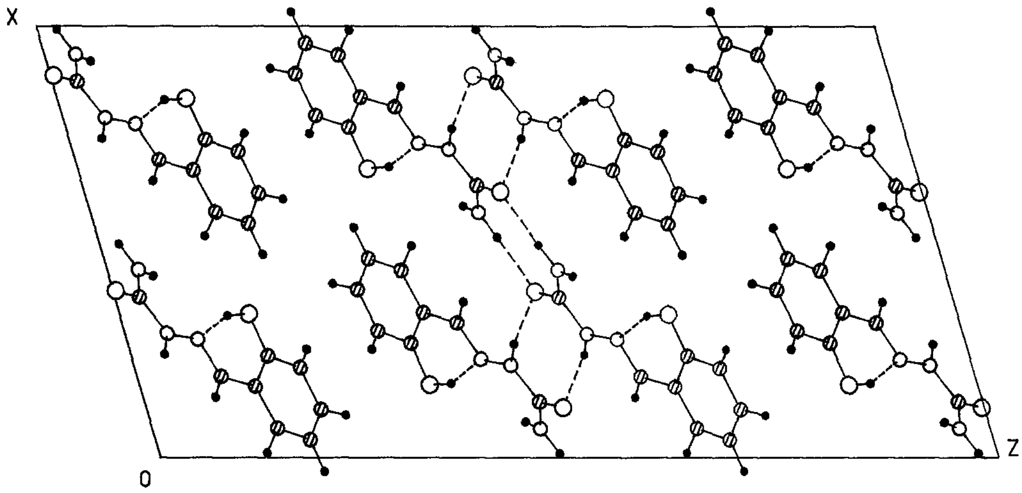

Fig. 2. Packing arrangement of the molecules

Table 1. Final positional parameters and equivalent isotropic temperature factors with e.s.d.'s in parentheses. $B_{eq} = 4/3 \sum_i \sum_j a_i \cdot a_j \beta_{ij}$

	x	y	z	B_{eq}(Å^2)
O 1	0.3315 (1)	1.0944 (4)	0.65414 (9)	6.6 (1)
O 2	0.3844 (1)	0.3224 (3)	0.50354 (7)	5.12 (7)
N 1	0.2725 (1)	0.7081 (3)	0.58452 (7)	4.00 (7)
N 2	0.2865 (1)	0.5160 (4)	0.55055 (7)	4.43 (8)
N 3	0.4333 (1)	0.7140 (4)	0.53726 (8)	4.44 (8)
C 1	0.1646 (2)	0.8829 (4)	0.63731 (8)	3.91 (8)
C 2	0.2351 (2)	1.0743 (4)	0.66249 (9)	4.35 (9)
C 3	0.2075 (2)	1.2466 (5)	0.6975 (1)	5.4 (1)
C 4	0.1108 (2)	1.2315 (5)	0.7075 (1)	5.6 (1)
C 5	0.0411 (2)	1.0446 (6)	0.6844 (1)	5.5 (1)
C 6	0.0674 (2)	0.8715 (5)	0.64943 (9)	4.8 (1)
C 7	0.1881 (2)	0.6983 (4)	0.60020 (9)	4.08 (9)
C 8	0.3705 (2)	0.5130 (4)	0.52947 (8)	3.96 (9)
H 1	0.328 (2)	0.939 (6)	0.628 (1)	8.4 (7)
H 2	0.238 (2)	0.395 (4)	0.540 (1)	4.8 (5)
H 3	0.250 (2)	1.365 (5)	0.711 (1)	6.3 (6)
H 3 A	0.491 (2)	0.711 (4)	0.5231 (9)	4.8 (4)
H 3 B	0.418 (2)	0.855 (5)	0.553 (1)	5.7 (5)
H 4	0.098 (2)	1.340 (5)	0.735 (1)	7.1 (6)
H 5	−0.032 (2)	1.029 (5)	0.691 (1)	6.1 (5)
H 6	0.011 (1)	0.727 (3)	0.6284 (6)	1.4 (2)
H 7	0.140 (2)	0.563 (4)	0.586 (1)	4.7 (4)

calization, due to the presence of the aryl group. The oxygen compounds appear to interact poorly with the aryl group, as has been pointed out by Palenik [17].

