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The Crystal Structure and Conformational Variations of 5′-Methylthioadenosine

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5′-Methylthioadenosine, $C_{11}H_{15}N_5O_3S$, crystallizes in space group $P2_1$, $Z = 4$, $a = 17{\cdot}215$ (4), $b = 4{\cdot}840$ (1), $c = 17{\cdot}302$ (4) Å and $\beta = 112{\cdot}49$ (1)°. The structure, with two independent molecules per asymmetric unit, was solved by direct methods and refined to a final R value of 0·075 for 2612 significant reflexions measured on an automatic four-circle diffractometer. The two independent molecules A and B show some significant conformational differences. The glycosidic torsion angle [O(1′)–C(1′)–N(9)–C(4)] is 163° in molecule A and −119° in molecule B and the ribose moiety is C(2′)-*exo*, C(3′)-*exo* in molecule A and C(2′)-*endo*, C(3′)-*exo* in molecule B. A feature common to both molecules is the disposition of the thiomethyl side group with respect to the sugar. In nucleotide nomenclature this is the *trans*,*gauche* conformation, rarely found in nucleotides. The molecules are linked by a three-dimensional network of hydrogen bonds between base–sugar and base–base residues.

Introduction

The X-ray analysis of 5′-methylthioadenosine (thiomethyladenosine or TMA), $C_{11}H_{15}N_5O_3S$, was undertaken as part of a project to determine the crystal structures of the related biological sulphonium compounds *S*-adenosylhomocysteine (SAH) and *S*-adenosylmethionine (SAM). TMA is one of the products resulting from the degradation of SAM (Shapiro & Mather, 1958) as follows:

adenine–ribose–S^+-methionine →
adenine–ribose–S–CH_3 + $C_4H_9NO_3$.
[SAM → TMA + homoserine]

SAM or 'active methionine' as it was formerly known (Cantoni, 1952; Borek & Srinivasan, 1966) is a methylating agent, acting *via* DNA for the provision of $-CH_3$ groups in protein synthesis. Knowledge of the structure of TMA may lead to a better understanding of this reaction.

Table 1. *Crystal data for TMA*

Molecular formula	$C_{11}H_{15}N_5O_3S$		
Crystal system	Monoclinic	μ(Cu $K\alpha_1$)	16·35 cm^{-1}
Space group	$P2_1$	Crystal size	0·4 × 0·3 × 0·3 mm
Formula weight	297·347	ω axis	b
Unit-cell volume	1331·973 Å^3	Unit cell	
Z	4	a	17·215 (4) Å
D_c	1·481 g cm^{-3}	b	4·840 (1)
D_m	1·473	c	17·302 (4)
F(000)	624	β	112·49 (1)°
λ(Cu $K\alpha_1$)	1·5404 Å	Systematic absences	$0k0$: $k = 2n + 1$

Experimental

TMA crystallized from an aqueous solution as thin colourless needles. Unit-cell and space-group data were obtained from rotation and Weissenberg films. Accurate cell dimensions were determined by least-squares refinement of 20 θ values measured on a four-circle diffractometer. The density was determined by flotation in 1,2-dibromoethane and chloroform. Crystal data are given in Table 1.

Integrated intensities were measured on a Hilger & Watts Y290 computer-controlled diffractometer using an ω–2θ scanning technique. The counts were recorded in 80 steps at intervals of $\theta = 0{\cdot}01°$, the count time per step being 1 s. The background on each side of the peak was estimated in a single step count of 8 s. Three reference reflexions showed no significant change in intensity over the ten-day period of data collection.

Reflexions were measured to a maximum θ value of 70°. 3290 reflexions were recorded, including 496 symmetry-related pairs. Of the 2794 independent intensities measured, 173 with $I \leq 3\sigma(I)$ were classified as unobserved. Lp corrections were applied but no absorption correction was made.

Structure determination and refinement

The structure was determined by direct methods using the program *MULTAN* (Germain, Main & Woolfson, 1971). The solution was based on 200 reflexions with $E \geq 1{\cdot}56$. The E map corresponding to the solution with the highest absolute figure of merit (FOM = 1·34) and the lowest R_{Karle} (19·83) revealed

Table 2. *Final positional parameters for the non-hydrogen atoms in TMA, with e.s.d.'s in parentheses*

