

In the 17 $\beta$  side chain, which lies approximately in the plane of the *C* and *D* rings, the H substituents at C(17) and C(20) are in an antiperiplanar conformation and C(22) is antiperiplanar with respect to the C(13)–C(17) bond; the torsion angle C(13)–C(17)–C(20)–C(22) is  $-179.2^\circ$ . C(21) is synclinal with respect to the C(13)–C(17) bond; the torsion angle C(13)–C(17)–C(20)–C(21) is  $-55.8^\circ$ . The conformation of this portion of the molecule is closely similar to that found in the structures of other sterols in which the *D* ring is fully saturated (Duax & Norton, 1975, and references cited therein).

The molecular packing is shown by a stereodrawing along the *b* axis in Fig. 3. The molecules pack in layers approximately parallel to (101). There are no intermolecular contacts that are significantly shorter than the sum of the corresponding van der Waals radii.

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## Crystal and Molecular Structure of 1,3,7-Trimethyl-2,6-purinedione Hydrochloride Dihydrate (Caffeine Hydrochloride Dihydrate)

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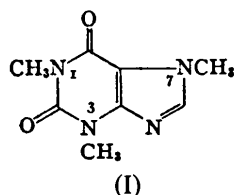
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Crystals of the compound  $C_8H_{11}ClN_4O_2 \cdot 2H_2O$  are monoclinic,  $a = 12.391(4)$ ,  $b = 6.524(1)$ ,  $c = 17.167(6)$  Å,  $\beta = 118.82(3)^\circ$ ,  $Z = 4$ , space group  $P2_1/c$ . The structure was determined by direct methods and refined by full-matrix least-squares procedures to a final  $R$  of 0.064 for 1752 reflections with  $I \geq 3\sigma(I)$ . The fused-ring system is essentially planar and protonated at the 9-position. The crystal contains two major types of hydrogen bonding involving N–H $\cdots$ O and O–H $\cdots$ Cl interactions.

### Introduction

The crystal structure determination of caffeine (I) hydrochloride dihydrate was undertaken primarily to provide the necessary information to complement an electron nuclear double resonance (ENDOR) study on this compound. The renewed interest in this area is due



to the discovery that caffeine will inhibit the post-radiation repair of chromosomal aberrations in irradiated DNA (e.g. Konoplyannikov, 1975).

### Experimental

The colourless, prismatic crystals were grown by evaporation from a saturated solution of caffeine in hydrochloric acid. The crystal chosen for study ( $ca\ 0.4 \times 0.3 \times 0.2$  mm) was mounted with *b* parallel to the goniostat axis. Unit-cell and space-group data were obtained from film and diffractometer measurements. The unit-cell parameters were refined by a least-squares treatment of  $\sin^2 \theta$  values for 22 reflections measured

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Table 1. *Final positional parameters (fractional,  $\times 10^4$ ; Cl  $\times 10^5$ , H  $\times 10^3$ ) with estimated standard deviations in parentheses*

A prime indicates a water molecule.

	x	y	z
Cl	98388 (8)	48847 (15)	35370 (6)
O(11)	6620 (2)	2332 (4)	1275 (2)
O(13)	5748 (2)	6992 (4)	2885 (2)
O(1)'	9101 (3)	7633 (5)	4695 (2)
O(2)'	8592 (3)	5884 (6)	1420 (2)
N(1)	6241 (2)	4670 (4)	2095 (2)
N(3)	7359 (2)	1630 (4)	2740 (2)
N(7)	7063 (2)	4033 (4)	4459 (2)
N(9)	7905 (3)	1232 (5)	4306 (2)
C(2)	6733 (3)	2827 (5)	1994 (2)
C(4)	7381 (3)	2219 (5)	3503 (2)
C(5)	6851 (3)	3971 (5)	3586 (2)
C(6)	6228 (3)	5376 (5)	2865 (2)
C(8)	7693 (3)	2367 (5)	4872 (2)
C(10)	5591 (4)	5916 (8)	1279 (3)
C(12)	8067 (5)	-150 (7)	2705 (3)
C(14)	6647 (4)	5653 (6)	4848 (3)
H(11)'	937 (4)	721 (7)	522 (3)
H(12)'	927 (5)	692 (9)	432 (4)
H(21)'	888 (4)	540 (8)	198 (3)
H(22)'	905 (7)	724 (13)	149 (4)
H(1)	792 (2)	205 (4)	547 (2)
H(2)	832 (4)	4 (7)	442 (3)
H(3)	543 (4)	727 (8)	149 (3)
H(4)	479 (6)	520 (10)	87 (4)
H(5)	610 (5)	609 (9)	96 (4)
H(6)	806 (5)	-18 (9)	218 (4)
H(7)	779 (6)	-137 (12)	282 (5)
H(8)	885 (5)	-16 (8)	329 (4)
H(9)	696 (4)	548 (7)	545 (3)
H(10)	584 (5)	584 (8)	449 (3)
H(11)	700 (4)	704 (8)	473 (3)

