

All of the above chemical factors, as well as geometric considerations, must be taken into account when attempting to relate pharmacological activity to stereochemical parameters.

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The Structure of 2,6-Dimethylpiperidinium Dithiosalicylate. X-ray Diffraction Study at 200 K and Neutron Diffraction Study at 20 K

BY PATRICK VAN ROEY* AND K. ANN KERR†

Departments of Chemistry and Physics, The University of Calgary, Calgary, Alberta, Canada T2N 1N4

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Abstract

2,6-Dimethylpiperidinium dithiosalicylate, $C_7H_{16}N^+ \cdot C_7H_5OS_2^-$, orthorhombic, $Pna2_1$, $Z = 4$, $a = 13.966$ (4), $b = 10.894$ (3), $c = 10.252$ (3) Å, $d_c = 1.207$, $d_m = 1.227$ Mg m⁻³, $V = 1559.8$ Å³ at 293 K. The X-ray structure at 200 K ($R = 0.0439$, $R_w = 0.0474$ for 1809 reflections) is compared with the neutron diffraction results at 20 K ($R = 0.080$, $R_w = 0.077$ for 1214 reflections). The ions are linked by one normal NH...S hydrogen bond and one symmetrically bifurcated NH...S hydrogen bond. The dithiosalicylate ion contains a very short OH...S hydrogen bond with an O...S distance of 2.848 (4) Å (X-ray). This is the shortest hydrogen bond of this class so far observed.

Introduction

In the course of their spectroscopic studies of thioamides, Fulea & Krueger (1977) used the Wilgerodt-Kindler reaction to prepare a number of compounds.

The reaction mixture contains the appropriate aldehyde and amine, and elemental sulphur. The reaction of 2,6-dimethylpiperidine with salicylaldehyde in the presence of elemental sulphur produced a dark-red compound with a yield of about 5%. The compound was thought to be 1-(2'-hydroxythiobenzoyl)-2,6-dimethylpiperidine. It had been anticipated that the steric hindrance introduced by the two methyl groups would rotate the piperidine ring out of the plane of the *o*-hydroxythiobenzoyl group. This would be the first reported example of a thioamide with no conjugation between the nitrogen lone pair and the thiocarbonyl and would provide a model for the transition state for rotation about the C–N bond in compounds of this type.

Spectroscopic data seemed consistent with this interpretation. Both IR and NMR data showed the presence of a strong intramolecular hydrogen bond. NMR signals from the N–CH protons remained coalesced even at low temperatures. However, crystal structure analysis has shown the compound to be the 2,6-dimethylpiperidinium salt of dithiosalicylic acid. Although xanthic (ROCS₂H) and dithiocarbamic (R₂NCS₂H) acids are commonly used as ligands in organic chemistry, dithio acids are seldom encountered; however, known examples are dark red in colour. A standard method of synthesis (Reid, 1962) involves

* Present address: Molecular Biophysics Department, Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, NY 14203, USA.

† To whom correspondence should be addressed.

reaction of the corresponding aldehyde with ammonium polysulphide. This would be a probable side-reaction of the Wilgerodt–Kindler synthesis.

Experimental

The crystals were grown by slow evaporation of benzene solutions. Both space groups $Pna2_1$ and $Pnma$ were consistent with the systematic absences observed on Weissenberg and precession photographs. The non-centrosymmetric space group $Pna2_1$ was selected on the basis of E statistics.

X-ray diffraction

The crystals diffracted poorly at room temperature. Therefore, the data were collected at approximately 200 K with a Cryo-Tip low-temperature apparatus (Air Products and Chemicals, Inc.). As described by Rudman (1976), the thermocouple read-out of this apparatus does not correspond exactly to the temperature of the sample, but it was considered sufficient to know that the temperature did not vary by more than ± 1 K during the course of the experiment.

The data were collected on a Picker FACS-1 diffractometer, using Mo $K\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$) with a graphite monochromator. A crystal of approximate dimensions $0.13 \times 0.20 \times 0.30 \text{ mm}$ was cut from a longer one. The crystal data are listed in Table 1. The data were collected in the $\theta/2\theta$ scan mode with a scan rate of 1° min^{-1} and a scan width of $\Delta 2\theta = (1.4 + 0.692 \tan \theta)^\circ$. Backgrounds were measured for 20 s at either end of the scan. Of the 2056 independent reflections measured in the range $2.0^\circ \leq 2\theta \leq 57^\circ$, 1363 reflections had intensity greater than $3\sigma(I)$, where $\sigma(I) = (I + k^2 B + 0.02 I^2)^{1/2}$, I is the peak count, B is the background count and k is the normalization factor. Lorentz and polarization corrections were applied to the data, but no absorption correction was included ($\mu = 0.328 \text{ mm}^{-1}$). Atomic scattering factors and anomalous-dispersion correction terms were taken from *International Tables for X-ray Crystallography* (1974).