	x	*y*	*z*
Molecule *A*			
C(1')	0·0755 (5)	0·5748 (19)	0·7266 (5)
C(2')	0·0064 (5)	0·3717 (23)	0·7250 (7)
C(3')	−0·0055 (6)	0·4444 (25)	0·8067 (5)
C(4')	0·0756 (5)	0·5504 (18)	0·8620 (5)
C(5')	0·1401 (6)	0·3449 (30)	0·9184 (6)
C(2)	0·0973 (4)	−0·0669 (20)	0·5532 (4)
C(4)	0·1432 (3)	0·2396 (18)	0·6537 (4)
C(5)	0·2245 (4)	0·2043 (17)	0·6617 (4)
C(6)	0·2392 (4)	0·0151 (19)	0·6072 (4)
C(7)	0·1472 (10)	0·4586 (24)	1·0792 (8)
C(8)	0·2277 (3)	0·5069 (14)	0·7514 (3)
N(1)	0·1727 (3)	−0·1246 (16)	0·5533 (3)
N(3)	0·0745 (3)	0·1112 (16)	0·5980 (3)
N(6)	0·3148 (3)	0·0363 (19)	0·6073 (4)
N(7)	0·2780 (3)	0·3744 (17)	0·7229 (3)
N(9)	0·1462 (3)	0·4366 (15)	0·7131 (3)
O(1')	0·1080 (4)	0·6983 (13)	0·8071 (4)
O(2')	0·0631 (5)	0·3938 (21)	0·6582 (5)
O(3')	−0·0641 (4)	0·6670 (21)	0·7907 (4)
S	0·1131 (2)	0·2055*	0·9993 (2)
Molecule *B*			
C(1')	0·4217 (3)	0·1653 (15)	0·2537 (4)
C(2')	0·4592 (3)	−0·1195 (15)	0·2531 (3)
C(3')	0·4910 (4)	−0·0787 (17)	0·1818 (4)
C(4')	0·4186 (4)	0·0798 (16)	0·1189 (4)
C(5')	0·3487 (4)	−0·1002 (20)	0·0592 (4)
C(2)	0·3955 (4)	0·6545 (18)	0·4555 (4)
C(4)	0·3589 (4)	0·3399 (16)	0·3546 (4)
C(5)	0·2829 (4)	0·2891 (15)	0·3629 (4)
C(6)	0·2661 (4)	0·4408 (18)	0·4242 (4)
C(7)	0·3718 (7)	0·0056 (23)	−0·0888 (6)
C(8)	0·2827 (4)	0·0348 (19)	0·2628 (5)
N(1)	0·3261 (4)	0·6228 (17)	0·4696 (4)
N(3)	0·4179 (3)	0·5237 (14)	0·3988 (3)
N(6)	0·1951 (4)	0·4225 (20)	0·4376 (4)
N(7)	0·2373 (3)	0·0977 (16)	0·3049 (4)
N(9)	0·3580 (3)	0·1783 (14)	0·2898 (3)
O(1')	0·3837 (3)	0·2459 (13)	0·1691 (2)
O(2')	0·5229 (3)	−0·1935 (12)	0·3296 (3)
O(3')	0·5611 (3)	0·1037 (14)	0·2089 (3)
S	0·3771 (2)	−0·2646 (3)	−0·0187 (2)

* Kept constant to define origin along **b**.

Table 3. *Positional and thermal parameters for the hydrogen atoms*

U = mean square amplitude ($\overline{U^2}$) of atomic vibration.

	x	*y*	*z*	*U*(Å²)
		MOLECULE A		
H(61)	0.3424	0.0807	0.5806	0.046
H(62)	0.3559	-0.1546	0.6473	0.046
H(2)	0.0478	-0.1860	0.5111	0.040
H(8)	0.2492	0.6542	0.7998	0.039
H(2')	0.0297	0.1647	0.7307	0.049
H(20')	0.4945	-0.3270	0.3617	0.034
H(3')	-0.0253	0.2821	0.8337	0.063
H(30')	-0.1230	0.6676	0.7488	0.068
H(4')	0.0657	0.6987	0.9016	0.046
H(51')	0.1983	0.4414	0.9450	0.056
H(52')	0.1444	0.1753	0.8806	0.056
H(1')	0.0492	0.7308	0.6807	0.045
H(71)	0.1328	0.3900	1.1300	0.085
H(72)	0.2132	0.4877	1.0980	0.085
H(73)	0.1141	0.6484	1.0550	0.085
		MOLECULE B		
H(61)	0.1430	0.5096	0.4029	0.045
H(62)	0.1838	0.2784	0.4703	0.045
H(2)	0.4391	0.7971	0.4942	0.033
H(8)	0.2643	-0.1084	0.2133	0.038
H(2')	0.4115	-0.2706	0.2362	0.026
H(20')	-0.0801	0.5803	0.6702	0.034
H(3')	0.5037	-0.2676	0.1378	0.029
H(30')	0.6084	0.2271	0.2271	0.042
H(4')	0.4412	0.2118	0.0844	0.029
H(51')	0.2959	0.0263	0.0283	0.045
H(52')	0.3332	-0.2536	0.0936	0.045
H(1')	0.4700	0.3017	0.2860	0.029
H(71)	0.3876	-0.0723	-0.1387	0.050
H(72)	0.3088	0.0865	-0.1140	0.050
H(73)	0.4145	0.1660	-0.0566	0.050

the positions of 14 non-hydrogen atoms of molecule *A*. The two complete molecules, with the exception of the H atoms, were located by several successive structure factor calculations and weighted Fourier syntheses based initially on these 14 atoms. The coordinates of the 40 atoms thus located were refined by five cycles of isotropic full-matrix least-squares refinement to R = 0·110. Six more cycles of refinement using anisotropic temperature factors reduced the R value to 0·085. The parameters for one molecule, *A* or *B*, were refined in alternate cycles. A difference electron density map was calculated from which positions of all the H atoms were obtained. After two further cycles of least-squares calculations with anisotropic temperature factors for non-hydrogen atoms (including H atoms in structure factor calculations only, with the isotropic temperature factors corresponding to the atom to which they are bonded) the refinement converged to a final R value of 0·075.

