Stereochemistry of Nucleic Acids and Their Constituents. XXII.[1] The Crystal and Molecular Structure of N^6-(Δ^2-Isopentenyl)-2-methylthioadenine, a Modified Base of Transfer Ribonucleic Acid Essential for Messenger Ribonucleic Acid Directed Ribosome Binding to Transfer Ribonucleic Acid[2]

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Abstract: The crystal structure of N^6-(Δ^2-isopentenyl)-2-methylthioadenine, $C_{11}H_{15}N_5S$, has been determined from three-dimensional X-ray diffraction data measured on an automated four-circle diffractometer. The crystals are triclinic, space group $P\bar{1}$, with $a = 5.907$, $b = 11.487$, $c = 10.595$ Å, $\alpha = 95.73$, $\beta = 100.00$, $\gamma = 114.27°$, and two molecules per unit cell. The structure was solved by Patterson and Fourier methods and refined on 137 observed reflections by full-matrix least-squares methods to an R value of 0.047. The molecules exist in the N(9)–H tautomeric form and are linked across inversion centers by hydrogen-bond pairs, N(9)–H···N(3) and N(6)–H···N(7), to form continuous ribbons. The methylthioadenine residues lie in the planes of the ribbons, while the isopentenyl groups are rotated 91° from these planes. The purine rings display parallel stacking typical of nucleic acid constituents in other crystal structures. This feature, together with hydrogen bonding and van der Waals interactions between the hydrophobic residues, appear to provide the important cohesive forces of the molecular arrangement in the crystal.

The alkylated nucleosides form a major subgroup of the rare nucleosides found in tRNA. Of these alkylated nucleosides the isoprene-containing nucleoside N^6-(Δ^2-isopentenyl)adenine is unique for it was the first naturally occurring compound with cytokynin activity (that which stimulates cell division and differentiation in plants) shown to be an integral part of tRNA.[4,5] It is located at the strategic position adjacent to the 3′ side of the anticodon triplet of all known tRNA's that respond to codons beginning with uridine.[6,7] Data are available on at least three different tRNA's, serine tRNA,[8] suppressor tyrosine tRNA,[9] and tyrosine tRNA (yeast),[10] which suggest that specific modification of the isopentenyl side chain greatly reduces the mRNA-directed ribosome binding activity of the tRNA's. The current notion is that the isopentenyl side chain may be essential both for the formation of the anticodon–messenger–ribosome complex and for the structural integrity of the anticodon loop itself. In the Fuller–Hodgson model,[11] this and other alkylated nucleosides on the 3′ side of the anticodon have been implicated in increasing the stacked conformation of the anticodon loop by hydrophobic interaction. In a continuing program of research in our laboratory on the stereochemistry of the rare nucleosides we now have determined the crystal structure of N^6-(Δ^2-isopentenyl)-2-methylthioadenine, the first compound in this series under investigation.

Experimental Section

Single crystals suitable for the structure determination were kindly supplied by Dr. Sidney Hecht of this department. The crystal symmetry and approximate lattice parameters for a reduced triclinic cell were determined from Weissenberg and oscillation photographs. The lattice parameters and the diffraction intensity data were measured on a Picker FACS 1 diffractometer using nickel-filtered Cu radiation ($\lambda = 1.5418$ Å). The unit-cell parameters (Table I) were determined by a least-squares procedure from angle settings of 12 accurately centered reflections. Intensity measurements were made using a θ–2θ scan technique with a scan range of 2°, a scan rate of 2° min^{-1}, and background counts of 10 sec at each scan limit. Intensities of all nonequivalent reflections accessible below 128° in 2θ were recorded from a wedge-shaped crystal (maximum dimension ~0.3 mm) mounted with the a axis parallel to the ϕ axis of the goniostat. During the course of the structure refinement, the data below 60° in 2θ (for *ca.* 400 re-

Table I. Crystal Data for N^6-(Δ^2-Isopentenyl)-2-methylthioadenine

Stoichiometry	$C_{11}H_{15}N_5S$
Space group	$P\bar{1}$
Cell dimensions, Å	$a = 5.907 \pm 0.002$
	$b = 11.487 \pm 0.006$
	$c = 10.595 \pm 0.004$
	$\alpha = 95.73 \pm 0.04°$
	$\beta = 100.00 \pm 0.04°$
	$\gamma = 114.27 \pm 0.04°$
Cell volume	633.24 Å^3
Z	2
Calcd density[a]	1.308 g cm^{-3}

[a] An experimental density value was not obtained due to the lack of suitable crystals.