Table 1. Crystal data for DMP–DTS

	$C_{14}H_{21}NOS_2$, $M_r = 283.46$, space group $Pna2_1$, $Z = 4$		
	293 K	200 K	20 K
	X-ray	X-ray	Neutron
	$\lambda = 0.71069 \text{ \AA}$	$\lambda = 0.71069 \text{ \AA}$	$\lambda = 1.1173 \text{ \AA}$
a (Å)	13.966 (4)	13.949 (6)	13.831 (3)
b (Å)	10.894 (3)	10.744 (5)	10.465 (3)
c (Å)	10.252 (3)	10.241 (4)	10.212 (2)
V (Å ³)	1559.8	1534.5	1478.1
μ (mm ⁻¹)		0.328	0.2400
d_x (Mg m ⁻³)	1.207	1.226	1.274
d_m (Mg m ⁻³)	1.227	–	–

The structure was solved by direct methods, using the program system *QTAN* at the Medical Foundation of Buffalo (Langs & DeTitta, 1975) with evaluation of the phase sets by the NQUEST figure-of-merit (DeTitta, Edmonds, Langs & Hauptman, 1975).

The structure was refined by full-matrix least squares. The function minimized was $\sum w(\Delta F)^2$ where $w = [4\sigma(I)^2 + 0.0004F^2]^{-1}$ for the 1809 reflections included in the refinement. Weak reflections with $F_{\text{calc}} < F_{\text{obs}}$ were given $w = 0$. The z coordinate of atom S(1) was fixed to define the origin in the c direction of the polar space group. The H atoms were refined only after the anisotropic refinement of the heavier atoms had converged. The extinction parameter refined to $g = 2.8(6) \times 10^{-4}$ (Larson, 1967). The standard deviation of an observation of unit weight is 1.032. The final residuals, weighted and unweighted, for the reflections used in the refinement are 0.0474 and 0.0439 respectively. The final unweighted residual for all 2056 reflections is 0.0826.* The final atomic coordinates are listed in Table 2.

Neutron diffraction

The crystal used for the data collection had a volume of approximately 1.30 mm^3 . The data were collected on an automated four-circle diffractometer at the Brookhaven High Flux Beam Reactor. The incident beam was monochromated by reflection from the (002) plane of a beryllium crystal. The selected wavelength of

* See deposition footnote.

Table 2. Atomic coordinates ($\times 10^4$) for DMP–DTS: X-ray data at 200 K

E.s.d. of U_{eq} approximately $1 \times 10^3 \text{ \AA}^2$ for S; $3 \times 10^3 \text{ \AA}^2$ for others.
 $U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$

	x	y	z	U_{eq} (Å ² × 10 ³)
S(1)	855 (1)	6020 (1)	4022 (†)	48
S(2)	1372 (1)	4708 (2)	1632 (2)	44
O	3384 (3)	4259 (3)	1600 (4)	76
C(1)	1715 (3)	5426 (4)	3038 (4)	44
C(2)	2744 (3)	5527 (4)	3395 (4)	41
C(3)	3495 (3)	4928 (4)	2714 (5)	52
C(4)	4437 (3)	5021 (5)	3174 (6)	60
C(5)	4665 (3)	5713 (4)	4240 (6)	64
C(6)	3942 (3)	6355 (5)	4886 (5)	44
C(7)	3011 (3)	6246 (4)	4472 (4)	64
N	–1006 (2)	5416 (3)	1958 (3)	45
C(8)	–1513 (4)	4750 (5)	3046 (5)	61
C(9)	–1106 (4)	3474 (6)	3172 (6)	65
C(10)	–2588 (4)	4778 (5)	2814 (6)	73
C(11)	–2961 (4)	6067 (6)	2519 (7)	88
C(12)	–2398 (4)	6687 (4)	1456 (6)	65
C(13)	–1339 (3)	6733 (4)	1723 (5)	49
C(14)	–738 (4)	7325 (4)	674 (5)	72

† Not refined.

1.1173 (1) Å was calibrated against a standard KBr crystal ($a = 6.6000$ Å). A temperature of 20.0 ± 0.5 K was maintained by means of a DISPLEX closed-cycle helium refrigerator (Air Products and Chemicals, Inc.).

