

## The Crystal Structure of 2'-Deoxy-6-thioguanosine Monohydrate

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$C_{10}H_{13}N_5O_3 \cdot H_2O$ , FW 301.3, orthorhombic,  $C222_1$ ,  $a = 12.389$  (3),  $b = 6.871$  (1),  $c = 32.586$  (6) Å,  $Z = 8$ ,  $D_x = 1.443$  g cm $^{-3}$ ,  $\mu(\text{Cu } K\alpha) = 21.7$  cm $^{-1}$ . Thioguanine bases are joined by N(1)H...N(7) and N(2)H...S hydrogen bonds and are assembled in parallel stacks involving sulfur–purine contacts. The crystal structure is almost identical to that of 6-thioguanosine monohydrate.

### Introduction

The purine analog 2'-deoxythioguanosine was first synthesized by Iwamoto, Acton & Goodman (1963) as a possible alternative to the antitumor agent thioguanine. Cellular resistance to thioguanine was thought to result from loss of cellular ability to reduce the riboside to the deoxyriboside, thereby preventing incorporation of the analog into DNA. Deoxythioguanosine by-passes resistance to thioguanine in certain systems (LePage, Junga & Bowman, 1964; LePage, 1968). It is possible that the biological activity of thioguanine might be related to the effects exerted by the S substituent on hydrogen-bond dimensions within nucleic acids (Bugg & Thewalt, 1970). We determined the crystal structure of deoxythioguanosine to gather additional information concerning the influence of S substituents on the hydrogen-bonding properties of thioguanine derivatives. Evaporation of a water–dimethylamine solution at room temperature yielded pale-yellow crystals. Oscillation and Weissenberg photographs showed Laue symmetry  $mmm$  and the systematic absences  $hkl$ :  $h + k$  odd and  $00l$ :  $l$  odd, indicating space group  $C222_1$ . A crystal with dimensions  $0.11 \times 0.16 \times 0.10$  mm was mounted on a Picker FACS-1 diffractometer with the crystal  $b$  axis inclined by  $4^\circ$  to the  $\phi$  axis of the goniostat. Unit-cell dimensions were calculated from a least-squares fit to the  $2\theta$  values (Cu  $K\alpha_1$ ,  $\lambda = 1.54051$  Å) of 20 reflections in the range  $70^\circ < 2\theta < 128^\circ$ . Intensity data for 1330 independent reflections ( $2\theta < 128^\circ$ ) were collected on the diffractometer with a scintillation counter, Ni-filtered Cu radiation, and a  $\theta$ – $2\theta$  scan mode. The scan speed was  $1^\circ \text{ min}^{-1}$ , and the  $2\theta$  scan width was based on  $1^\circ$  and was varied to allow for spectral dispersion. Stationary background counts of 20 s were recorded at each of the  $2\theta$  scan limits. Three reference reflections (400, 040, 0,0,10) that were monitored periodically showed no appreciable fluctuations during the data collection. The strongest reflections were remeasured at reduced tube currents to test for counter coincidence losses. Reflec-

tions that had scan counts below background level were assigned negative intensity values and were retained in all subsequent calculations. Variances of the intensities were estimated according to counting statistics plus the additional term  $(0.03S)^2$ , where  $S$  is the scan count. The intensities and their variances were corrected for Lorentz and polarization factors, and absorption corrections (transmission factors range from 0.766 to 0.826) were applied by using the computer program *ORABS* (Wehe, Busing & Levy, 1962). The data were then scaled by Wilson's (1942) method.

The crystal structure of deoxythioguanosine monohydrate is isomorphous with that of thioguanosine monohydrate (Thewalt & Bugg, 1972). A structure factor calculation using Thewalt & Bugg's coordinates for the 16 nonhydrogen atoms comprising the sugar and the substituted-purine rings gave  $R = 0.38$ . All other atoms, including hydrogens, were later identified from difference Fourier maps. The structure was refined using the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962). The quantity minimized was  $\sum w(F_o^2 - F_c^2/k^2)^2$ , where  $k$  is the scale factor and the weight  $w$  is equal to  $1/\sigma^2(F_o^2)$ . Atomic scattering factors for C, N, and O were from Doyle & Turner (1968); those for S were from Dawson (1960); and those for H were from Stewart, Davidson & Simpson (1965). Anomalous-dispersion components ( $\Delta f'$  and  $\Delta f''$ ) for C, N, O, and S were from Cromer & Liberman (1970). During the latter stages of refinement, limited core storage prevented simultaneous variation of all parameters, and the structure was divided into two parameter blocks that were refined alternately. One block included positional and thermal parameters for atoms of the thioguanine moiety; the other included parameters for atoms of the deoxyribose moiety. Both blocks contained, in addition, the atomic parameters for the water molecule, the scale factor  $k$ , and an isotropic extinction parameter  $g$  (Zachariasen, 1963; Coppens & Hamilton, 1970). Refinement was terminated when all parameter shifts were less than  $\frac{1}{6}$  of their estimated standard errors. A