Results

The final parameters of the non-hydrogen atoms, together with their estimated standard deviations, are given in Table 2. The positions and isotropic temperature factors for the H atoms are given in Table 3. Bond distances and angles involving the non-hydrogen atoms are shown in Fig. 1(*a*) and (*b*). Bond distances and angles involving H atoms are listed in Table 4.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33068 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond lengths* (Å) *and angles* (°) *involving hydrogen*

	Molecule *A*	Molecule *B*
N(6)–H(61)	0·96	0·96
N(6)–H(62)	0·96	0·96
C(2)–H(2)	1·05	1·05
C(8)–H(8)	1·05	1·05
C(2′)–H(2′)	1·06	1·05
O(2′)–H(20′)	1·00	1·08
C(3′)–H(3′)	1·03	1·05
O(3′)–H(30′)	0·99	0·89
C(4′)–H(4)	1·04	1·04
C(5′)–H(51′)	1·03	1·05
C(5′)–H(52′)	1·07	1·05
C(1′)–H(1′)	1·06	1·04
C(7)–H(71)	1·05	1·06
C(7)–H(72)	1·06	1·07
C(7)–H(73)	1·07	1·07
C(6)–N(6)–H(61)	123·7	124·1
C(6)–N(6)–H(62)	124·2	123·7
N(1)–C(2)–H(2)	114·6	115·8
N(3)–C(2)–H(2)	114·8	116·1
N(7)–C(8)–H(8)	123·1	123·7
N(9)–C(8)–H(8)	123·1	123·8
O(2′)–C(2′)–H(2′)	109·8	109·4
C(1′)–C(2′)–H(2′)	109·7	110·1
C(3′)–C(2′)–H(2′)	107·8	110·1
C(2′)–O(2′)–H(20′)	98·9	106·7
O(3′)–C(3′)–H(3′)	109·2	112·8
C(2′)–C(3′)–H(3′)	115·1	113·1
C(4′)–C(3′)–H(3′)	111·1	113·1
C(3′)–O(3′)–H(30′)	126·1	114·2
C(3′)–C(4′)–H(4′)	107·5	109·5
O(1′)–C(4′)–H(4′)	108·4	109·4
C(5′)–C(4′)–H(4′)	106·7	109·3
O(1′)–C(1′)–H(1′)	110·1	109·9
N(9)–C(1′)–H(1′)	110·1	108·7
C(2′)–C(1′)–H(1′)	109·5	108·8
C(4′)–C(5′)–H(51′)	109·5	108·3
C(4′)–C(5′)–H(52′)	108·1	108·8
S–C(5′)–H(52′)	107·1	108·6
S–C(7)–H(71)	108·7	109·5
S–C(7)–H(72)	109·1	109·4
S–C(5′)–H(51′)	108·7	107·9
S–C(7)–H(73)	108·6	109·4

Discussion

Molecule A

Adenine. Bond lengths in the adenine ring of molecule *A* are all within 3σ of average values reported for the neutral (unprotonated) base (Rao & Sundaralingam, 1970; Saenger, 1973), with the exception of C(8)–N(9) = 1·343 (6) Å which is marginally shorter (4σ) than the reported average value of 1·367 Å. The greatest difference in bond angles in this ring compared with reported averages (Saenger, 1973) is for N(1)–C(2)–N(3) = 130·5 (4)°, which is about 4σ larger than the reported average of 128·9°. As expected the base is planar within experimental error

Table 5. *Least-squares planes*

Atoms marked with an asterisk have not been included in the calculations of the planes. Deviations from the planes are in Å. The equations for the planes are in the form: $PX' + QY' + RZ' = S$, and are defined with repect to orthogonal axes $X'(a^*)$, $Z'(c)$, $Y'(b)$, expressed in Å.

		MOLECULE A	MOLECULE B
ADENINE RING	N(1)	0.020	-0.028
	C(2)	0.009	0.163
	N(3)	-0.028	0.003
	C(4)	0.002	-0.009
	C(5)	0.012	-0.010
	C(6)	-0.003	0.024
	N(6)	-0.017	0.030
	N(7)	0.001	0.007
	C(8)	0.001	-0.014
	N(9)	0.004	-0.018
RIBOSE 3-ATOM PLANE	C(1)	0.000	0.000
	C(2)*	-0.247	-0.481
	C(3)*	-0.664	0.217
	C(4)	0.000	0.000
	O(1)	0.000	0.000
	C(5)*	1.403	-1.310
RIBOSE 4-ATOM PLANE	C(1)	0.051	0.1 3
	C(2)	-0.030	-0.060
	C(4)	0.032	0.064
	O(1)	-0.053	-0.107
	C(3)*	-0.479	0.607
	C(5)*	1.432	-1.274

	P	Q	R	S
MOLECULE A				
ADENINE RING	0.1209	-0.7236	0.6794	6.4795
SUGAR(3-ATOM PLANE)	0.7748	-0.6313	-0.0330	-1.2235
SUGAR(4-ATOM PLANE)	0.6956	-0.7169	-0.0454	-1.7569
MOLECULE B				
ADENINE RING	0.4306	-0.7233	0.5397	3.2799
SUGAR(3-ATOM PLANE)	0.7160	0.6841	-0.1386	5.1224
SUGAR(4-ATOM PLANE)	0.8573	0.5063	-0.0930	5.8974

(Table 5). All the H atoms were located in the structure analysis, showing the lack of protonation at N(1) in keeping with the molecular geometry (Saenger, 1973). N(6) of molecule *A* acts as a donor in the formation of two intermolecular hydrogen bonds, to atoms N(1) and O(2′) respectively of molecule *B* (Table 6). N(1) of molecule *A* accepts a hydrogen bond through N(6) of molecule *B* (Table 6).