The cell dimensions (Table 1) were determined from the least-squares refinement of the 2θ angles of 32 reflections in the range $34^\circ < 2\theta < 48^\circ$. The data were collected in a $\theta/2\theta$ step-scan mode. Reflections with $2\theta \leq 50^\circ$ were measured with a fixed scan width of 3.0° with 75 steps per scan (0.04° step size). For reflections with $2\theta > 50^\circ$ the scan width was varied with $\Delta 2\theta = 1.12^\circ + 4.75^\circ \tan \theta$. The number of steps per scan in this region was allowed to vary from 65 to 100 resulting in a step size ranging from 0.06 to 0.12° . In total, 1882 independent reflections were measured with $2\theta \leq 95^\circ$. Backgrounds were estimated from 10% of the steps at either end of the scan.

Lorentz and analytical absorption corrections were applied to the data. The linear absorption coefficient of $\mu = 0.2400 \text{ mm}^{-1}$ was calculated on the basis of an atomic mass-absorption coefficient for H of $(\mu/\rho)_{\lambda=1.1173 \text{ \AA}} = 25.218 \times 10^2 \text{ mm}^2 \text{ g}^{-1}$ (Koetzle & McMullan, 1979). The transmission coefficients ranged from 0.771 to 0.879.

Coordinates of the heavy atoms obtained from the refined X-ray structure were used to calculate structure factors for an inverted difference-Fourier map which revealed the positions of the H atoms. The atomic scattering lengths were taken from Koester (1977).

The refinement was based on F^2 with minimization of the function $\sum w(F_o^2 - kF_c^2)^2$, where $w = 1/\sigma^2(F^2)$ for the 1214 observed reflections [$F^2 > 3\sigma(F^2)$] and $w = 0$ for the unobserved reflections and $\sigma(F^2) = [\sigma^2(I) + (0.01F^2)^2]^{1/2}$. Some of the unobserved reflections were greatly affected by the broad aluminium lines caused by diffraction from the cryostat. Because of the small number of reflections, only the peripheral atoms (the H atoms and the methyl C atoms) were refined anisotropically. The z coordinate of the N atom was fixed in order to define the origin in the polar space group $Pna2_1$. The extinction parameter used was a type I isotropic extinction correction with Lorentzian distribution (Becker & Coppens, 1974) and refined to $g = 0.06(2) \times 10^{-4}$. The correction factor was applied to F_{calc}^2 and varied from 1.000 to 0.951.

The final values of the weighted and unweighted residuals based on F^2 were 0.077 and 0.080. The final atomic coordinates are listed in Table 3.* Bond lengths and angles are in Tables 4 and 5. A view of the ion pair is in Fig. 1.

* Tables of structure factors and anisotropic thermal parameters for both the X-ray and neutron structures, hydrogen atom coordinates (X-ray structure) and bond angles involving hydrogen atoms (neutron structure) have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36075 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. Atomic coordinates ($\times 10^4$) for DMP-DTS: neutron data at 20 K

E.s.d. of U_{eq} approximately $2 \times 10^3 \text{ \AA}^2$ for C; $5 \times 10^3 \text{ \AA}^2$ for H.
 $U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.