(1) For part XXI of this series, see D. Stout, M. Sundaralingam, and H. Y. Lin, *Acta Crystallogr.*, in press.
(2) Abbreviations used are: transfer ribonucleic acid (tRNA), messenger ribonucleic acid (mRNA).
(3) To whom correspondence should be addressed.
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Table II. Final Atomic Coordinates and Thermal Parameters[a]

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N-1	0.1440 (6)	0.2015 (3)	0.1875 (3)	0.0379 (13)	0.0068 (3)	0.0089 (3)	0.0079 (5)	0.0060 (5)	0.0018 (2)
C-2	0.1835 (7)	0.0948 (3)	0.1761 (3)	0.0370 (15)	0.0076 (3)	0.0078 (3)	0.0085 (6)	0.0039 (6)	0.0013 (3)
N-3	0.3252 (6)	0.0644 (3)	0.1050 (3)	0.0399 (14)	0.0073 (3)	0.0092 (3)	0.0091 (5)	0.0060 (5)	0.0022 (2)
C-4	0.4316 (7)	0.1583 (3)	0.0382 (3)	0.0370 (15)	0.0071 (3)	0.0077 (3)	0.0091 (6)	0.0045 (6)	0.0014 (3)
C-5	0.4077 (7)	0.2732 (3)	0.0403 (3)	0.0409 (16)	0.0064 (3)	0.0077 (3)	0.0083 (6)	0.0050 (6)	0.0012 (3)
C-6	0.2561 (7)	0.2940 (3)	0.1198 (3)	0.0361 (15)	0.0067 (3)	0.0081 (3)	0.0079 (6)	0.0036 (6)	0.0008 (3)
N-7	0.5409 (6)	0.3452 (3)	−0.0430 (3)	0.0517 (16)	0.0075 (3)	0.0099 (3)	0.0013 (6)	0.0098 (6)	0.0028 (3)
C-8	0.6411 (8)	0.2733 (3)	−0.0902 (4)	0.0526 (20)	0.0082 (4)	0.0099 (4)	0.0115 (7)	0.0112 (8)	0.0029 (3)
N-9	0.5846 (6)	0.1607 (3)	−0.0449 (3)	0.0497 (16)	0.0078 (3)	0.0098 (3)	0.0129 (6)	0.0083 (6)	0.0020 (3)
N-6	0.2186 (6)	0.4017 (3)	0.1311 (3)	0.0462 (15)	0.0069 (3)	0.0118 (4)	0.0097 (5)	0.0106 (6)	0.0021 (3)
S-2	0.0405 (2)	−0.0250 (1)	0.2658 (1)	0.0549 (5)	0.0087 (1)	0.0116 (1)	0.0109 (2)	0.0108 (2)	0.0042 (1)
C-10	−0.1417 (10)	0.0380 (5)	0.3440 (5)	0.0563 (22)	0.0126 (5)	0.0120 (5)	0.0109 (8)	0.0128 (9)	0.0033 (4)
C-11	0.0671 (8)	0.4275 (5)	0.2141 (4)	0.0434 (17)	0.0082 (3)	0.0121 (4)	0.0091 (7)	0.0084 (7)	0.0009 (3)
C-12	0.2302 (8)	0.5246 (4)	0.3366 (4)	0.0399 (17)	0.0114 (4)	0.0099 (4)	0.0117 (7)	0.0068 (7)	0.0022 (3)
C-13	0.1830 (7)	0.6149 (3)	0.3971 (3)	0.0439 (16)	0.0096 (4)	0.0105 (4)	0.0077 (6)	0.0104 (7)	0.0019 (3)
C-14	−0.0469 (11)	0.6337 (5)	0.3545 (5)	0.0717 (27)	0.0155 (6)	0.0153 (6)	0.0229 (11)	0.0120 (11)	0.0021 (5)
C-15	0.3669 (12)	0.7054 (6)	0.5211 (6)	0.0631 (27)	0.0184 (7)	0.0141 (6)	0.0086 (12)	0.0070 (10)	−0.0051 (6)
H									
H-6	0.302 (6)	0.461 (3)	0.094 (3)	3.47					
H-8	*0.751 (6)*	*0.295 (3)*	*−0.147 (3)*	*3.55*					
H-9	0.640 (5)	0.111 (3)	−0.063 (3)	2.96					
H-101	−0.282 (6)	0.056 (3)	0.273 (3)	4.19					
H-102	−0.240 (6)	−0.018 (3)	0.394 (3)	4.19					
H-103	−0.047 (6)	0.105 (3)	0.404 (3)	4.19					
H-111	−0.021 (6)	0.353 (3)	0.239 (3)	3.48					
H-112	−0.053 (6)	0.463 (3)	0.163 (3)	3.48					
H-12	0.376 (6)	0.515 (3)	0.377 (3)	3.78					
H-141	−0.160 (7)	0.590 (3)	0.266 (3)	5.12					
H-142	−0.130 (7)	0.625 (3)	0.415 (3)	5.12					
H-143	−0.017 (7)	0.717 (4)	0.331 (3)	5.12					
H-151	0.300 (7)	0.706 (4)	0.593 (4)	6.50					
H-152	0.518 (8)	0.690 (4)	0.537 (4)	6.50					
H-153	0.416 (7)	0.797 (4)	0.510 (4)	6.50					