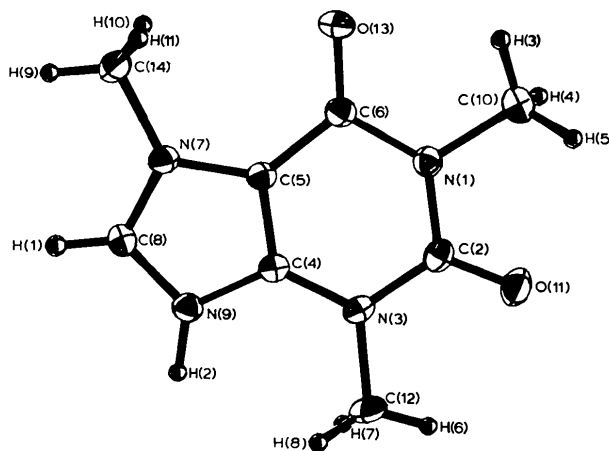


Fig. 1. A general view of the structure showing the crystallographic numbering scheme.

on a diffractometer with Cu  $K\alpha$  radiation. Intensity data were measured for 2208 independent reflections ( $2\theta < 140^\circ$ ) of which 451 had intensities less than  $3\sigma(I)$  above the background [where  $\sigma^2(I) = S + B + (0.05S)^2$ , and  $S$  = scan count and  $B$  = background count] and were classified as unobserved.

#### Crystal data

$C_8H_{11}ClN_4O_2 \cdot 2H_2O$ ,  $M_r = 266.7$ , monoclinic,  $a = 12.391(4)$ ,  $b = 6.524(1)$ ,  $c = 17.167(6)$  Å,  $\beta = 118.82(3)^\circ$ ,  $U = 1215.9(8)$  Å<sup>3</sup>,  $D_m = 1.46$ ,  $D_c = 1.457$  g cm<sup>-3</sup>,  $Z = 4$ ,  $F(000) = 560$ . Space group  $P2_1/c$  ( $C_2^5$ , No. 14) from absent reflections  $h0l$ ,  $l \neq 2n$  and  $0k0$ ,  $k \neq 2n$ .  $\mu(\text{Cu } K\alpha \text{ radiation}) = 29.19$  cm<sup>-1</sup>.

Table 2. *Rigid-body thermal parameters for the nine-membered fused-ring system*

Axes of reference are  $a$ ,  $b$ ,  $c^*$ . E.s.d.'s of components of  $L$  are given in parentheses in units of the last places shown.

$$L(\times 10 \text{ deg}^2) = \begin{pmatrix} 81(11) & 22(9) & -37(13) \\ & 58(12) & -6(11) \\ & & 96(35) \end{pmatrix}$$

#### Principal axes of L

R.m.s. amplitude	Direction cosines ( $\times 10^3$ )		
3.6°	643	247	-725
2.6	389	709	588
2.0	659	-660	360

#### Principal axes of T

R.m.s. amplitude	Direction cosines ( $\times 10^3$ )		
0.19 Å	18	-82	996
0.17	355	-931	-83
0.17	935	355	12

$$\text{R.m.s. } \Delta U_{ij} (\text{Å}^2) \quad 0.0015$$

#### Structure determination and refinement

The structure was determined by direct methods (Long, 1965). From the resulting  $E$  map the positions of the 17 non-hydrogen atoms were indicated from the 17 highest peaks. Two cycles of full-matrix least-squares refinement produced an  $R$  factor of 0.129 with isotropic temperature factors, while a further cycle using anisotropic temperature factors lowered the  $R$  factor to 0.088. A difference Fourier map computed at this stage revealed the positions of the 15 H atoms. Further refinement with an anomalous scattering correction for the Cl atom, anisotropic temperature factors for the non-hydrogen atoms, isotropic temperature factors for the H atoms and an overall extinction-coefficient correction produced convergence at  $R = 0.064$  for 1752 reflections with  $I \geq 3\sigma(I)$ .\* The atomic scattering

\* Five reflections were given zero weight in the final stages of refinement because of suspected instrumental errors: 102, 1,2,16, 142, 3,6,12, 754.