	x	y	z	U_{iso} ($\text{\AA}^2 \times 10^4$)
S(1)	847 (6)	5970 (8)	4000 (10)	53 (18)
S(2)	1341 (7)	4567 (9)	1605 (10)	141 (21)
O	3393 (4)	4264 (4)	1451 (6)	137 (10)
C(1)	1697 (3)	5340 (3)	2996 (5)	76 (8)
C(2)	2736 (3)	5467 (4)	3328 (5)	90 (8)
C(3)	3507 (3)	4898 (4)	2606 (5)	99 (9)
C(4)	4465 (3)	5001 (4)	3052 (5)	105 (8)
C(5)	4696 (3)	5699 (4)	4157 (5)	88 (9)
C(6)	3960 (3)	6313 (4)	4848 (5)	80 (8)
C(7)	3014 (3)	6184 (4)	4451 (5)	64 (8)
N	-1018 (2)	5442 (3)	1941 (†)	63 (6)
C(8)	-1542 (3)	4798 (4)	3030 (5)	93 (8)
C(10)	-2634 (3)	4840 (4)	2778 (5)	92 (9)
C(11)	-3007 (3)	6174 (4)	2453 (5)	104 (9)
C(12)	-2405 (3)	6782 (4)	1374 (5)	101 (9)
C(13)	-1332 (3)	6807 (4)	1679 (5)	65 (8)
				U_{eq} ($\text{\AA}^2 \times 10^3$)
C(9)	-1158 (3)	3457 (4)	3168 (6)	14
C(14)	-719 (3)	7383 (4)	610 (5)	10
H(1)	2682 (7)	4225 (9)	1274 (10)	27
H(2A)	-287 (6)	5447 (9)	2185 (8)	21
H(2B)	-1078 (6)	4920 (9)	1053 (9)	22
H(4)	5016 (6)	4503 (10)	2477 (10)	28
H(5)	5445 (6)	5787 (9)	4470 (10)	31
H(6)	4129 (7)	6913 (10)	5690 (10)	32
H(7)	2424 (7)	6640 (9)	4997 (10)	27
H(8)	-1366 (7)	5352 (9)	3904 (9)	27
H(9A)	-1309 (8)	2896 (10)	2308 (11)	37
H(9B)	-390 (7)	3472 (9)	3305 (11)	38
H(9C)	-1482 (8)	2974 (10)	4030 (11)	38
H(10A)	-2807 (6)	4179 (8)	1962 (10)	25
H(10B)	-2995 (6)	4437 (9)	3664 (9)	28
H(11A)	-2972 (7)	6779 (8)	3332 (9)	28
H(11B)	-3763 (6)	6128 (10)	2205 (10)	30
H(12A)	-2644 (7)	7779 (7)	1220 (10)	26
H(12B)	-2515 (6)	6259 (8)	443 (10)	24
H(13)	-1205 (6)	7291 (8)	2642 (8)	19
H(14A)	-842 (7)	6890 (9)	-323 (10)	30
H(14B)	-887 (7)	8395 (8)	502 (11)	30
H(14C)	58 (6)	7294 (10)	864 (10)	33

† Not refined.

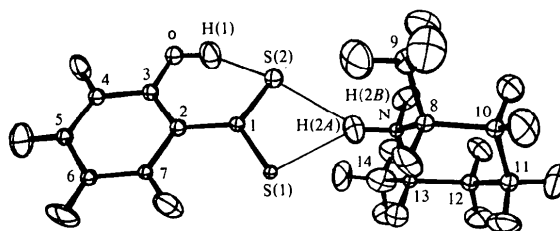


Fig. 1. ORTEP drawing (Johnson, 1965) of the ion pair whose coordinates are listed in Table 3, showing the numbering scheme used in the text. Neutron diffraction at 20 K. Thermal ellipsoids correspond to 70% probability.

Table 4. Bond lengths (Å) and angles (°) for DMP-DTS

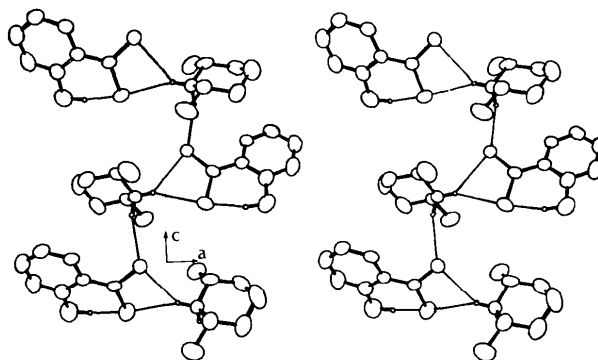
	Neutron	X-ray		Neutron	X-ray
S(1)—C(1)	1.693 (10)	1.692 (4)	S(1)—C(1)—S(2)	119.3 (5)	118.4 (2)
S(2)—C(1)	1.707 (11)	1.702 (5)	S(1)—C(1)—C(2)	119.9 (4)	120.8 (3)
C(1)—C(2)	1.483 (5)	1.485 (6)	S(2)—C(1)—C(2)	120.8 (5)	120.8 (3)
C(2)—C(3)	1.426 (6)	1.413 (6)	C(1)—C(2)—C(3)	124.7 (4)	124.2 (4)
C(2)—C(7)	1.423 (6)	1.397 (6)	C(1)—C(2)—C(7)	119.5 (4)	119.5 (4)
C(3)—O	1.363 (8)	1.358 (6)	C(3)—C(2)—C(7)	115.8 (4)	116.3 (4)
C(3)—C(4)	1.405 (6)	1.400 (7)	C(2)—C(3)—O	124.4 (4)	124.8 (4)
C(4)—C(5)	1.382 (7)	1.358 (8)	C(2)—C(3)—C(4)	120.3 (4)	119.8 (5)
C(5)—C(6)	1.396 (6)	1.390 (7)	O—C(3)—C(4)	115.3 (4)	115.3 (4)
C(6)—C(7)	1.377 (6)	1.371 (6)	C(3)—C(4)—C(5)	121.6 (4)	122.0 (5)
N—C(8)	1.488 (5)	1.502 (6)	C(4)—C(5)—C(6)	119.2 (4)	119.0 (4)
N—C(13)	1.517 (5)	1.508 (5)	C(5)—C(6)—C(7)	119.9 (4)	119.8 (5)
C(8)—C(9)	1.507 (6)	1.489 (8)	C(6)—C(7)—C(2)	123.1 (4)	123.0 (4)
C(8)—C(10)	1.533 (6)	1.518 (7)	C(8)—N—C(13)	114.7 (3)	114.9 (3)
C(10)—C(11)	1.525 (6)	1.510 (9)	N—C(8)—C(9)	108.7 (3)	108.8 (4)
C(11)—C(12)	1.521 (7)	1.499 (9)	N—C(8)—C(10)	109.9 (3)	109.9 (4)
C(12)—C(13)	1.517 (6)	1.503 (7)	C(9)—C(8)—C(10)	112.9 (3)	114.1 (5)
C(13)—C(14)	1.508 (6)	1.504 (7)	C(8)—C(10)—C(11)	113.3 (3)	113.0 (4)
			C(10)—C(11)—C(12)	110.8 (3)	111.9 (5)
			C(11)—C(12)—C(13)	113.1 (4)	113.4 (5)
			C(12)—C(13)—C(14)	114.1 (4)	115.6 (4)
			C(12)—C(13)—N	107.5 (3)	107.5 (3)
			C(14)—C(13)—N	110.0 (3)	109.8 (4)