final difference Fourier map contained residual density ranging from  $-0.20$  to  $+0.26 \text{ e } \text{Å}^{-3}$ . The agreement index  $R = \Sigma |F_o| - |F_c| / \Sigma |F_o|$  is  $0.04$ ; and the goodness-of-fit  $\{[\Sigma w(F_o^2 - F_c^2)^2 / (m - s)]^{1/2}\}$ , where  $m$  is the number of reflections and  $s$  is the number of parameters} is  $1.31$ . The final atomic parameters are in

Table 1. *Nonhydrogen-atom parameters* ( $\times 10^5$ )

Estimated standard deviations appear in parentheses.

|       | X          | Y           | Z           |
|-------|------------|-------------|-------------|
| S     | 16816 (6)  | 24387 (20)  | 4879 (2)    |
| N(1)  | 5350 (18)  | 25383 (59)  | -2045 (7)   |
| C(2)  | 3316 (22)  | 25996 (73)  | -6152 (8)   |
| N(2)  | -6966 (23) | 26604 (76)  | -7327 (9)   |
| N(3)  | 11139 (18) | 26100 (58)  | -8950 (6)   |
| C(4)  | 21061 (21) | 25494 (82)  | -7297 (8)   |
| C(5)  | 23782 (22) | 25169 (81)  | -3149 (8)   |
| C(6)  | 15503 (22) | 25056 (67)  | -231 (9)    |
| N(7)  | 34890 (19) | 25012 (56)  | -2701 (7)   |
| C(8)  | 38562 (25) | 25272 (99)  | -6487 (9)   |
| N(9)  | 30570 (17) | 25299 (59)  | -9411 (7)   |
| C(1') | 32137 (24) | 23980 (75)  | -13837 (8)  |
| O(1') | 37649 (24) | 6624 (41)   | -14678 (8)  |
| C(2') | 39002 (43) | 39826 (73)  | -15644 (12) |
| C(3') | 42876 (33) | 30459 (61)  | -19591 (10) |
| O(3') | 35306 (25) | 32053 (52)  | -22817 (8)  |
| C(4') | 43661 (34) | 9080 (64)   | -18421 (11) |
| C(5') | 55046 (35) | 1959 (76)   | -17720 (14) |
| O(5') | 55235 (24) | -18485 (47) | -17028 (8)  |
| O     | 14876 (33) | 17518 (56)  | -24062 (11) |

Table 2. *Hydrogen-atom parameters*

The thermal parameters are defined by the expression  $\exp[-8\pi^2 U \times \sin^2\theta/\lambda^2]$ . All values are  $\times 10^3$ . Estimated standard deviations appear in parentheses.

|         | X        | Y        | Z        | U        |
|---------|----------|----------|----------|----------|
| H(N1)   | 1 (2)    | 245 (7)  | -3 (1)   | 32 (8)   |
| H(N2)   | -124 (3) | 253 (8)  | -52 (1)  | 81 (12)  |
| H'(N2)  | -79 (3)  | 308 (6)  | -94 (1)  | 48 (13)  |
| H(C8)   | 460 (2)  | 239 (6)  | -73 (1)  | 34 (8)   |
| H(C1')  | 253 (2)  | 267 (6)  | -150 (1) | 29 (8)   |
| H(C2')  | 446 (3)  | 428 (7)  | -140 (1) | 73 (15)  |
| H'(C2') | 342 (3)  | 520 (5)  | -161 (1) | 53 (11)  |
| H(C3')  | 502 (3)  | 356 (5)  | -203 (1) | 46 (10)  |
| H(O3')  | 358 (3)  | 435 (6)  | -235 (1) | 42 (12)  |
| H(C4')  | 410 (3)  | 17 (5)   | -204 (1) | 48 (11)  |
| H(C5')  | 586 (3)  | 111 (6)  | -154 (1) | 69 (13)  |
| H'(C5') | 596 (3)  | 35 (6)   | -203 (1) | 79 (14)  |
| H(O5')  | 571 (3)  | -202 (6) | -144 (1) | 54 (11)  |
| H'      | 222 (4)  | 209 (10) | -231 (2) | 129 (23) |
| H       | 124 (5)  | 192 (10) | -217 (2) | 137 (28) |

Tables 1 and 2.\* The final value of the extinction parameter  $g$  is  $0.016 (2)$ .

