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## Structural Chemistry of N(7)-Substituted Purines: The Crystal and Molecular Structure of 7-Methylxanthine Hydrochloride Monohydrate

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(Received 25 July 1974; accepted 27 September 1974)

7-Methylxanthine hydrochloride monohydrate,  $C_6N_4O_2H_6 \cdot HCl \cdot H_2O$ , crystallizes in the monoclinic system, systematic absences  $0k0$ ,  $k = 2n + 1$  and  $h0l$ ,  $l = 2n + 1$  consistent with the space group  $P2_1/c$ , with crystal data:  $a = 7.047$  (1),  $b = 8.630$  (3),  $c = 15.000$  (7) Å,  $\beta = 91.09$  (3)°,  $V = 912.1$  Å<sup>3</sup>,  $D_m = 1.59$  (1),  $D_c$  (four formula units per unit cell) =  $1.61$  g cm<sup>-3</sup>,  $\mu(\text{Mo } K\alpha) = 4.1$  cm<sup>-1</sup>. Intensities for 2111 independent reflections were collected by counter methods. Full-matrix least-squares refinement has led to final unweighted and weighted  $R$  values of 0.065 and 0.046, respectively. The crystal structure contains an extensive array of hydrogen bonds and some stacking of the pyrimidine rings of the substituted xanthine moieties.

### Introduction

The crystal structure of 7-methylxanthine hydrochloride monohydrate was undertaken in order to establish

that methylation of the xanthine ligand in the complex [bis(dimethylglyoximato)(xanthinato)(tri-*n*-butylphosphine)cobalt(III)] had taken place exclusively at the N(7) position. The analysis also forms an integral

part of our studies on N(7)-substituted purines (Kistenmacher & Shigematsu, 1974, 1975).

### Experimental

7-Methylxanthine was prepared by methylation, using  $\text{CH}_3\text{I}$ , of the complex [bis(dimethylglyoximate)-(xanthinato)(tri-n-butylphosphine)cobalt(III)] (Marzilli, Epps, Kistenmacher & Sorrell, 1974). The 7-methylxanthine was then dissolved in aqueous hydrochloric acid; single crystals of the monohydrochloride monohydrate were collected after several days. The crystals grew as elongated prisms with [100] as the prism axis. The crystals are air sensitive, and we found it necessary to coat them with a thin film of grease and mount them in thin-walled glass capillaries. The crystal system is monoclinic with systematic absences ( $0k0$ ,  $k=2n+1$ ;  $h0l$ ,  $l=2n+1$ ) consistent with the centrosymmetric space group  $P2_1/c$ . Unit-cell dimensions and standard deviations were derived from a least-squares fit to the  $2\theta$ ,  $\omega$  and  $\chi$  settings for 15 reflections; the density was measured by neutral buoyancy methods in a mixture of bromoform and cyclohexane.

In total, 2614 reflections (the  $hkl$ ,  $hk\bar{l}$  quadrant to  $2\theta \leq 55^\circ$ ) were measured on a Syntex  $P\bar{1}$  computer-controlled diffractometer; molybdenum graphite-monochromatized radiation was employed. The crystal used in data collection was a cut cube about 0.2 mm on an edge. Intensity data were collected by the  $\theta$ - $2\theta$  scan technique; individual scan speeds were determined by a rapid scan at the calculated Bragg peak, and the rate of scanning was varied from  $1.5^\circ \text{ min}^{-1}$  to  $24^\circ \text{ min}^{-1}$  to achieve constant counting statistics. Three standards were monitored after every 100 reflections, and their intensities showed no unusual variations over the course of the data collection. The 2614 measured intensities, which included standards and systematic absences as well as some symmetry-related data, were then reduced to yield a set of 2111 independent values. All reflections were assigned observational variances based on the following equation:

$$\sigma^2(I) = S + (B_1 + B_2) (T_S/2T_B)^2 + (pI)^2,$$

where  $S$ ,  $B_1$  and  $B_2$  are the scan and background counts,  $T_S$  and  $T_B$  are the scan and individual background counting times ( $T_B = \frac{1}{2}T_S$ ), and  $p$  was taken to be 0.03 and represents the expected error proportional to the diffracted intensity (Busing & Levy, 1957). Intensities and their standard deviations were corrected for Lorentz and polarization effects; the amplitudes of reflections with negative intensities were set equal to zero. Due to the small size of the crystal and the low value for  $\mu$  ( $4.1 \text{ cm}^{-1}$ ), no correction for absorption was deemed necessary (the maximum error introduced by the neglect of the absorption effects is about 3% in  $I$ ). The squared structure factors were placed on an approximate absolute scale by the method of Wilson (1942).

The position of the chlorine atom was determined from a three-dimensional Patterson synthesis, and a subsequent Fourier map ( $R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.63$ ) allowed the positioning of 11 of the 13 remaining heavy atoms in the asymmetric unit. A second Fourier map gave the positions of the other two heavy atoms. Adjustment of the positions of all 14 heavy atoms based on this Fourier map and three cycles of isotropic least-squares calculations, minimizing  $\sum w(|F_o| - |F_c|)^2$  where  $w = 1/\sigma^2(F_o)$ , reduced the  $R$  value to 0.16. A difference Fourier map calculated at this stage revealed the positions of the 9 hydrogen atoms. Two further cycles of refinement, including anisotropic temperature factors for all the heavy atoms, reduced the  $R$  value to 0.10. At this point a detailed scan of the individual contributions to  $\sum w(|F_o| - |F_c|)^2$  showed that about 60  $hk\bar{l}$  reflections accounted for nearly half of the sum total. Recourse to the data collection output indicated that several (about 200)  $hk\bar{l}$  reflections had very asymmetric backgrounds, and in general indicated that the  $hk\bar{l}$  octant was inferior to the  $hkl$  octant. Subsequently, the crystal was remounted on the diffractometer, and the complete  $hk\bar{l}$  octant of data was recollected. Replacement of the old  $hk\bar{l}$  octant by this new set of data and one cycle of refinement immediately reduced

Table 1. Final heavy-atom parameters ( $\times 10^4$ ), hydrogen-atom coordinates ( $\times 10^3$ ) and hydrogen-atom temperature parameters

Estimated standard deviations are enclosed in parentheses. The form of the anisotropic ellipsoid is:  $\exp [-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$ .

	$x$	$y$	$z$	$B_{11}$	$B_{22}$	$B_{33}$	$B_{12}$	$B_{13}$	$B_{23}$
Cl	2305 (0.8)	-3361 (0.6)	2898 (0.3)	222 (1.3)	120 (0.8)	25 (0.2)	-12 (0.8)	-3 (0.4)	14 (0.3)
N(1)	2345 (2)	-400 (2)	-145 (1)	183 (4)	91 (2)	18 (1)	-5 (2)	4 (1)	0 (1)
N(3)	1816 (2)	-1036 (2)	1346 (1)	192 (4)	92 (2)	21 (1)	-8 (2)	7 (1)	10 (1)
N(7)	3315 (2)	2851 (2)	1402 (1)	142 (3)	92 (2)	26 (1)	8 (2)	1 (1)	-3 (1)
N(9)	2445 (2)	1113 (2)	2372 (1)	170 (4)	117 (3)	18 (1)	5 (3)	9 (1)	1 (1)
O(2)	1302 (2)	-2803 (2)	240 (1)	281 (4)	100 (2)	31 (1)	-38 (2)	12 (1)	-1 (1)
O(6)	3520 (2)	1920 (2)	-612 (1)	262 (4)	115 (2)	25 (1)	-18 (2)	12 (1)	10 (1)
O(10)	903 (3)	24 (2)	3832 (1)	358 (6)	122 (3)	41 (1)	75 (3)	59 (2)	21 (1)
C(2)	1799 (3)	-1497 (2)	470 (1)	152 (4)	96 (3)	25 (1)	4 (3)	4 (1)	3 (1)
C(4)	2367 (3)	429 (2)	1554 (1)	125 (4)	98 (3)	21 (1)	13 (3)	2 (1)	4 (1)
C(5)	2925 (3)	1491 (2)	938 (1)	131 (4)	87 (3)	22 (1)	9 (3)	1 (1)	2 (1)
C(6)	2993 (3)	1107 (2)	2 (1)	133 (4)	97 (3)	20 (1)	13 (3)	2 (1)	4 (1)
C(7)	4082 (4)	4285 (3)	1024 (2)	227 (6)	95 (3)	38 (1)	-25 (3)	6 (2)	-1 (1)
C(8)	3011 (3)	2578 (2)	2257 (1)	159 (5)	111 (3)	25 (1)	14 (3)	0 (2)	-8 (1)