Table 5. Bond lengths (Å) involving hydrogen in DMP-DTS

	Neutron	X-ray
O—H(1)	1.000 (11)	0.99 (5)
C(4)—H(4)	1.094 (10)	0.93 (4)
C(5)—H(5)	1.088 (10)	0.97 (4)
C(6)—H(6)	1.090 (11)	0.86 (4)
C(7)—H(7)	1.098 (10)	1.00 (3)
N—H(2A)	1.042 (8)	0.91 (4)
N—H(2B)	1.062 (9)	0.96 (4)
C(8)—H(8)	1.091 (10)	0.92 (4)
C(9)—H(9A)	1.076 (12)	1.08 (5)
C(9)—H(9B)	1.073 (11)	0.86 (4)
C(9)—H(9C)	1.109 (12)	0.76 (4)
C(10)—H(10A)	1.108 (10)	1.07 (4)
C(10)—H(10B)	1.116 (10)	0.93 (5)
C(11)—H(11A)	1.099 (10)	0.96 (5)
C(11)—H(11B)	1.078 (10)	0.95 (5)
C(12)—H(12A)	1.105 (9)	1.04 (4)
C(12)—H(12B)	1.107 (11)	1.10 (3)
C(13)—H(13)	1.120 (10)	0.94 (4)
C(14)—H(14A)	1.097 (11)	0.85 (5)
C(14)—H(14B)	1.090 (9)	0.91 (5)
C(14)—H(14C)	1.109 (10)	1.06 (5)

Discussion

A dominant feature of the structure is the hydrogen-bonding network which links the ions into chains running parallel with the *c* axis of the unit cell. The ion pairs are oriented so that the plane defined by N, C(8), C(13) of the 2,6-dimethylpiperidinium cation is almost perpendicular to the plane of the dithiosalicylate anion. The equatorial hydrogen, H(2A), on N is involved in a bifurcated hydrogen bond with the two S atoms of the

Fig. 2. Stereoview of the interionic hydrogen-bonding scheme in DMP-DTS viewed perpendicular to the *ac* plane.

dithiosalicylate anion, while the axial hydrogen, H(2B), is hydrogen bonded to S(1) of the anion at $-x, 1-y, \frac{1}{2}-z$. The resulting chain is illustrated in Fig. 2.

Dimensions of the N—H...S hydrogen bonds as determined by X-ray and neutron diffraction are shown in Figs. 3 and 4, respectively. The unusual feature observed here is that the bifurcated hydrogen bond is very nearly symmetrical. A recent review (Olovsson & Jönsson, 1976) shows that most N—H...O bifurcated hydrogen bonds can be regarded as the combination of a normal hydrogen bond and a very weak N—H...O interaction with the H...O separation of the latter approaching the van der Waals limit of 2.4 Å.