## Discussion

The structure, conformation, and dimensions of the deoxythioguanosine molecule are shown in Fig. 1. The molecule exists in the crystal in the thiolactam form; this is the favored tautomer in crystals of other thiopurine and thiopyrimidine derivatives. The nine atoms of the purine ring are coplanar to within  $0.01$ – $0.02 \text{ Å}$ , while the substituent atoms S, N(2), and C(1') are displaced from the mean purine plane by  $-0.02$ ,  $0.03$ , and  $-0.13 \text{ Å}$  respectively. The pucker of the sugar ring is *C(2')-endo-C(1')-exo* or  ${}^2T_1$  (Sundaralingam, 1971); C(2') and C(1') are displaced by  $-0.41$  and  $0.19 \text{ Å}$ , respectively, from the plane defined by O(1'), C(3'), and C(4'). The torsion angle  $\varphi_{OO} = O(5')-C(5')-C(4')-O(1')$  is  $66.3^\circ$ , and the angle  $\varphi_{OC} = O(5')-C(5')-C(4')-C(3')$  is  $-174.4^\circ$ . Thus the conformation of the hydroxymethyl group with respect to the sugar ring is *gauche-trans* (Shefter & Trueblood, 1965). The relative orientation of the sugar and base at the glycosidic linkage is *anti* (Donohue & Trueblood, 1960), with the torsion angle  $O(1')-C(1')-N(9)-C(8)$  equal to  $58.6^\circ$ . There is good overall agreement between the bond lengths and angles of deoxythioguanosine (Fig. 1) and the corresponding values found for thioguanosine (Thewalt & Bugg, 1972). For example, the greatest difference in a bond length occurs in the C(2')–C(3') bond, which is  $0.025 \text{ Å}$  ( $2.8\sigma$ ) longer in thioguanosine than in deoxythioguanosine. This difference is probably significant and is explainable in terms of the different substituents at C(2'). The

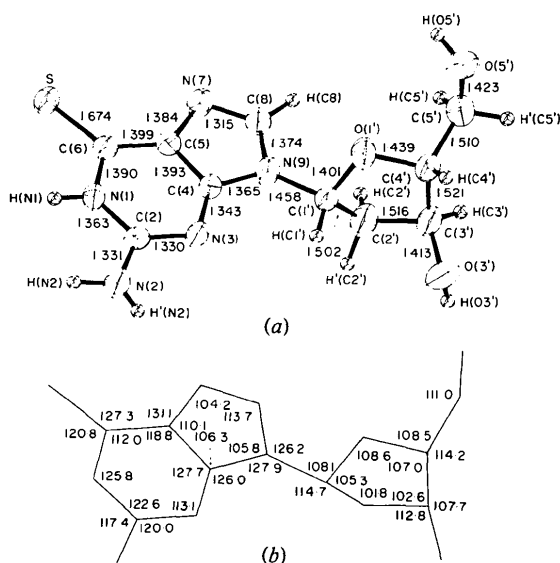


Fig. 1. The molecular structure, conformation, and dimensions of 2'-deoxy-6-thioguanosine. Nonhydrogen-atom thermal ellipsoids are scaled to include 50% probability. Estimated standard deviations are (a) about  $0.005 \text{ Å}$  for bond lengths and (b) about  $0.3^\circ$  for bond angles. Bond lengths and angles that involve H atoms are in the normal range for X-ray determinations and are not reported. [Figs. 1 and 2 were prepared with the computer program ORTEP (Johnson, 1965).]

\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32769 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

conformation of the deoxyribose moiety is only slightly different from that of the ribose group in the crystal of thioguanosine; all corresponding torsion angles agree within  $6^\circ$ .