[a] The anisotropic temperature parameters are of the form: $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

flections) were remeasured from a somewhat smaller crystal mounted about the b axis. The intensities of duplicate reflections agreed within one $\sigma_c(I)$, the standard error from counting statistics, except for 32 reflections, for which the remeasured values were in better accord with the calculated intensities. Of the 2096 recorded reflections, 725 had intensities less than 1.5 $\sigma_c(I)$ and were considered unobservable. The data were scaled relative to the intensity of a standard reflection and reduced to structure factor amplitudes without applying corrections for absorption effects. The structure factors were converted to E values using the mean temperature factor and scale factor determined by Wilson's method.[12] The statistical average values $\langle|E|\rangle$ and $\langle|E^2 - 1|\rangle$ were 0.778 and 1.050, as compared with the theoretical values 0.798 and 0.968 expected for centrosymmetric space groups.[13]

Structure Determination and Refinement

Since the statistical distribution of E values indicated a centrosymmetric crystal structure, the space group was assumed to be $P\bar{1}$. This choice and the assumed Z of two molecules per unit cell were confirmed by the subsequent structure determination. The three-dimensional $(E^2 - 1)$ Patterson function was interpreted to obtain trial coordinates for the sulfur atoms and the ten carbon and nitrogen atoms of the adenine residue. The difference electron density map from which these atoms were removed revealed positions for the six carbon atoms of the side chains, thereby completing the model except for location of the hydrogen atoms.

Refinement of the atomic parameters and one scale factor was carried out by successive cycles of full-matrix least-squares calculations based on the 1371 reflections having $I(hkl) > 1.5\ \sigma_c I(hkl)$. The discrepancy index $R\ (= \Sigma||F_o| - |F_c||/\Sigma|F_o|)$ was 0.16 after two isotropic cycles and was reduced to 0.12 after two anisotropic cycles. At this stage the low-angle reflections were remeasured and the 32 original amplitudes which showed discrepancies were replaced by the remeasured values. The 15 nonequivalent hydrogen atoms were then located in a difference Fourier synthesis and were given the same thermal parameters as the atoms to which they were covalently bonded. The final refinement involved adjusting the positional parameters of all atoms and the anisotropic thermal parameters of the nonhydrogen atoms. After the last cycle there were no shifts in carbon, nitrogen, or sulfur coordinates exceeding 0.6σ and the refinement was terminated. The maximum error in the final differences map was less than 0.1 Å^{-3}. The terminal value of the R index was 0.047 for the 1371 reflections included in the refinement.