The interionic bonding scheme observed in the title compound (DMP-DTS) is similar to that observed in pyrrolidinium 1-pyrrolidinecarbodithioate, P-PCDT

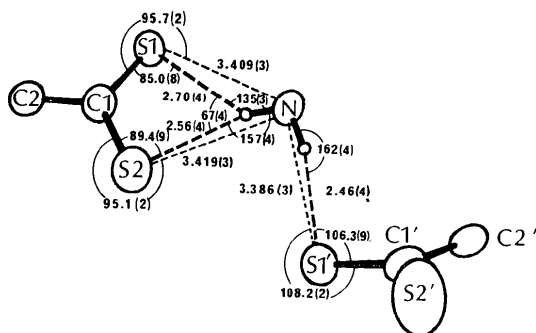


Fig. 3. Interionic hydrogen bonding. X-ray data at 200 K. (Distances in Å and angles in deg here and in Figs. 4–6.)

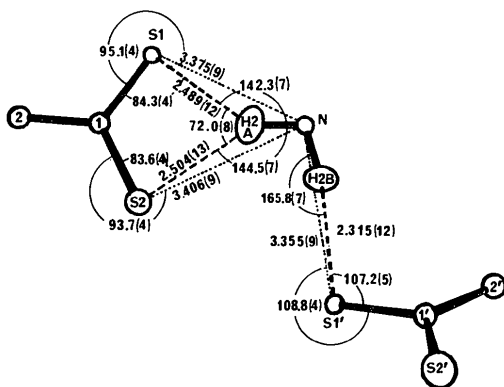


Fig. 4. Interionic hydrogen bonding. Neutron data at 20 K.

(Wahlberg, 1979), in that two active H atoms are donated by one N atom to form one normal and one bifurcated hydrogen bond with the dithiocarboxylate group, but the additional OH...S hydrogen bond in the dithiosalicylate anion results in some interesting differences.

In the P-PCDT example, H(1) lies roughly in the plane of the dithiocarboxylate group and forms an unsymmetrically bifurcated hydrogen bond with S(1) the acceptor for the shorter bond and S(2) the acceptor for the longer bond with an N...S distance near the van der Waals limit of 2.85 Å: H(1)...S(1), 2.51 (4); N...S(1), 3.223 (3) Å; H(1)...S(2), 2.84 (4); N...S(2), 3.432 (3) Å. However, S(1) also acts as acceptor for a normal hydrogen bond of length H(2)...S(1), 2.51 (4) [N...S(1), 3.297 (3) Å]. The hydrogen-bonding directions lie in the plane of the dithiocarboxylate group and perpendicular to that plane and hence correspond to directions of the σ and π orbitals on the S atom. It seems reasonable to rationalize the hydrogen-bonding scheme in both P-PCDT and DMP-DTS in terms of orbital stabilization.

Since H(1) of P-PCDT lies roughly in the plane of the dithiocarboxylate anion its σ orbital would be expected to overlap with the σ orbitals of the S atoms. The additional interaction H(2) with S(1) produces an inequivalence between the two S atoms with the long

1.732 (2) Å C–S distance associated with the acceptor for the two hydrogen bonds and the short 1.706 (3) Å distance associated with the weak interaction.

In DMP-DTS, we have an analogous situation with S(1) acting as acceptor for a 'normal' hydrogen bond from H(2B), the axial H from N, while the equatorial hydrogen H(2A) lies in the equatorial plane between the two S atoms. However, S(2) is involved in a very short intramolecular OH...S hydrogen bond which is almost collinear with the N–H(2A)...S(2) interaction. The OH...S bond stabilizes the σ orbital of S(2) with respect to the π orbital and so enhances the N–H(2A)...S(2) interaction. The result is a fortuitous near-equivalence of both the N–H...S distances of the bifurcated hydrogen bond and the C–S distances of the dithiocarboxylate moiety.