Ribose. There are two exceptionally short bond lengths in the ribose group of molecule *A*, namely C(3′)–C(4′) = 1·451 (13) Å, which is 7σ less than the reported average of 1·53 Å found in nucleosides and nucleotides (Saenger, 1973), and C(2′)–O(2′) = 1·321 (11) Å, which is 9σ less than the reported average of 1·41 Å. Bond angles in this group conform to normal values except for C(2′)–C(3′)–C(4′), C(1′)–C(2′)–O(2′) and O(1′)–C(4′)–C(3′) which are slightly larger, and C(4′)–C(3′)–O(3′), which is slightly smaller than average values would suggest.

The torsion angles (Table 7) for the molecule *A* ribose group reveal its exceptional conformation, one which, to the best knowledge of the authors, is a hitherto unreported ribose conformation for a β-purine deriva-

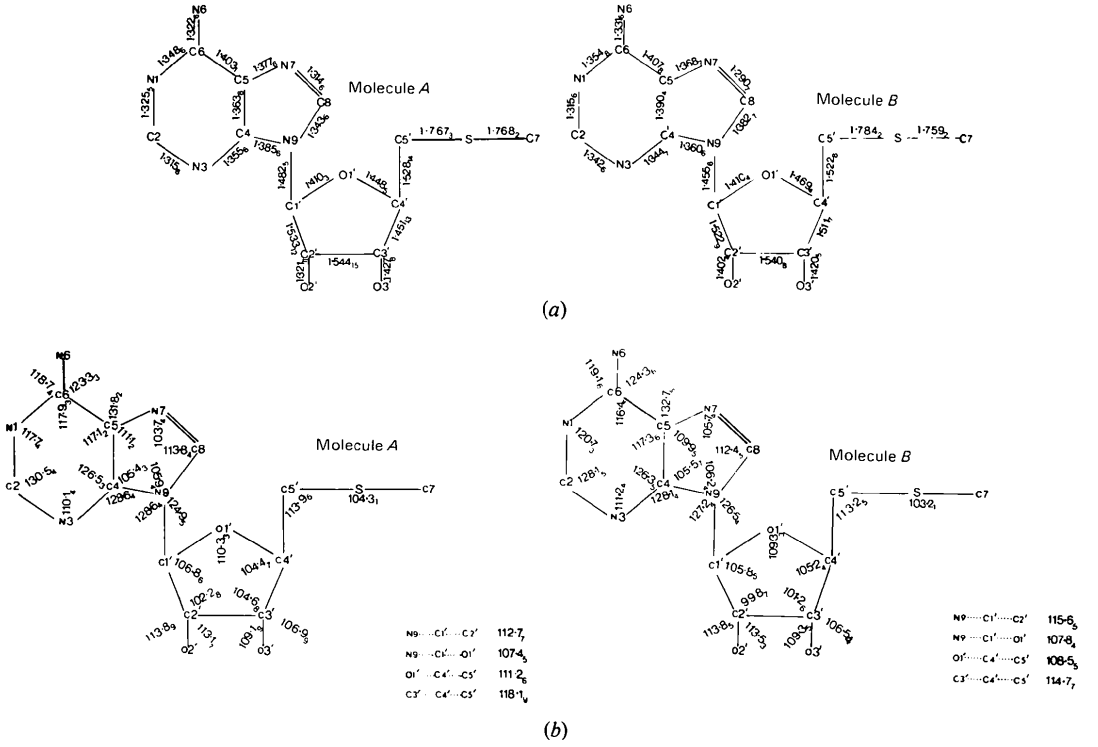

Fig. 1. (*a*) Bond distances (Å) and (*b*) bond angles (°). E.s.d.'s are shown subscripted.

Table 6. *Bond lengths* (Å) *and angles* (°) *for the intermolecular hydrogen bonds*

Bond number					Code number and symmetry operation for atom*
1(*a*)	$N(6)^A\cdots O(2')^{*B}$	3·062	$N(6)^A$–$H(61)^A\cdots O(2')^{*B}$	145	(ii) $1-x, -\frac{1}{2}+y, 1-z$
	$H(61)^A\cdots O(2')^{*B}$	2·790			
1(*b*)	$N(6)^B\cdots O(2')^{*A}$	3·193	$N(6)^B$–$H(62)^B\cdots O(2')^{*A}$	152	(iii) $-x, \frac{1}{2}+y, 1-z$
	$H(62)^B\cdots O(2')^{*A}$	2·309			
2(*a*)	$N(6)^A\cdots N(1)^{*B}$	2·963	$N(6)^A$–$H(62)^A\cdots N(1)^{*B}$	145	(i) x, y, z
	$H(62)^A\cdots N(1)^{*B}$	2·871			
2(*b*)	$N(6)^B\cdots N(1)^{*A}$	3·086	$N(6)^B$–$H(61)^B\cdots N(1)^{*A}$	172	(i) x, y, z
	$H(61)^B\cdots N(1)^{*A}$	2·469			
3(*a*)	$O(3')^A\cdots N(7)^{*B}$	2·821	$O(3')^A$–$H(30')^A\cdots N(7)^{*B}$	162	(iii) $-x, \frac{1}{2}+y, 1-z$
	$H(30')^A\cdots N(7)^{*B}$	1·881			
3(*b*)	$O(3')^B\cdots N(7)^{*A}$	2·787	$O(3')^B$–$H(30')^B\cdots N(7)^{*A}$	168	(ii) $1-x, -\frac{1}{2}+y, 1-z$
	$H(30')^B\cdots N(7)^{*A}$	1·992			
4	$O(2')^B\cdots N(3)^{*B}$	2·866	$O(2')^B$–$H(20')^B\cdots N(3)^{*B}$	161	(iv) $x, -1+y, z$
	$H(20')^B\cdots N(3)^{*B}$	1·821			