The atomic scattering factors used in the calculations were those of Cromer and Waber[14] for carbon, nitrogen, and sulfur and that of Stewart, Davidson, and Simpson[15] for hydrogen. The quantity minimized in the least-squares refinement was $\Sigma w(F_o - F_c)^2$; the weights w in the initial stages of refinement were those obtained from counting statistics; in final refinement the weights were assigned as follows: $\sqrt{w} = 1$ for $F_o < 2.14$ electrons and $\sqrt{w} = 8.55/F_o$ for $F_o > 2.14$ electrons.

Results

A table of F_o and final F_c values will appear in the microfilm edition of this volume of the journal.[16] The

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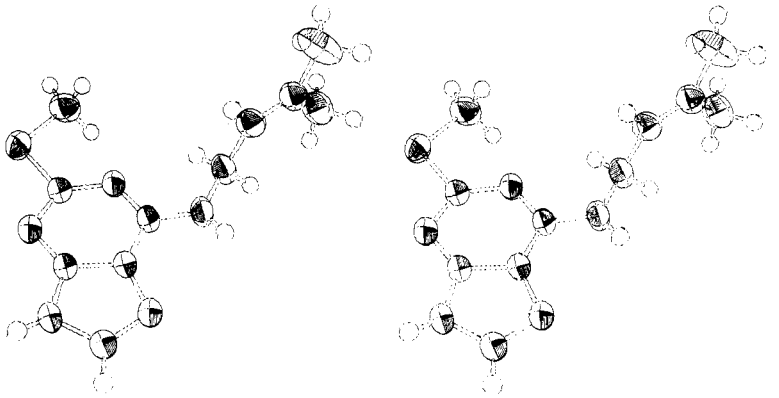

Figure 1. Stereoscopic view of the molecule representing the anisotropic thermal parameters. The thermal ellipsoids of carbon, nitrogen, and sulfur are scaled to include 50% probability surfaces. This and other drawings in the text were made using programs written by C. K. Johnson (Oak Ridge National Laboratory Report No. ORNL 3794, Oak Ridge, Tenn., 1965).

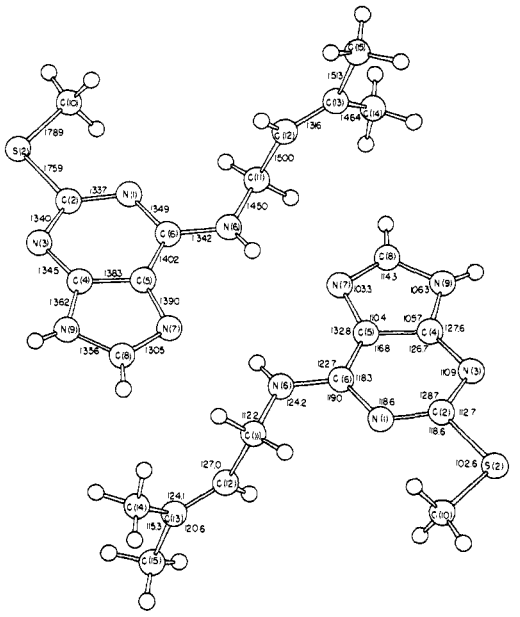

Figure 2. The bond lengths (left) and valence bond angles for the nonhydrogen atoms of the molecule. The average estimated standard deviations are 0.006 Å in distances and 0.3° in angles.

final values of atomic parameters along with the estimated standard deviations are given in Table II. The thermal parameters of the nonhydrogen atoms are represented in Figure 1 by a stereoplot showing the ellipsoids drawn at the 50% probability level. The bond lengths and valence angles are shown in Figure 2 together with the atomic notation used in the text. No corrections for thermal effects were applied to the reported bond-length values. The limits of correction[17] were determined for bonds involving atoms at the side chains for which the apparent thermal motion is observed to be unusually large. The upper limits of correction vary between 0.048 Å for the C(2)–S(2) bond and 0.097 Å for the C(13)–C(14) bond. The least-squares planes through the nine atoms of the purine ring (plane I) and through the five carbon atoms of the isopentenyl group (plane II) were calculated giving all atoms equal weights. These results are given in Table III. The arrangement of molecules in the crystal is illustrated in Figure 3, in a stereoscopic view along the a^* axis. The closest van der Waals separation distances are shown in Figures 4–6, where important aspects of molecular packing are illustrated.