Table 2. Bond lengths (Å) and angles (deg) for non-H atoms with e.s.d.'s in parentheses

O1−C2	1.353 (3)	O2−C8	1.243 (2)
N1−C7	1.284 (3)	N1−N2	1.371 (2)
N2−C8	1.358 (3)	N3−C8	1.327 (3)
C1−C2	1.394 (3)	C1−C6	1.401 (3)
C1−C7	1.446 (3)	C2−C3	1.388 (3)
C3−C4	1.371 (4)	C4−C5	1.365 (4)
C5−C6	1.380 (3)		
C7−N1−N2	116.4 (2)	C8−N2−N1	121.4 (2)
N1−C7−C1	122.5 (2)	O2−C8−N3	123.1 (2)
N3−C8−N2	118.5 (2)	O2−C8−N2	118.4 (2)
C2−C1−C6	117.9 (2)	C2−C1−C7	122.8 (2)
C6−C1−C7	119.3 (2)	O1−C2−C3	118.2 (2)
O1−C2−C1	121.7 (2)	C3−C2−C1	120.1 (2)
C4−C3−C2	120.3 (2)	C5−C4−C3	120.9 (2)
C4−C5−C6	119.4 (2)	C5−C6−C1	121.4 (2)

Table 3. A comparison of the distances found in salicyclaldehyde semicarbazone and related compounds

Compound	C(7)−N(1)	N(1)−N(2)	N(2)−C(8)	C(8)−O(2)	C(8)−N(3)
Urea [13]				1.326 (6)	1.270 (7)
ASC [9]	1.278 (3)	1.385 (2)	1.361 (3)	1.242 (2)	1.328 (3)
BSC [9]	1.278 (3)	1.378 (3)	1.370 (3)	1.239 (3)	1.331 (3)
SASC	1.284 (3)	1.371 (2)	1.358 (3)	1.243 (2)	1.327 (3)
SATSC [10]	1.276 (3)	1.380 (4)	1.346 (4)	[a]	1.317 (4)
HAT [12]	1.297 (3)	1.392 (3)	1.334 (3)	[a]	1.322 (3)
MeOPhTSC [11]	1.267 (9)	1.388 (9)	1.339 (10)	[a]	1.333 (9)
ATSC [14]	1.286 (7)	1.398 (6)	1.342 (6)	[a]	1.344 (3)

[a] Contains a C−S rather than a C−O bond

Table 4. Selected distances (Å) and σ−π bond orders

	SASC		
Bond	Distance	σ	π
C(7)−N(1)	1.285 (3)	0.948	1.001
N(1)−N(2)	1.372 (3)	0.906	0.088
N(2)−C(8)	1.359 (3)	0.819	0.177
C(8)−N(3)	1.326 (3)	0.884	0.263
C(8)−O(2)	1.241 (3)	0.957	0.692
O(1)−H(1)	1.02 (3)	0.856	
H(1)...N(1)	1.68 (3)	0.015	

Table 5. Hydrogen bonds in *SASC*

D–H...*A*	Position of *A*	*D*–H	H...*A*	*D*...*A*	<*D*=H...*A*
N(3)–H(3A)..O(2)	1-*x*, 1-*y*, 1-*z*	0.93 (2)	1.95 (2)	2.880 (2)	175.4 (2)
N(2)–H(2)...O(2)	1/2-*x*, 1/2-*y*, 1-*z*	0.89 (2)	2.03 (3)	2.895 (2)	163.3 (2)
O(1)–H(1)...N(1)	*x*, *y*, *z*	1.04 (3)	1.67 (3)	2.659 (3)	157.5 (2)

The crystal structure contains both intra- and intermolecular hydrogen bonds. The dimensions of the hydrogen bonds are summarized in Table 5. The conformation of the semicarbazone fragment is such that the imine N atom is oriented in a way to form an intermolecular hydrogen bond between N(1) and the H atom from the O(1)–H hydroxyl group of the salicylidene part of the molecule, resulting in the formation of a planar six-member ring. In addition, there are two polar H atoms on the semicarbazone fragment, one on N(2) and the other on N(3) participating on the hydrogen bond scheme.

A comparative theoretical study of the electronic structure between *SC* and *TSC* is under progress and will be published elsewhere.

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