Table 3. Bond lengths (Å) and angles (°) with standard deviations in parentheses

Bond	Uncorrected	Corrected	Bond	Uncorrected
N(1)—C(2)	1.396 (4)	1.400	C(8)—H(1)	0.95 (3)
C(2)—N(3)	1.376 (4)	1.379	N(9)—H(2)	0.92 (5)
N(3)—C(4)	1.351 (4)	1.354	C(10)—H(3)	1.01 (5)
C(4)—C(5)	1.360 (4)	1.363	C(10)—H(4)	1.02 (7)
C(5)—C(6)	1.431 (5)	1.434	C(10)—H(5)	1.02 (6)
C(6)—N(1)	1.407 (4)	1.410	C(12)—H(6)	0.89 (6)
C(4)—N(9)	1.369 (4)	1.372	C(12)—H(7)	0.92 (8)
N(9)—C(8)	1.343 (4)	1.346	C(12)—H(8)	1.00 (6)
C(8)—N(7)	1.327 (4)	1.330	C(14)—H(9)	0.92 (5)
N(7)—C(5)	1.392 (4)	1.394	C(14)—H(10)	0.89 (5)
N(1)—C(10)	1.477 (5)	1.477	C(14)—H(11)	1.07 (5)
N(3)—C(12)	1.474 (5)	1.476	O(1)'—H(11)'	0.84 (4)
N(7)—C(14)	1.469 (5)	1.471	O(1)'—H(12)'	0.89 (6)
C(2)—O(11)	1.217 (4)	1.218	O(2)'—H(21)'	0.90 (5)
C(6)—O(13)	1.218 (4)	1.220	O(2)'—H(22)'	1.03 (8)

Angles for the non-hydrogen atoms and H(1) and H(2)

N(1)—C(2)—N(3)	117.2 (3)	C(2)—N(3)—C(12)	119.2 (3)
C(2)—N(3)—C(4)	118.6 (3)	C(4)—N(3)—C(12)	121.9 (3)
N(3)—C(4)—C(5)	123.8 (3)	N(3)—C(4)—N(9)	128.4 (3)
C(4)—C(5)—C(6)	122.3 (3)	N(7)—C(5)—C(6)	131.0 (3)
C(5)—C(6)—N(1)	111.0 (3)	C(5)—C(6)—O(13)	126.7 (3)
C(6)—N(1)—C(2)	127.0 (3)	N(1)—C(6)—O(13)	122.4 (3)
C(4)—C(5)—N(7)	106.8 (3)	C(6)—N(1)—C(10)	117.6 (3)
C(5)—N(7)—C(8)	107.9 (3)	C(2)—N(1)—C(10)	115.3 (3)
N(7)—C(8)—N(9)	109.6 (3)	C(5)—N(7)—C(14)	125.8 (3)
C(8)—N(9)—C(4)	107.8 (3)	C(8)—N(7)—C(14)	126.3 (3)
N(9)—C(4)—C(5)	107.9 (3)	N(7)—C(8)—H(1)	123 (2)
N(1)—C(2)—O(11)	120.7 (3)	N(9)—C(8)—H(1)	127 (2)
N(3)—C(2)—O(11)	122.0 (3)	C(8)—N(9)—H(2)	128 (2)
		C(4)—N(9)—H(2)	124 (2)

Angles involving H atoms not attached directly to the fused-ring system

N(1)—C(10)—H(3)	105 (3)	H(6)—C(12)—H(8)	122 (5)
N(1)—C(10)—H(4)	108 (4)	H(7)—C(12)—H(8)	94 (5)
N(1)—C(10)—H(5)	112 (3)	N(7)—C(14)—H(9)	112 (3)
H(3)—C(10)—H(4)	111 (4)	N(7)—C(14)—H(10)	108 (3)
H(3)—C(10)—H(5)	111 (4)	N(7)—C(14)—H(11)	105 (2)
H(4)—C(10)—H(5)	109 (5)	H(9)—C(14)—H(10)	121 (4)
N(3)—C(12)—H(6)	110 (4)	H(9)—C(14)—H(11)	109 (4)
N(3)—C(12)—H(7)	113 (5)	H(10)—C(14)—H(11)	100 (4)
N(3)—C(12)—H(8)	106 (3)	H(11)'—O(1)'—H(12)'	119 (4)
H(6)—C(12)—H(7)	111 (6)	H(21)'—O(2)'—H(22)'	105 (5)

factors for Cl, O, N, and C were taken from Cromer & Mann (1968), anomalous-scattering correction from Cromer & Liberman (1970), and scattering factors for the H atoms from Stewart, Davidson & Simpson (1965). The weighting scheme  $w = 1/\sigma^2(F)$ , where  $\sigma^2(F)$  is derived from the previously defined  $\sigma^2(I)$ , gave constant average values of  $w(F_o - F_c)^2$  over ranges of  $|F_o|$  and was employed in the final stages of refinement. The final positional parameters are in Table 1.\*

### Thermal motion and correction of molecular geometry

The ellipsoids of thermal motion for the non-hydrogen atoms (excluding the chloride ion and the water molecules) are shown in Fig. 1. The thermal motion has been analysed in terms of the rigid-body modes of translation (T), libration (L), and screw (S) motion (Schomaker & Trueblood, 1968) using the computer program *MGTLS*. The r.m.s. standard deviation in the temperature factors  $U_{ij}$  is 0.0017 Å<sup>2</sup> indicating that the whole molecule (r.m.s.  $\Delta U_{ij} = 0.0022$  Å<sup>2</sup>) is a reasonable rigid body and that the thermal motion of the nine-membered fused-ring system is remarkably well described by the rigid-body thermal parameters given in Table 2 (r.m.s.  $\Delta U_{ij} = 0.0015$  Å<sup>2</sup>).

