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Studies on Modified Nucleic Acid Bases: Structure of 3-Isobutyl-1-methylxanthine

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Abstract. $C_{10}H_{14}N_4O_2$, $M_r = 222{\cdot}3$, monoclinic, $P2_1/c$, $a = 4{\cdot}882\,(3)$, $b = 8{\cdot}715\,(1)$, $c = 25{\cdot}955\,(3)$ Å, $\beta = 92{\cdot}28\,(1)°$, $V = 1103{\cdot}4\,(9)$ Å^3, $Z = 4$, $D_m = 1{\cdot}34$, $D_x = 1{\cdot}338$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 7{\cdot}62$ cm^{-1}, $F(000) = 472$, $T = 294$ K, $R = 0{\cdot}058$ for 984 reflections, $I > 3\sigma(I)$. The isobutyl chain is oriented almost perpendicular to the xanthine ring [C(2)—N(3)—C(31)—C(32) ±99·8 (4)°]. The isobutyl chain torsion angles are N(3)—C(31)—C(32)—C(33) ±62·2 (4) and N(3)—C(31)—C(32)—C(34) ±174·1 (3)°. The structure forms self-paired dimers of xanthine bases with a pair of N—H···O and a pair of weaker C—H···N hydrogen bonds across centers of inversion. There is a partial stacking of the xanthine bases.

Introduction. We have been attempting to crystallize a number of modified bases and nucleosides in the hydrated forms with a view to discovering the underlying reasons that would lead to water molecules being 'sandwiched' between the bases (Parthasarathy, Srikrishnan, Ginell & Guru Row, 1982). In this line of investigation, we obtained crystals of some nucleic acid bases in the anhydrous forms as well. Crystals of 6-methyluracil (m^6U) and 3-isobutyl-1-methylxanthine were two such alkylated bases whose structures were investigated by us (Srikrishnan & Parthasarathy, 1984) with a view to understanding the hydrogen-bonding patterns of alkylated bases. This paper reports the crystal and molecular structure of 3-isobutyl-1-methylxanthine.

Experimental. Crystals were grown from aqueous methanol at room temperature as very fine needles; D_m by flotation (bromoform and benzene); unit-cell parameters on CAD-4 diffractometer using 25 reflections with $14 < \theta < 22°$; crystal of dimensions 0·75 × 0·2 × 0·05 mm, three-dimensional data ($2\theta < 154°$ for Cu $K\alpha$ radiation), $\omega/2\theta$ scan; scan widths calculated using the expression $(0{\cdot}8 + 0{\cdot}4\tan\theta)°$ and aperture widths using $(3{\cdot}0 + 1{\cdot}2\tan\theta)$ mm; max. time spent on any reflection measurement 100 s; faster scan used for strong reflections; intensities of three reflections measured after every hour of exposure; variation of intensities in these three reflections <6% during the course of data collection; crystal orientation checked after every 100 reflections; a total number of 2326 reflections measured out of which 984 were significant $[I > 3\sigma(I)]$; h 0–±6; k 0–11, l 0–32; Lorentz and polarization corrections applied; intensities of three reflections at $\chi \sim 90°$ were measured for different values of φ from 0 to 360° in steps of 10° and the resultant curve of transmission as a function of φ was used to calculate the absorption for all reflections; max. and min. transmission 0·99 and 0·86 with an average of 0·92. Structure solved using *MULTAN* (Germain, Main & Woolfson, 1971); 164 E values ($|E| > 1{\cdot}85$) used as input to *MULTAN* and the correct set with the figure of merit of 1·19 and residual of 0·135 gave all atoms in the molecule; refinement at first with isotropic thermal parameters and later with anisotropic thermal parameters led to an $R = 0{\cdot}089$; difference electron density maps revealed positions of all H atoms; final cycles of refinement with anisotropic thermal parameters for non-H atoms, isotropic for H atoms and extinction-parameter refinement ($g = 6{\cdot}6 \times 10^{-6}$) led to $R = 0{\cdot}058$ for 984 reflections; $wR = 0{\cdot}068$, $S = 2{\cdot}21$, $w[|F_o| - (1/k)|F_c|]^2$ minimized; $w = 4|F_o|^2/\sigma^2(|F_o|)^2$ and $\sigma^2(|F_o|)^2 = [\sigma^2(I) + p^2I^2]/\mathrm{Lp}$ where $p = 0{\cdot}05$, $\sigma(I)$ is standard deviation of intensity I based on counting statistics, k is scale factor; max. and av. $\Delta/\sigma = 0{\cdot}2$ and 0·02; final $|\Delta\rho| = 0{\cdot}2$ e Å^{-3}. Programs and atomic scattering factors as in Enraf–Nonius (1979) *SDP*; Fourier and torsion-angle programs by Dr S. T. Rao and *ORTEP* by Johnson (1965).