tive. This ribose ring is in an approximate half-chair conformation with a pseudo twofold axis bisecting C(3′)–C(4′). The corresponding asymmetry parameter (Duax & Norton, 1975), $\Delta C_2^{C_{1'}} = 0{\cdot}7°$, is very small. This conformation, with respect to the plane C(1′)–O(1′)–C(4′), is C(2′)-*exo*, C(3′)-*exo* (Table 4). The pseudorotation phase angle P (Altona & Sundaralingam, 1972) is 217°. This is outside both the ranges commonly found in β-purines. In fact, only one structure, β-pyrimidine deoxycytidine 5′-phosphate (dCMP) (Viswamitra, Reddy, Lin & Sundaralingam, 1971), has been reported with a comparable value of P (213·6°). It is also of interest to note that the deoxyribose sugar of dCMP is also C(2′)-*exo*, C(3′)-*exo* with similar deviations from the C(1′)–O(1′)–C(4′) plane as reported here (Table 4).

Atom O(3′) of the molecule *A* ribose acts as a donor in the formation of a strong intermolecular hydrogen bond to N(7) of molecule *B* and O(2′) accepts a hydrogen bond from N(6) of molecule *B*.

Table 7. *Selected torsion angles* (°)

The positive sense of rotation is clockwise from *P* to *S* while looking down bond *QR*. Greek letters correspond to Sundaralingam's (1969) notation.

	P	*Q*	*R*	*S*	Molecule *A*	Molecule *B*
χ	O(1′)	C(1′)	N(9)	C(4)	163	−119
τ_0	C(4′)	O(1′)	C(1′)	C(2′)	10	−19
τ_1	O(1′)	C(1′)	C(2′)	C(3′)	11	38
τ_2	C(1′)	C(2′)	C(3′)	C(4′)	−28	−42
τ_3	C(2′)	C(3′)	C(4′)	O(1′)	34	31
τ_4	C(3′)	C(4′)	O(1′)	C(1′)	−28	−8
	O(1′)	C(4′)	C(5′)	S	170	169
	C(3′)	C(4′)	C(5′)	S	−69	−73
	C(4′)	C(5′)	S	C(7)	−83	75

Thiomethyl conformation. Torsion angles S–C(5′)–C(4′)–O(1′) 169·6° and S–C(5′)–C(4′)–C(3′) −69·4° correspond to the *trans*, *gauche* conformation in nucleotide nomenclature.

Glycosyl bond and glycosyl torsion angle. The number of permissible conformations produced by rotation about the glycosidic bond C(1′)–N(9) is restricted by interactions between the substituents of the base and sugar. This is borne out by the observation that the glycosidic torsion angle χ, defined by O(1′)–C(1′)–N(9)–C(4), tends to occur in several relatively small ranges for both purine and pyrimidine derivatives (Altona & Sundaralingam, 1972). The observed ranges of χ also tend to correspond to specific sugar conformations. It has been shown for type *S* pyrimidine derivatives that an approximate correlation exists between the glycosidic bond length and the torsion angle χ, with C(1′)–N tending to increase as χ decreases (Lin, Sundaralingam & Arora, 1971). This is presumably the result of strain imposed by rotating away from positions of preferred conformation. Molecule *A* of TMA shows a similar tendency, having an unusual χ value of 163° (*anti*) and an unusually long C(1′)–N(9) bond distance of 1·482 (5) Å, compared with the average value for purine derivatives of 1·46 Å (Sundaralingam & Abola, 1973). In contrast, molecule *B* has a χ value of 241° (*anti*), which is close to the value for the commonly occurring type *S* β-purines (Altona & Sundaralingam, 1972), and a normal C(1′)–N(9) distance of 1·455 (6) Å.

Molecule B

Adenine. Apart from C(4)–C(5) [1·390 (4) Å], which is a little longer than expected, bond lengths in the adenine moiety of molecule *B* are all within 3σ of the accepted values for the neutral base. Bond angles also agree well with those expected for the neutral base, with the exception of C(6)–N(1)–C(2) = 120·7 (3)° which is about 7σ greater than the normally accepted value. The base is planar within experimental error (Table 5). As for molecule *A* there is no protonation at N(1) and differences in bond lengths and angles are much greater when compared with those for a protonated adenine ring (Rao & Sundaralingam, 1970) than comparison with those for a neutral base reveals. N(6) of molecule *B* acts as a donor in the formation of intermolecular hydrogen bonds to atoms N(1) and O(2′) of molecule *A*, and N(1) of molecule *B* accepts a hydrogen bond through N(6) of molecule *A*. By coincidence, this system is similar to the hydrogen-bond scheme described previously for molecule *A*.