Fig. 2 illustrates the molecular packing in the crystal structure, and Table 3 gives hydrogen-bonding distances and angles. Each thioguanine residue is linked by  $N(1)-H \cdots N(7)$  and  $N(2)-H \cdots S$  hydrogen bonds with two screw-related neighbors to form planar ribbons of bases that extend along *a* and lie nearly parallel to (010). The hydrogen-bonded ribbons are arranged in parallel stacks along *b*; adjacent ribbons, which are related by diad axes, intersect the *y* axis at approximately  $\frac{1}{4}$  and  $\frac{3}{4}$  and have an average separation of about 3.4 Å. The stacks of bases are flanked by hydrophilic regions consisting of the deoxyribose groups, which project from both sides of the stacks, plus waters of hydration. All potential proton donors,

except for the amino hydrogen  $H'(N2)$ , participate in the formation of hydrogen bonds [in thioguanosine,  $H'(N2)$  forms an inter-ribbon hydrogen bond with  $O(2')$ ;  $O(2')$  is absent in the deoxynucleoside].  $O(5')-H$  is the donor in a hydrogen bond that joins nucleosides of adjacent ribbons, whereas water molecules function as bridges between sugar groups that may belong either to the same or to different stacks of nucleosides. Fig. 2 shows the stacking pattern of bases in adjacent ribbons. The thioketo groups are sandwiched between pyrimidine portions of the purine rings so that S atoms are close to  $C(4)-C(5)$  bonds. The S atoms are in van der Waals contact (3.5–3.6 Å) with the  $C(4)$  and  $C(5)$  atoms of bases above and below. Similar stacking patterns are found in the crystal structures of other nucleic acid constituents. Base overlap is usually minimal and is accomplished by positioning carbon-hetero-atom bonds of one base over the ring system of another (Bugg, Thomas, Sundaralingam & Rao, 1971).

The same hydrogen-bonded assembly of bases has now been found in the crystal structures of deoxythioguanosine, thioguanosine, guanosine (Thewalt, Bugg & Marsh, 1970), and guanine (Thewalt, Bugg & Marsh, 1971). These results imply that the thio-analogs have hydrogen-bonding capabilities similar to those of the natural bases. There is, however, a significant distortion in the dimensions of hydrogen-bonded base pairs formed by the thio-bases as compared with those formed by the natural bases. The distortion arises because of the greater lengths of the bonds  $C=S$  (1.7 Å) and  $NH \cdots S$  (3.3 Å) versus  $C=O$  (1.2 Å) and

Table 3. *Hydrogen-bonding distances and angles*

Superscripts refer to the following symmetry-equivalent positions: (a)  $-\frac{1}{2} + x, \frac{1}{2} - y, -z$ ; (b)  $\frac{1}{2} - x, \frac{1}{2} + y, -\frac{1}{2} - z$ ; (c)  $\frac{1}{2} + x, -\frac{1}{2} + y, z$ ; (d)  $-\frac{1}{2} + x, \frac{1}{2} + y, z$ .

| <i>D</i>                     | <i>A</i> | <i>D</i> ... <i>A</i> | <i>H</i> ... <i>A</i> | <i>D</i> - <i>H</i> ... <i>A</i> |
|------------------------------|----------|-----------------------|-----------------------|----------------------------------|
| $N(1)-H(N1) \cdots N(7)^a$   |          | 2.969 Å               | 2.11 Å                | 164°                             |
| $N(2)-H(N2) \cdots S^a$      |          | 3.345                 | 2.58                  | 136                              |
| $O(3')-H(O3') \cdots O^b$    |          | 2.640                 | 1.83                  | 169                              |
| $O(5')-H(O5') \cdots N(3)^c$ |          | 2.757                 | 1.87                  | 179                              |
| $O-H \cdots O(3')$           |          | 2.751                 | 1.80                  | 162                              |
| $O-H' \cdots O(5')^d$        |          | 2.758                 | 1.96                  | 161                              |

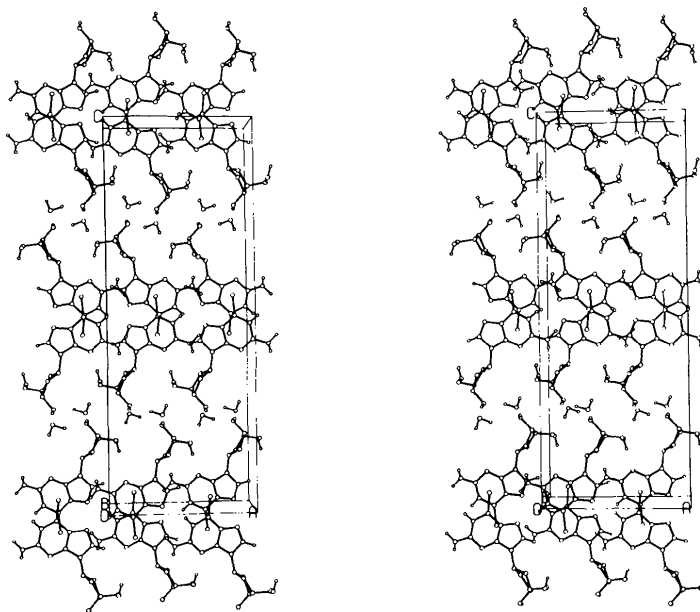


Fig. 2. Stereographic illustration of the crystal structure of 2'-deoxy-6-thioguanosine monohydrate. H atoms that are bonded to C atoms of the deoxyribose group are not shown. Successive ribbons of bases in the stacks parallel to (010) intersect *b* at about  $y = \frac{1}{4}$  and  $y = \frac{3}{4}$ .