The bond distances in the fused-ring system have been corrected for libration (Cruickshank, 1956, 1961) using shape parameters  $q^2$  of 0.08 for all the atoms involved. Independent motion corrections based on the  $\Delta U_{ij}$  (Busing & Levy, 1964; Johnson, 1970) have been applied to the bond lengths for the non-hydrogen atoms attached to the fused-ring system. The corrected and uncorrected bond lengths and uncorrected angles are in

\* Tables of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32954 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

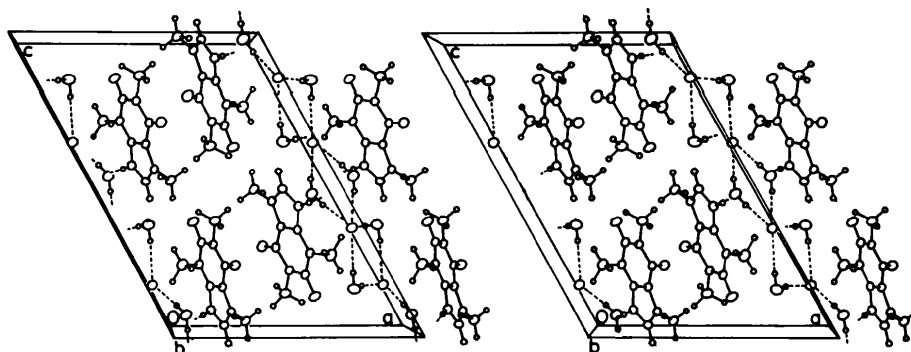


Fig. 2. A stereoscopic diagram of the unit cell viewed down *b*, showing postulated intermolecular hydrogen bonding as dashed lines.

Table 4. Distances and angles in the interatomic contacts of the type  $D-H\cdots A$ 

A prime indicates water molecules.

D	H	A	D-H (Å)	H...A (Å)	D...A (Å)	$\angle D-H\cdots A$ (°)
O(1)'	H(11)	Cl	0.84 (8)	2.32 (5)	3.12 (1)	162 (4)
O(1)'	H(12)	Cl	0.89 (6)	2.23 (6)	3.12 (1)	172 (5)
O(2)'	H(21)	Cl	0.90 (5)	2.37 (5)	3.24 (1)	167 (4)
O(2)'	H(22)	Cl	1.03 (9)	2.22 (8)	3.24 (1)	169 (6)
N(9)	H(2)	O(1)'	0.92 (5)	1.76 (5)	2.684 (4)	176 (4)

Table 3 (angles changed by no more than  $0.05^\circ$ , and the corrected angles are not reported).

### Description and discussion of the structure

Caffeine hydrochloride dihydrate contains a caffeine molecule protonated at N(9) (Fig. 1). Comparison of bond distances with those in other caffeine derivatives (e.g. Sutor, 1958; Sobell & Tomita, 1964; Shefter, 1968; Shefter, Brennan & Sackman, 1971; Rasmussen & Sletten, 1973; Craven & Gartland, 1974; Kistenmacher & Shigematsu, 1975; Kistenmacher & Sorrell, 1975) indicates little significant difference between protonated and unprotonated species. Some changes in angles in the imidazole ring do seem to occur on protonation, in particular an increase in the angle at N(9) and decreases at C(4) and C(8).

The protonated caffeine ion in the present structure is approximately planar, except for methyl H atoms. A plane calculated through all the non-hydrogen atoms and H(1) and H(2) has a maximum deviation of only  $0.19 \text{ \AA}$  [for C(12)]. The six-membered ring is slightly puckered (maximum deviation  $0.03 \text{ \AA}$ ) and the five-membered ring planar within experimental error; as in several purine-type derivatives (references above; Sletten & Jensen, 1969), the ion is slightly folded ( $0.85^\circ$ ) along the C(4)–C(5) bond.

The crystal contains O–H...Cl and N–H...O hydrogen bonds (Table 4, Fig. 2). The N–H...O bond is very strong, and seems to result in a distortion of the H–O–H angle of the water molecule involved [ $119(5)^\circ$  for water 1, in comparison with the more normal  $105(5)^\circ$  for water 2]. In this structure, unlike many other purine-type derivatives, there appears to be no significant stacking of layers of molecules and hence no significant dipole overlap of hetero C–O and C–N bonds contributing to the stability of the crystal.

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