Ribose. Bond lengths and angles in the molecule *B* ribose agree well with the average values reported by Saenger (1973). The only notable differences (in the range 6 to 8σ) are in the bond angles around C(2′), where C(1′)–C(2′)–O(2′) and O(2′)–C(2′)–C(3′) are both slightly larger than expected, and in the exocyclic angle C(4′)–C(3′)–O(3′), which is low.

Unlike the molecule *A* ribose, the ribose in molecule *B* displays a conformation commonly found in type *S* β-purines (Altona & Sundaralingam, 1972). It is a half-chair with an approximate twofold axis bisecting C(2′)–C(3′); $\Delta C_2^{O_{1'}} = 9{\cdot}2°$ and $P = 172°$. With respect to plane C(1′)–O(1′)–C(4′) the conformation is C(2′)-*endo*, C(3′)-*exo* (Table 5).

Atom O(3′) acts as a donor in the formation of a strong intermolecular hydrogen bond to N(7) of molecule *A* and O(2′) accepts a hydrogen bond from N(6) of molecule *A*.

Thiomethyl conformation. As for molecule *A*, the thiomethyl substituent is in the unusual *trans*,*gauche* conformation to the sugar.

Glycosyl bond and glycosyl torsion angle. As mentioned previously, the adenine moiety in molecule *B* is *anti* to the sugar with $\chi = 241°$ and the glycosidic bond length C(1′)–N(9) = 1·455 (6) Å. These values agree closely with those found in type *S* β-purines, in sharp contrast to the corresponding parameters for molecule *A*, which are outside the normal ranges.

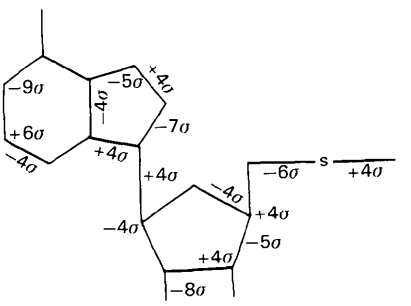

Fig. 2. Major differences in bond lengths and angles between molecules *A* and *B* (+ indicates bond length or angle in molecule *A* greater than that in *B*, and *vice versa* for −).

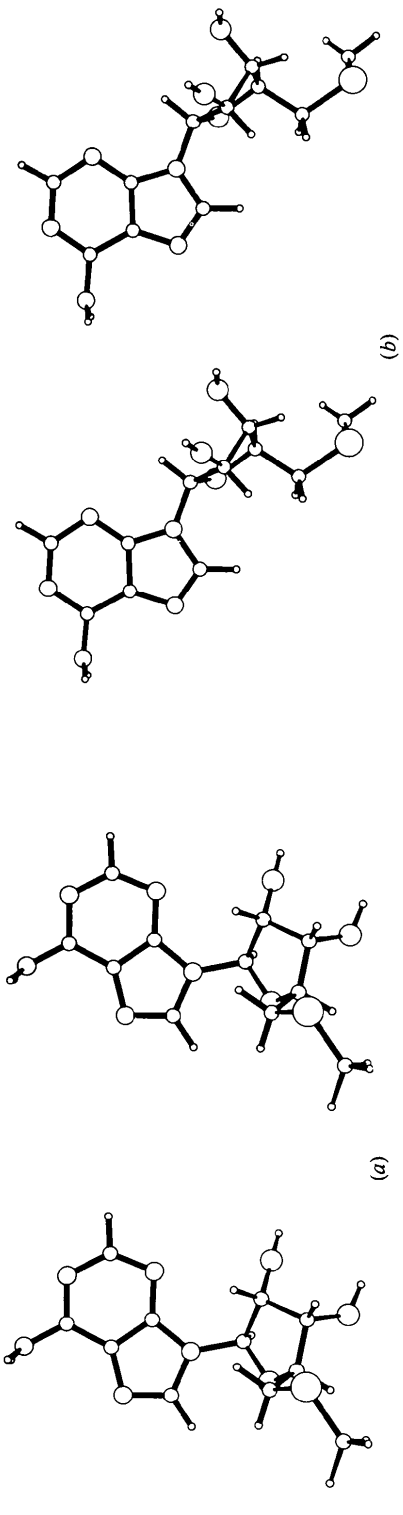

Fig. 3. Stereoviews of the two independent molecules viewed perpendicular to the adenine ring (*a*) in molecule *A* and (*b*) in molecule *B*. Atoms are shown with radii increasing with increasing atomic number.

Comparison of the two independent TMA molecules

From the above it is evident that molecule *B* displays many of the normal characteristics associated with β-purine derivatives, whereas molecule *A* has several unusual features. Other features are common to both molecules. Since the two molecules crystallize together a significant quantitative comparison may be made of their geometries.

Bond lengths and angles. Fig. 2 indicates differences greater than 3σ, where σ has been taken as the larger of the two values in Fig. 1(*a*) and (*b*). Differences at the 4σ level are marginally significant, representing variations in distance of about 0·026 Å and in angle of about 3·0° (apart from values involving S atoms for which the corresponding values are much less).