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Discussion. The final positional parameters are given in Table 1.* Fig. 1 gives the atom numbering followed in the compound. The bond distances and angles are given in Table 2. The bond lengths and angles are very similar to those found in other methylated xanthine structures such as 3-methylxanthine (Low, Tollin, Brand & Wilson, 1986) and 7-methylxanthine hydrochloride monohydrate (Kistenmacher & Sorrell, 1975). The isobutyl chain is oriented almost perpendicular to the xanthine base [C(2)–N(3)–C(31)–C(32) ±99·8 (4)°]; this is a preferred conformation for $X\text{–}CH_2\text{–}Y$ groups (X is an sp^2 atom) (Soriano-García & Parthasarathy, 1975). The other torsion angles in the isobutyl chain are: N(3)–C(31)–C(32)–C(33) ±62·2 (4) and N(3)–C(31)–C(32)–C(34) ±174·1 (3)°. The packing of the molecule in the crystal is shown in the stereo diagram in Fig. 2. The molecules related by a center of inversion are stacked on top of each other along the crystallographic **a** direction, which is the shortest cell translation of the unit cell. The crystal structure is stabilized by N–H···O hydrogen bonds [N(7)–H(N7)···O(6) 2·732 (4), H(N7)···O(6) 1·85 (4) Å, N(7)–H(N7)···O(6) 165 (3)°]. The structure forms self-paired dimers of xanthine bases using a pair of N–H···O hydrogen bonds across a center of inversion thereby forming ten-membered hydrogen-bonded rings. A pair of C(8)–H(C8)···N(9) hydrogen bonds [C(8)–H(C8)···N(9) 3·447 (5), H(C8)···N(9) 2·63 (5) Å, C(8)–H(C8)···N(9) 141(3)°] is formed across a center of inversion. The N(7)–H(N7)···O(6) and C(8)–H(C8)···N(9) bonds connect the bases together along the **b** and **c** directions giving rise to sheets of bases partially stacked on top of each other along the **a** direction.

Table 1. *Final fractional positional and isotropic thermal parameters with e.s.d.'s given in parentheses*

	x	y	z	B(Å^2)
O(2)	−0·3512 (2)	0·0426 (3)	0·1617 (1)	4·79 (7)
O(6)	0·3278 (5)	0·1416 (3)	0·0503 (1)	3·94 (6)
N(1)	−0·0157 (6)	0·0894 (4)	0·1050 (1)	3·37 (6)
N(3)	−0·2070 (6)	−0·1591 (4)	0·1140 (1)	3·24 (6)
N(7)	0·2759 (6)	−0·1972 (4)	0·0188 (1)	3·33 (6)
N(9)	−0·0242 (6)	−0·3506 (4)	0·0564 (1)	3·71 (7)
C(2)	−0·2023 (8)	−0·0069 (5)	0·1294 (1)	3·45 (8)
C(4)	−0·0378 (7)	−0·2071 (5)	0·0763 (1)	3·03 (7)
C(5)	0·1408 (7)	−0·1091 (4)	0·0539 (1)	2·90 (7)
C(6)	0·1665 (7)	0·0474 (5)	0·0677 (1)	3·02 (7)
C(8)	0·1658 (8)	−0·3375 (5)	0·0219 (2)	3·74 (8)
C(1)	−0·010 (1)	0·2509 (5)	0·1222 (2)	5·4 (1)
C(31)	−0·3837 (7)	−0·2691 (5)	0·1403 (1)	3·43 (8)
C(32)	−0·2273 (8)	−0·3660 (5)	0·1806 (1)	3·60 (8)
C(33)	−0·4237 (9)	−0·4863 (6)	0·2010 (2)	6·0 (1)
C(34)	−0·101 (1)	−0·2677 (6)	0·2237 (2)	5·6 (1)
H(N7)	0·425 (6)	−0·173 (4)	0·001 (1)	3·3 (8)*
H(C8)	0·224 (8)	−0·423 (6)	0·001 (2)	6 (1)*
H1(C1)	0·04 (1)	0·260 (8)	0·155 (2)	13 (2)*
H2(C1)	−0·18 (1)	0·295 (9)	0·124 (2)	13 (2)*
H3(C1)	0·086 (9)	0·321 (6)	0·095 (2)	7 (1)*
H1(C31)	−0·540 (6)	−0·202 (4)	0·158 (1)	2·7 (7)*
H2(C31)	−0·473 (6)	−0·341 (4)	0·112 (1)	3·5 (8)*
H(C32)	−0·074 (6)	−0·422 (4)	0·166 (1)	2·3 (7)*
H1(C33)	−0·52 (1)	−0·544 (7)	0·175 (2)	11 (2)*
H2(C33)	−0·597 (9)	−0·444 (6)	0·221 (2)	7 (1)*
H3(C33)	−0·33 (1)	−0·55 (1)	0·229 (3)	10 (2)*
H1(C34)	0·066 (9)	−0·194 (6)	0·211 (2)	8 (1)*
H2(C34)	−0·03 (1)	−0·327 (6)	0·248 (2)	8 (1)*
H3(C34)	−0·262 (9)	−0·211 (6)	0·243 (2)	7 (1)*

Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of the equivalent isotropic displacement parameter defined as: $\frac{4}{3}[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

Table 2. *Bond distances* (Å) *and bond angles* (°) *between the non-*H *atoms with e.s.d.'s given in parentheses*

N(1)–C(2)	1·408 (4)	N(7)–C(8)	1·339 (4)
C(2)–N(3)	1·385 (4)	C(8)–N(9)	1·319 (4)
C(2)–O(2)	1·211 (3)	C(4)–N(9)	1·356 (4)
N(3)–C(4)	1·371 (3)	N(1)–C(1)	1·477 (4)
C(4)–C(5)	1·367 (4)	N(3)–C(31)	1·475 (4)
C(5)–C(6)	1·415 (4)	C(31)–C(32)	1·526 (4)
C(6)–N(1)	1·389 (3)	C(32)–C(33)	1·529 (4)
C(6)–O(6)	1·236 (3)	C(32)–C(34)	1·519 (5)
C(5)–N(7)	1·380 (3)		

N(1)–C(2)–N(3)	116·4 (2)	C(6)–N(1)–C(1)	117·3 (3)
C(2)–N(3)–C(4)	119·7 (2)	C(2)–N(1)–C(1)	115·9 (3)
N(3)–C(4)–C(5)	121·8 (3)	N(1)–C(2)–O(2)	121·1 (3)
C(4)–C(5)–C(6)	123·1 (2)	N(3)–C(2)–O(2)	122·5 (3)
C(5)–C(6)–N(1)	112·2 (2)	C(2)–N(3)–C(31)	119·5 (2)
C(6)–N(1)–C(2)	126·9 (2)	C(4)–N(3)–C(31)	120·7 (3)
N(3)–C(4)–N(9)	126·5 (3)	N(3)–C(31)–C(32)	113·0 (2)
C(4)–C(5)–N(7)	105·3 (2)	C(31)–C(32)–C(33)	108·3 (3)
C(6)–C(5)–N(7)	131·6 (3)	C(31)–C(32)–C(34)	111·8 (3)
C(5)–C(4)–N(9)	111·8 (2)	C(34)–C(32)–C(33)	111·9 (3)
C(5)–N(7)–C(8)	105·3 (2)	C(5)–C(6)–O(6)	126·8 (3)
N(7)–C(8)–N(9)	114·5 (3)	N(1)–C(6)–O(6)	121·1 (2)
C(4)–N(9)–C(8)	103·1 (2)		

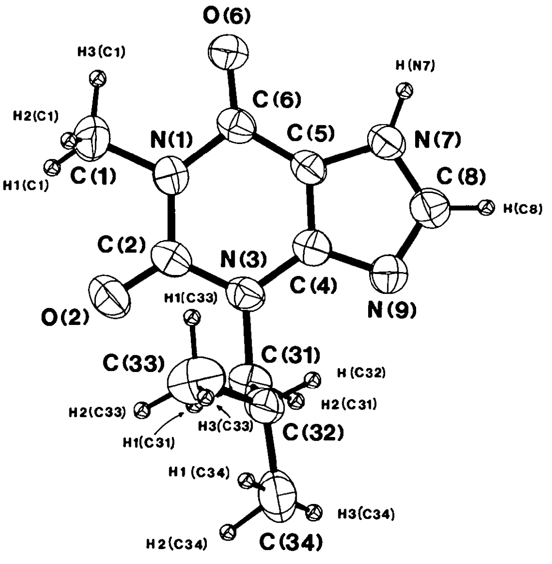

Fig. 1. An *ORTEP* drawing of 3-isobutyl-1-methylxanthine giving the atom numbering of the molecule in the crystal.