Table III. Deviation (Δ) of Atoms in Ångstroms from Least-Squares Planes through Base (Plane I) and through Isopentenyl Group (Plane II)[b,c]

	Plane I		Plane II	
Atom	ÅΔ	Δ/σ[d]	Δ	Δ/σ
N-1	0.006	2.6		
C-2	0.013	4.5		
N-3	−0.003	1.3		
C-4	−0.007	2.4		
C-5	−0.013	4.6		
C-6	−0.010	3.6		
N-7	0.009	3.7		
C-8	0.012	3.5		
N-9	−0.007	2.7		
N-6	−0.023		−0.003	0.6
C-11	−0.045[a]		−0.004	1.1
C-12	−1.404[a]		0.009	3.1
C-13	−1.676[a]		−0.003	0.7
C-14	−0.660[a]		−0.003	0.5
C-15	−3.109[a]			
S-2	0.014[a]			
C-10	0.100			

[a] Atoms not included in least-squares fit. [b] Rms deviation = 0.009 Å. [c] The equations of the least-squares planes are: $-0.5642x - 0.3152y - 0.7631z = 1.7676$ through atoms of the base; $0.3408x + 0.7644y - 0.5474z = -1.2120$ through atoms of isopentenyl group with x, y, z in ångström units referred to crystallographic axes. [d] σ is the standard deviation in positional parameters.

Discussion of the Structure

The Molecular Geometry. The molecular configuration found in the crystal is shown in Figure 1. The molecules occur in the N(9)–H tautomeric form rather than the N(7)–H form as found in crystals of purine,[18] 6-thiopurine monohydrate,[19,20] and 6-thio-

(16) The observed and calculated structure amplitudes for N^6-(Δ^2-isopentenyl)-2-methylthioadenine will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washigton, D. C. 20030, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

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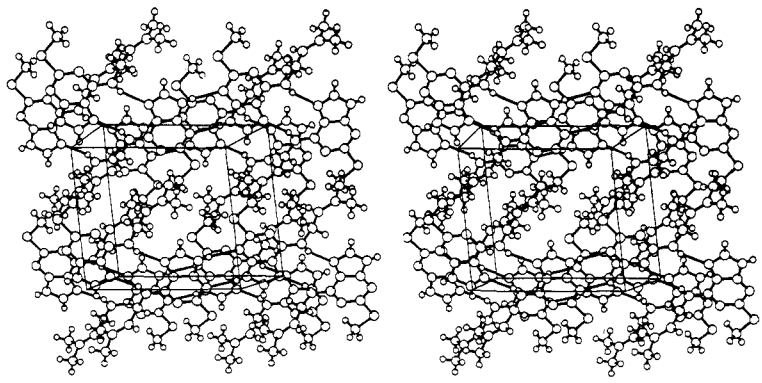

Figure 3. Stereoscopic view of the crystal structure along the a^* direction with the b axis horizontal. The parallelepiped outlining the unit cell is centered on the point 1/2, 0, 1/2.