In the adenine group, differences occur mainly either in the neighbourhood of hydrogen bonding [affecting N(1) and C(3)] or towards the ribose where differences are presumably caused by steric interactions due to conformational variations (Fig. 3*a* and *b*) about the glycosidic bond (χ values). These stereoviews reveal several features of interest. For example, in molecule *B* H(8) is much closer to the centroid of the sugar ring (3·107 compared with 3·409 Å in molecule *A*), while in molecule *A* H(8) is closer to O(1′) (2·462 compared with 2·992 Å in molecule *B*). With respect to the C(2′) proton H(2′) its closest approach to the adenine is H(2′)···N(3) = 2·452 Å in molecule *A* (4·470 Å in *B*) and H(2′)···H(8) = 2·535 Å in molecule *B* (4·284 Å in *A*). The effects of steric hindrance associated with H(2′) have been discussed for several nucleosides and nucleotides by Haschemeyer & Rich (1967).

The differences in bond lengths and angles associated with the ribose moieties are on the whole not very great and are probably accountable in terms of the conformational differences discussed above. The large difference (8σ) in bond length for C(2′)–O(2′) is not easily explained, however, but may be due to the different hydrogen-bonding environments of the two molecules.

Hydrogen bonding. There are no intramolecular hydrogen bonds. Intermolecular hydrogen bonds are listed in Table 6 and illustrated in part in Fig. 4 which shows three pairs of corresponding interactions between symmetry-related molecules *A* to *B* or *B* to *A* [designated 1, 2, 3 (*a*) or (*b*) respectively in Table 6]. In this way an inner spiral (with molecules *A* acting as donors) and an outer spiral (with molecules *B* acting as donors) forms around the 2_1 axis at $(\frac{1}{2},y,\frac{1}{2})$ and similarly at $(\frac{1}{2},y,0)$. The link in the **b** direction is hydrogen bond 4 (Table 6) between O(2′) in molecule B^{i} and N(3) in molecule B^{iv}. Thus there is *B*-to-*B* hydrogen bonding, but no *A*-to-*A* hydrogen bonding. O(2′) of molecule *A* is therefore somewhat surprisingly excluded from the hydrogen-bond scheme, except as an acceptor in bond 1(*b*) (Table 6), unless a

weak interaction from O(2′) in A^{i} to N(6) of B^{ii} is considered, where O(2′)···N(6) = 3·193 Å, but the angle O(2′)–H(2O′)···N(6) = 125° is very low. It is reasonable to assume that the transition C(3′)-*exo* (molecule *A*) to C(2′)-*endo* (molecule *B*) which is not subject to energy-barrier restriction (Wilson & Rahman, 1971) is the result of the different packing forces coming into play with respect to the two molecules.

Short contacts not associated with hydrogen bonding are given in Table 8.

C–S *bonds and thiomethyl conformation.* The average C–S bond length in TMA is 1·770 Å, with similar values in molecule *A* (1σ) but two distinct values in molecule *B* ($\pm$7σ from the average value). As already mentioned, the disposition of the C–S–CH_3 groups is similar in both molecules, being *trans,gauche* to the sugar. This conformation has been observed only once in nucleotide studies, for deoxyuridine 5′-phosphate (5′-dUMP) (Viswamitra, Seshadri & Post, 1975). All

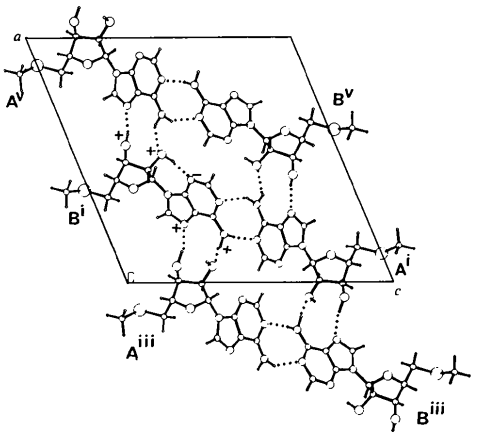

Fig. 4. A *b*-axis projection showing hydrogen-bonded spirals round the 2_1 axes [$\frac{1}{2}$,*y*,$\frac{1}{2}$] and [0,*y*,$\frac{1}{2}$]. The numbering scheme for the different molecules is (i) *x*,*y*,*z*, (iii) $-x$, $\frac{1}{2}+y$, $1-z$, (v) $1-x$, $\frac{1}{2}+y$, $1-z$. In addition $\pm$ against a particular atom indicates a translation of $\pm$**b** to the next molecule.