Dimensions of the intramolecular hydrogen bond in the dithiosalicylate anion as determined by X-rays and neutrons are shown in Figs. 5 and 6. The geometry of the OH...S hydrogen bond is essentially the same in the X-ray structure at 200 K and in the neutron structure at 20 K. The O...S separation is nearly 0.4 Å shorter than the sum of the van der Waals radii. Comparison with O...O separations in 'very short' hydrogen bonds suggests that this must be among the

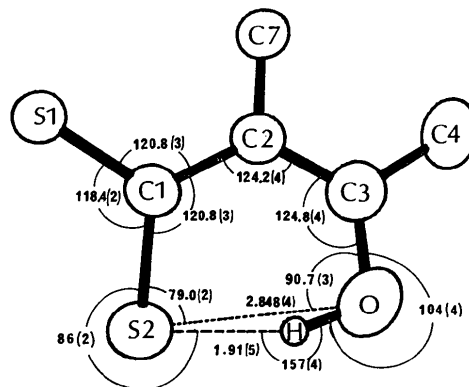


Fig. 5. Geometry of the intramolecular OH...S hydrogen bond. X-ray data at 200 K.

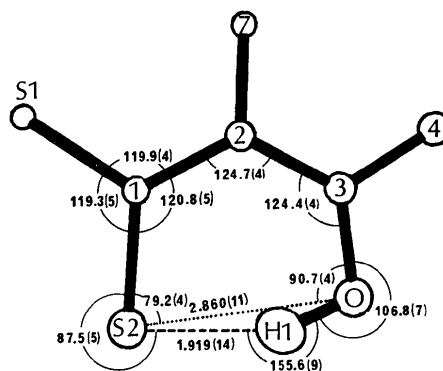


Fig. 6. Geometry of the intramolecular OH...S hydrogen bond. Neutron data at 20 K.

Table 6. Neutron diffraction studies of O—H(D)···S hydrogen bonds

	O···S	O—H	H···S	∠O—H···S	Reference
BaS ₂ O ₃ ·H ₂ O	3.298 (4)	0.960 (5)	2.367 (4)	163.0 (3)	Manojlović-Muir (1975)
Na ₂ S ₂ O ₃ ·5H ₂ O	3.351 (3)	0.958 (4)	2.399 (4)	172.1 (3)	Lisensky & Levy (1978)
	3.337 (3)	0.960 (4)	2.390 (4)	168.4 (3)	
	3.336 (3)	0.956 (4)	2.418 (5)	160.8 (3)	
	3.359 (3)	0.956 (4)	2.408 (4)	172.8 (3)	
Na ₂ SbS ₄ ·9D ₂ O	3.343 (6)	0.967 (4)	2.379 (6)	175.4 (4)	Mereiter, Preisinger & Guth (1979)
	3.358 (6)	0.959 (5)	2.408 (7)	173.9 (4)	
	3.319 (6)	0.961 (5)	2.362 (6)	173.2 (4)	
C ₁₂ H ₁₅ NOS(HTBP)	3.214 (5)	0.975 (5)	2.262 (6)	165.2 (4)	Van Roey & Kerr (1981)
DMP—DTS	2.860 (11)	1.000 (11)	1.919 (14)	155.6 (9)	This work

shortest possible hydrogen bonds of this type. It is certainly much shorter than other OH···S hydrogen bonds in the literature (Table 6).

It is unusual for a hydrogen bond to be described as strong when the angle subtended at H is 155.6 (9)°. However, the long OH distance [1.00 (1) Å], the short H···S contact [1.92 (1) Å] and the infrared spectroscopic evidence [$\nu_{\text{OH}\cdots\text{S}} < 3000 \text{ cm}^{-1}$ in $3 \times 10^{-3} \text{ M CCl}_4$ (Fulea & Krueger, 1977)] all confirm that this is a very strong bond of its type. In contrast, the intramolecular hydrogen bond in salicylic acid (Bacon & Jude, 1973) has been shown to be a weak bond. The major difference in hydrogen-bonding geometry between the two molecules is that in the dithiosalicylate the H···S bonding direction lies along the axis of an orbital on S while in salicylic acid there is a substantial angle between the O···H direction and the lone-pair orbital on O. This observation is in agreement with the suggestion (Desmeules & Allen, 1980) that the angle that is important in determining the energy of a hydrogen bond is the angle between the line H···acceptor and the axis of the lone pair on the acceptor molecule.

The dithiosalicylate anion is significantly non-planar. The torsional angle (Table 7) between the dithiocarboxylate group and the phenyl ring is about 7° at 200 K and is reduced to about 4° at 20 K. Three short non-bonded contacts are relieved by this rotation: S(2)···C(3), S(1)···C(7) and S(1)···H(7) [X-ray: 3.170 (5), 3.053 (4) and 2.67 (3) Å; neutron:

3.183 (10), 3.040 (9) and 2.506 (13) Å]. Steric demands of the S atoms are likely responsible for increasing the torsional angle from the values of 3.1° in nicotinylic salicylate (Kim & Jeffrey, 1971) and 1.1° in salicylic acid (Sundaralingam & Jensen, 1965).