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* Lists of structure factors, anisotropic thermal parameters and distances and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51257 (34 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

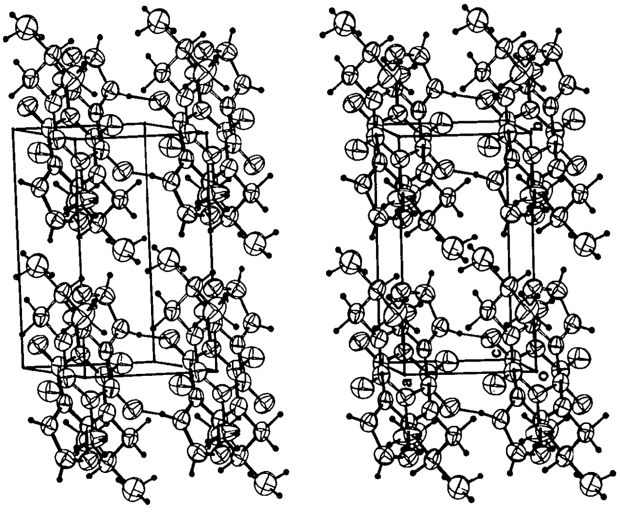

Fig. 2. A stereoscopic representation of the packing of the molecules in the unit cell showing the hydrogen-bonding details and the stacking of the xanthine bases in the crystal structure. Molecules of opposite hands are distinguished by open and filled bonds.

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Structure of Adenosine-5′-mononicotinate (AMN) Trihydrate: an Analog of NAD for Testing Intramolecular Stacking

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Abstract. $C_{16}H_{16}N_6O_5.3H_2O$, $M_r = 426{\cdot}4$, monoclinic, $P2_1$, $a = 9{\cdot}535$ (2), $b = 13{\cdot}932$ (2), $c = 7{\cdot}138$ (2) Å, $\beta = 93{\cdot}13$ (2)°, $V = 946{\cdot}85$ Å^3, $Z = 2$, $D_x = 1{\cdot}495$ g cm^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1{\cdot}5418$ Å, $\mu = 9{\cdot}93$ cm^{-1}, $F(000) = 428$, $T = 294$ K, $R = 0{\cdot}045$ and $wR = 0{\cdot}059$ for 1460 observed reflections [$I > 3\sigma(I)$]. The AMN molecules, unlike NAD or other model structures of NAD, are not charged and exhibit intra- as well as intermolecular stacking of pyridine ring over adenine ring. There is extensive hydrogen bonding in the crystal involving the pyridine and adenine rings and the three water molecules. Rather surprisingly, the ester carbonyl O atom is not involved in the hydrogen bonding.

Introduction. Solution NMR studies on the structure of NAD suggest an equilibrium existing between a folded, stacked conformation and an extended, unstacked one (Sarma, Ross & Kaplan, 1968). The shift towards an unfolded structure at acidic pH was attributed to the protonation of the adenine N1 atom. X-ray studies of a lithium salt of NAD (Reddy, Saenger, Muhlegger & Weimann, 1981) and the free acid form of NAD (Parthasarathy & Fridey, 1984) revealed only intermolecular stacking between the bases, though they showed different conformations of NAD. The absence of intramolecular base stacking was presumed to be due to the low pH (for the lithium salt of NAD: Reddy *et al.*, 1981) or to the charged bases (for the free acid form of NAD: Parthasarathy & Fridey, 1984). In previous years, there have been several structural reports on model compounds for NAD (Johnson, Frank & Paul, 1973; Johnson, Maier & Paul, 1973; Sakaki, Inoue, Senda & Tomita, 1978; Voet, 1973). These were either complexes containing adenine and nicotinamide rings (Sakaki *et al.*, 1978; Voet, 1973) or trimethylene-bridged adenine and nicotinamide rings (Johnson,

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