Table 1 (*cont.*)

	x	y	z	B
H(1)	233 (3)	-73 (2)	-68 (1)	3.0 (4)
H(3)	170 (3)	-172 (3)	169 (2)	3.6 (6)
H(8)	317 (3)	331 (2)	270 (1)	3.2 (4)
H(9)	194 (3)	76 (2)	285 (1)	3.4 (4)
H(11)	93 (4)	-76 (4)	405 (2)	5.5 (8)
H(12)	26 (4)	57 (4)	409 (2)	5.3 (8)
H(71)	340 (4)	455 (3)	48 (2)	5.9 (7)
H(72)	547 (4)	404 (3)	90 (2)	6.1 (7)
H(73)	395 (4)	508 (3)	146 (2)	5.1 (6)

the *R* value to 0.08. The refinement was then continued with the addition of the hydrogen atom positional and isotropic temperature factors to the list of variables. In the final cycle of refinement no shift/error exceeded 1.0. The final unweighted and weighted residuals are  $R=0.065$ , and  $R_w = [\sum w(F_o - F_c)^2 / \sum wF_c^2]^{1/2} = 0.046$ . The final value of the goodness-of-fit,  $\{[\sum w(F_o - F_c)^2 / (NO - NV)]^{1/2}\}$ , where  $NO=2111$  observations and  $NV=163$  parameters, was 1.3. Neutral scattering-factor curves for Cl, O, N and C were taken from the compilation of Hanson, Herman, Lea & Skillman (1964); the scattering curve for H was that of Stewart, Davidson & Simpson (1965). The real part of the scattering curve for Cl was corrected for anomalous dispersion effects (Cromer, 1965). Final atomic parameters for all atoms are given in Table 1. A complete list of calculated and observed structure factor amplitudes, bond angles involving the hydrogen atoms, and least-squares plane calculations is available.\*

\* These tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30696 (17 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

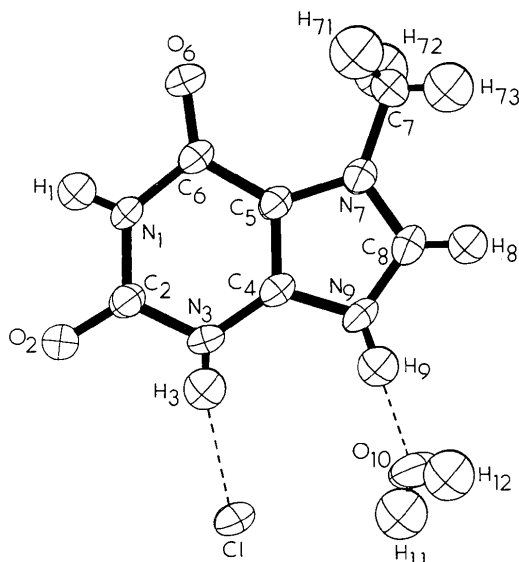


Fig. 1. A view normal to the molecular plane of the protonated 7-methylxanthine cation. The water molecule and the chloride anion are also shown. The thermal ellipsoids are drawn at the 50% probability level.