NH...O (2.9 Å). Such distortions, resulting from the substitution of a thio-base for the natural base, may be of sufficient magnitude to disrupt certain biological processes.

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#### References

- BUGG, C. E. & THEWALT, U. (1970). *J. Amer. Chem. Soc.* **92**, 7441–7445.
- BUGG, C. E., THOMAS, J. M., SUNDARALINGAM, M. & RAO, S. T. (1971). *Biopolymers*, **10**, 175–219.
- BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS*. Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee.
- COPPENS, P. & HAMILTON, W. C. (1970). *Acta Cryst.* **A26**, 71–83.
- CROMER, D. T. & LIBERMAN, D. (1970). *J. Chem. Phys.* **53**, 1891–1898.
- DAWSON, B. (1960). *Acta Cryst.* **13**, 403–408.
- DONOHUE, J. & TRUEBLOOD, K. N. (1960). *J. Mol. Biol.* **2**, 363–371.
- DOYLE, P. A. & TURNER, P. S. (1968). *Acta Cryst.* **A24**, 390–397.
- IWAMOTO, R. H., ACTON, E. M. & GOODMAN, L. (1963). *J. Med. Chem.* **6**, 684–688.
- JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.
- LEPAGE, G. A. (1968). *Canad. J. Biochem.* **46**, 655–661.
- LEPAGE, G. A., JUNGA, I. G. & BOWMAN, B. (1964). *Cancer Res.* **24**, 835–840.
- SHEFTER, E. & TRUEBLOOD, K. N. (1965). *Acta Cryst.* **18**, 1067–1077.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
- SUNDARALINGAM, M. (1971). *J. Amer. Chem. Soc.* **93**, 6644–6647.
- THEWALT, U. & BUGG, C. E. (1972). *J. Amer. Chem. Soc.* **94**, 8892–8898.
- THEWALT, U., BUGG, C. E. & MARSH, R. E. (1970). *Acta Cryst.* **B26**, 1089–1101.
- THEWALT, U., BUGG, C. E. & MARSH, R. E. (1971). *Acta Cryst.* **B27**, 2358–2363.
- WEHE, D. J., BUSING, W. R. & LEVY, H. A. (1962). *ORABS*. Report ORNL-TM-229. Oak Ridge National Laboratory, Tennessee.
- WILSON, A. J. C. (1942). *Nature, Lond.* **150**, 151–152.
- ZACHARIASEN, W. H. (1963). *Acta Cryst.* **16**, 1139–1144.

*Acta Cryst.* (1977). **B33**, 3681–3684

## Solid-State Phase Transition in Carbon Tetrabromide CBr<sub>4</sub>. I. The Crystal Structure of Phase II at Room Temperature

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Phase II of CBr<sub>4</sub> is monoclinic, space group *C2/c*, with  $a = 21.43$ ,  $b = 12.12$ ,  $c = 21.02$  Å,  $\beta = 110.88^\circ$ ,  $Z = 32$ . The structure was solved by direct methods and refined to  $R = 7.0\%$  for 856 counter data. The monoclinic system can be converted into a pseudocubic system which facilitates the description of the structure.

### Introduction

At atmospheric pressure, CBr<sub>4</sub> undergoes a transition at 47°C; phase I is stable between 92°C (melting point) and 47°C, phase II below 47°C. Finbak & Hassel (1937) have shown that phase II is monoclinic with  $a = 21.12$ ,  $b = 12.26$ ,  $c = 24.14$  Å,  $\beta = 125^\circ 3'$ ,  $Z = 32$ . These results disagree with those of Mark (1924). Harris (1962) gives  $a_1 = 20.9$ ,  $a_2 = 21.2$ ,  $a_3 =$

$12.1$  Å,  $\beta = 110^\circ 30'$ . He suggests that the space group is *C2/c* but did not determine the structure.

Phase I is face-centred cubic with  $Z = 4$  (Wyckoff, 1964), and is characterized by molecular reorientations ('plastic' crystal). It is interesting to consider why and how the transition occurs.

In this paper, the structure of phase II at room temperature is reported. An attempt to prove the pseudocubic structure is given [the structure of the