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Table 7. Torsional angles (°) for DMP—DTS

	Neutron (20 K)	X-ray (200 K)
S(1)—C(1)—C(2)—C(3)	175.3 (5)	172.0 (4)
S(1)—C(1)—C(2)—C(7)	−3.8 (6)	−7.7 (6)
S(2)—C(1)—C(2)—C(3)	−4.8 (7)	−7.8 (6)
S(2)—C(1)—C(2)—C(7)	176.1 (5)	172.5 (6)
C(1)—C(2)—C(3)—O	6.3 (7)	4.7 (7)
C(7)—C(2)—C(3)—O	−174.6 (4)	−175.6 (4)
C(5)—C(4)—C(3)—O	175.2 (4)	176.6 (5)
C(4)—C(3)—O—H(1)	177.3 (7)	
C(2)—C(3)—O—H(1)	4.5 (8)	

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Structure of Thyroxine: Role of Thyroxine Hydroxyl in Protein Binding

BY VIVIAN CODY

Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, New York 14203, USA

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Abstract

The crystal and molecular structures of thyroxine (3,5,3',5'-tetraiodo-L-thyronine, T_4) have been accurately determined from an X-ray diffraction study on crystals of a T_4 -*N*-diethanolamine (NDEA) salt $[\text{C}_{15}\text{H}_{10}\text{I}_4\text{NO}_4]^- \cdot [\text{C}_4\text{H}_{12}\text{NO}_2]^+$. There are two independent thyroxine conformations in the crystal: *cisoid* and *transoid*. This is the first observation of both conformers in the same crystal. The geometry of the thyroxine 4'-oxygen is consistent with phenoxide-ion formation: short C(4')–O(4') bond length, contraction of the C(3')–C(4')–C(5') angle and expansion of the C(3') and C(5') angles. The amino-acid function is a zwitterion. The conformations of the amino-acid side chain with respect to the inner phenyl ring differ significantly between the two T_4 molecules; one is nearly perpendicular, normal for aromatic amino acids, while the other is nearly coplanar, an unusual observation among thyroid-hormone structures. The crystal structure shows a directional specificity of the hydrogen bonds and illustrates specific hydrogen-bonding patterns between the thyroid hormones, thyroxine and triiodothyronine. This structure determination reveals geometrical and conformational differences consistent with the degree of iodination and ionization state of the 4'-OH which may explain protein-binding differences among thyroactive compounds. The crystals are triclinic, space group $P1$, $Z = 2$, with $a = 7.842$ (1), $b = 14.108$ (2), $c = 12.194$ (2) Å, $\alpha = 95.67$ (1), $\beta = 108.47$ (1), $\gamma = 77.45$ (1)°, $V = 1248.4$ Å³, $M_r = 881.97$, $D_c = 2.35$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu = 5.08$ mm⁻¹. Final $R = 0.039$ for 4573 observed reflections.

Introduction

Thyroid-hormone-protein binding is central to the transport, distribution in tissue, and metabolic rates of the various thyroid hormones, analogues and precursors. Specifically, the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) bind to three classes of proteins: plasma proteins which transport the hormones through the general circulation, membrane-bound proteins which interact with the hormones at the cell surface, and nuclear proteins through which hormonal activity is expressed (Jorgensen, 1978). Since thyroid-hormone binding is postulated to involve hydrogen-bond formation through the 4'-OH, the nature of these intermolecular interactions is of importance. Theoretical energy calculations of the hydrogen-bond strengths of *ortho*-substituted phenols and phenoxides were computed (Dietrich, Jorgensen, Kollman & Rothenberg, 1976; Andrea, Dietrich, Murray, Kollman, Jorgensen & Rothenberg, 1979) in order to predict likely orientations of the thyroid hormones at their binding sites. These studies predict an average O...O distance of 2.63 Å and a C–O...O angle of 125°, irrespective of whether the 4'-OH is acting as a hydrogen-bond donor or acceptor.

The acidity of the 4'-OH increases with *ortho* iodine substitution and has values of 6.73 and 8.45 for T_4 and T_3 respectively. At physiological pH the phenolic hydroxyl of T_4 is about 80% ionized whereas in T_3 it is only about 10% ionized (Korcek & Tabachnick, 1976). In previous crystal-structure determinations of T_3 , the 4'-oxygen has been consistently observed as a hydroxyl group (Cody, 1979*a*). However, in previous studies of thyroxine (Camerman & Camerman, 1974*a*), the