The structure-factor and Fourier calculations were performed by the X-RAY 67 series of programs (Stewart, 1967); the least-squares refinements were performed using an extensively modified version of ORFLS (Busing, Martin & Levy, 1962); the least-squares plane calculations were performed using the program of Pippy & Ahmed (1968); the illustrations were prepared with the aid of the computer program ORTEP (Johnson, 1965).

## Discussion

A view normal to the molecular plane of the 7-methylxanthine cation is shown in Fig. 1. Complete heavy-atom bond lengths and angles are given in Table 2. The C-H bond lengths average to 0.97 (4) Å, while the N-H bond lengths average to 0.84 (4) Å. The two water O(10)-H distances are 0.75 (4) and 0.76 (4) Å and the angle H-O(10)-H is 110(3)°. The heavy-atom bond lengths and angles are in general typical of those found in other N(7)-substituted xanthine studies [e.g. caffeine (Sutor, 1958; Shefter, 1968) and theobromine (Shefter, Brennan & Sackman, 1971)]. As expected however (Kistenmacher & Shigematsu, 1974, 1975), there are significant adjustments in the interior bond angles in the imidazole ring due to the protonation at N(9). In particular, the endocyclic imidazole bond angles in the protonated 7-methylxanthine nucleus show the following deviations compared with the averaged values in caffeine and theobromine [ $\angle - \angle_{AVE}$ ]: C(5)-N(7)-C(8) 2.3, C(4)-N(9)-C(8) 4.2, N(9)-C(4)-C(5) 5.2, N(7)-C(5)-C(4) 0.6 and N(7)-C(8)-N(9) -3.6°. Furthermore, the values in protonated 7-methylxanthine agree within 0.6° of those found in 7-methyladenine dihydrochloride (Kistenmacher & Shigematsu, 1975) suggesting that the nature of the substituents on the pyrimidine ring and the charge on the molecule have little effect on the adjustments due to the protonation on N(9).

Table 2. Bond lengths (Å) and angles (°) involving only heavy atoms

Bond-length e.s.d.'s about 0.004 Å, bond-angle e.s.d.'s about 0.3°.

N(1)-C(2)	1.382	N(9)-C(4)	1.362
N(1)-C(6)	1.395	N(9)-C(8)	1.338
N(3)-C(2)	1.373	O(2)-C(2)	1.228
N(3)-C(4)	1.357	O(6)-C(6)	1.221
N(7)-C(5)	1.389	C(4)-C(5)	1.365
N(7)-C(7)	1.469	C(5)-C(6)	1.444
N(7)-C(8)	1.325	N(3)-C(4)-N(9)	128.1
C(2)-N(1)-C(6)	128.9	N(3)-C(4)-C(5)	123.7
C(2)-N(3)-C(4)	119.2	N(9)-C(4)-C(5)	108.2
C(5)-N(7)-C(7)	126.1	N(7)-C(5)-C(4)	106.6
C(5)-N(7)-C(8)	107.5	N(7)-C(5)-C(6)	132.1
C(7)-N(7)-C(8)	126.2	C(4)-C(5)-C(6)	121.3
C(4)-N(9)-C(8)	107.5	N(1)-C(6)-O(6)	121.3
N(1)-C(2)-N(3)	116.3	N(1)-C(6)-C(5)	110.5
N(1)-C(2)-O(2)	121.5	C(5)-C(6)-O(6)	128.1
N(3)-C(2)-O(2)	122.2	N(7)-C(8)-N(9)	110.3

The nine-atom framework of the substituted xanthine moiety is roughly planar with a maximum deviation of 0.028 Å at N(1). As is typical of the purine fused-ring system (Sletten & Jensen, 1969; Voet & Rich, 1970), the imidazole and pyrimidine rings are tilted about the C(4)–C(5) bond with a dihedral angle of 2.03 (3)°. Details of the least-squares plane calculations are available.\*

The crystal packing in 7-methylxanthine hydrochloride monohydrate is illustrated in Fig. 2. A wide variety of hydrogen bonds is exhibited; details of the parameters in these hydrogen bonds are given in Table 3. Inversion-related 7-methylxanthine cations show significant stacking (Fig. 3) which can be characterized as a slightly skewed dipolar overlap of the hetero-bonds C(2)–O(2), C(2)–N(1) and C(6)–N(1). The mean separation between molecular planes is 3.35 Å.