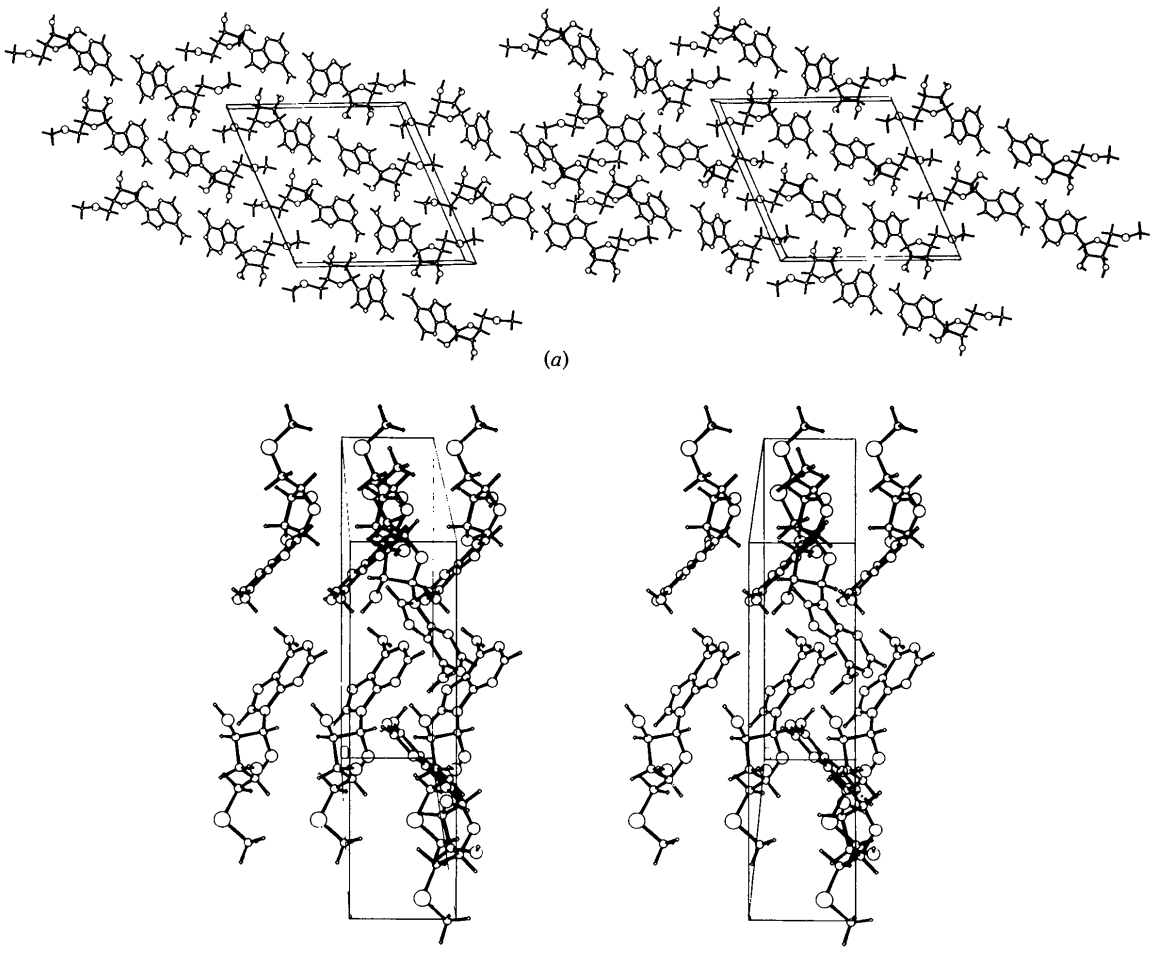

Fig. 5. (*a*) Stereoview along **b** showing molecular packing. Note the S–CH_3 groups strung along **a** separating hydrophilic regions. (*b*) Stereoview along **a***.

Table 8. *Some intermolecular contacts* (≤3·5 Å)

		Symmetry operation for atom*
$O(2')^A \cdots N(1)^{*A}$	3·41 Å	$-x, \frac{1}{2}+y, 1-z$
$O(2')^A \cdots N(6)^{*B}$	3·40	$-x, \frac{1}{2}+y, 1-z$
$O(2')^A \cdots N(7)^{*B}$	3·44	$-x, \frac{1}{2}+y, 1\ z$
$O(2')^A \cdots C(2)^{*A}$	3·48	$-x, \frac{1}{2}+y, 1-z$
$N(3)^A \cdots C(2)^{*A}$	3·48	$-x, \frac{1}{2}+y, 1-z$
$O(3')^B \cdots C(8)^{*A}$	3·46	$1-x, -\frac{1}{2}+y, 1-z$
$C(7)^B \cdots O(3')^{*B}$	3·35	$1-x, -\frac{1}{2}+y, -z$

other nucleotides studied in the solid state exhibit the *gauche,gauche* conformation associated with double-helical DNA.

Crystal packing

Fig. 5(*a*) is a stereoview of the crystal packing along **b**. The hydrogen-bonded spirals along **b** are interlinked to form extended hydrogen-bonded regions parallel to **a**. These regions are not hydrogen bonded across **a** since the S–CH_3 groups from molecules *A* and *B* together with their symmetry equivalents are packed along the *a* axis. The S atoms in molecules *A* and *B* are separated by an almost exact *a*/2 translation to produce a pseudo $P2_1/a$ arrangement for the S atoms which is not carried through to the other atoms to any great extent. Fig. 5 thus shows clearly the existence of hydrogen-bonded hydrophilic regions separated by hydrophobic ribbons parallel to **a**.

Conclusions

This study has revealed a degree of flexibility in the TMA molecule with a sugar conformation and a glycosidic torsion angle 'normal' in molecule *B*, and 'abnormal' in molecule *A*. The *trans,gauche* conformation about the C(5′)–C(4′) bond common to both molecules of TMA may also be a feature of the biologically active *S*-adenosylmethionine (SAM). If this is found to be so it may well have an important bearing on the mode of interaction of SAM with DNA. It has already been established that the *trans,gauche* nucleotide conformation cannot easily be incorporated in double-helical DNA (Viswamitra *et al.*, 1975; Rodley, Scobie, Bates & Lewitt, 1976).

All calculations were carried out on the London University CDC 6600 computer. We thank Dr D. B. Davies for suggesting this study, and Dr F. Schlenk who supplied the compound. One of us (NB) acknowledges the receipt of an award from the Science Research Council during the course of this work.

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