Table 3. Distances and angles in the intermolecular contacts of the type  $D-H \cdots A$

D	H	A	D–H	H $\cdots$ A	D $\cdots$ A	$\angle D-H \cdots A$
N(1)	H(1)	Cl <sup>a</sup>	0.85 Å	2.27 Å	3.124 Å	179°
N(3)	H(3)	Cl <sup>b</sup>	0.79	2.33	3.088	161
C(8)	H(8)	O(6) <sup>c</sup>	0.92	2.54	3.239	133*
N(9)	H(9)	O(10) <sup>b</sup>	0.87	1.77	2.636	180
O(10)	H(11)	O(2) <sup>d</sup>	0.75	2.18	2.862	150
O(10)	H(12)	O(2) <sup>e</sup>	0.76	2.06	2.820	175

Symmetry code

a	$x, -\frac{1}{2}-y, -\frac{1}{2}+z$	d	$x, -\frac{1}{2}-y, \frac{1}{2}+z$
b	$x, y, z$	e	$-x, \frac{1}{2}+y, \frac{1}{2}-z$
c	$x, \frac{1}{2}-y, \frac{1}{2}+z$		

\* All entries except this one may be considered to be hydrogen bonds.

We wish to thank Professor Luigi G. Marzilli and Mr Leon A. Epps for the synthesis of 7-methylxanthine and to acknowledge support of this investigation through a National Institutes of Health Biomedical Sciences Support Grant.

\* See footnote on p. 491.

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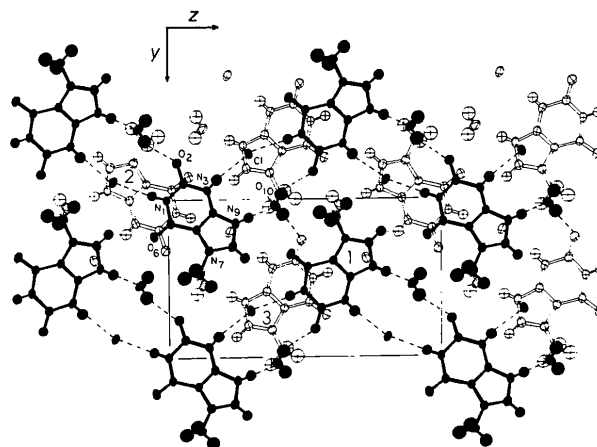


Fig. 2. Crystal packing in 7-methylxanthine hydrochloride monohydrate. The view direction is normal to the  $bc$  plane. The labeled molecule is at  $xyz$ , while the numbered molecules have the following symmetry transforms relative to Table 2: (1)  $x, \frac{1}{2}-y, \frac{1}{2}+z$ ; (2)  $-x, -y, -z$ ; (3)  $-x, \frac{1}{2}+y, \frac{1}{2}-z$ . Dashed lines indicate hydrogen bonds; the dotted lines show the interaction  $-C(8)-H(8) \cdots O(6)$ .

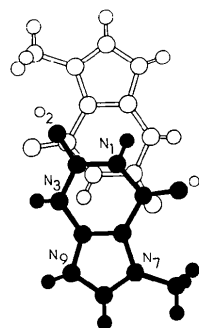


Fig. 3. Molecular overlap of the 7-methylxanthine cations. The mean separation of molecular planes is 3.35 Å.

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