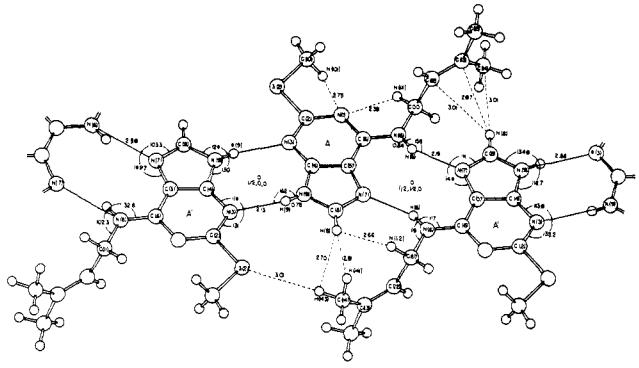

Figure 4 The ribbon of hydrogen-bonded molecules viewed down the a^* axis. The single unbroken lines represent H···N and N···N hydrogen bonds; the dashed lines indicate closest nonbonded approaches between atoms.

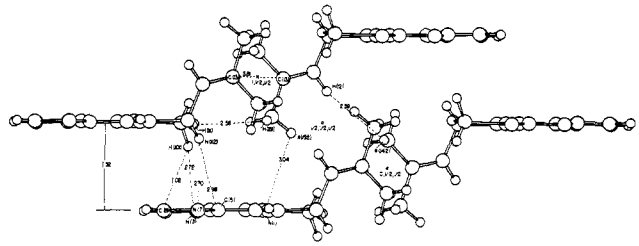

Figure 5. Projection parallel to the base plane showing the pattern of base stacking along the a direction and the perpendicular distance between adjacent planes. The dashed lines indicate closest nonbonded approaches between atoms.

guanine.[21] The N(9)–H tautomer form is also found in the crystal structure of guanine monohydrate.[22] The tautomeric form observed in crystals appears to be determined by hydrogen bonding as well as the electronic properties of the base.

The purine moiety is not exactly planar; the displacements from the least-squares plane through the nine ring atoms (Table III), though small, are in general significant. It is noteworthy that the deviations found here and in 3′-*O*-acetyladenosine[23] are in the same sense, except for atoms N-9 and C-6 to which different substituents are attached in the two molecules. The

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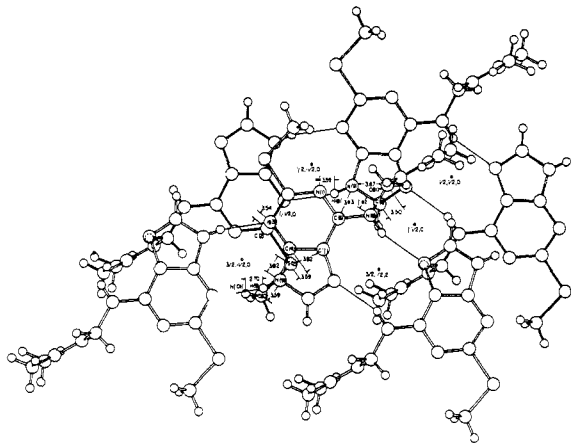

Figure 6. Projection normal to the base plane showing the superposition of molecules in two ribbons related by the a lattice translation and the shortest distances between atoms of the ribbons. Note the overlap of base molecules related by the inversion center 1, −1/2, 0 along the chain of atoms N-9 through C-10.

substituent atoms (S-2 and N-6) are displaced on opposite sides of the plane. The appreciable deviation of N-6 is probably a result both of hydrogen bonding (Figure 4) and nonbonding repulsions between ring atoms and the isopentenyl atoms.

The plane of the isopentenyl group is rotated 91° from that of the purine ring by concerted twists about bonds C(6)–N(6), N(6)–C(11), and C(11)–C(12). The torsional angles which give the orientation of both side chains relative to the ring are listed in Table IV. The C–C–C valence angles in the isopentenyl group, other than C(12)–C(13)–C(15), depart significantly from a value of 120°, as seen in Figure 2. The observed values

Table IV. Torsion Angles and Their Estimated Standard Deviations in the Last Digit in Parentheses

N(1)–C(2)–S(2)–C(10)	±3.1 (4)[a]
N(3)–C(2)–S(2)–C(10)	∓177.9 (3)
N(1)–C(6)–N(6)–C(11)	±1.2 (6)
C(5)–C(6)–N(6)–C(11)	∓178.8 (4)
N(7)–C(5)–C(6)–N(6)	∓2.1 (7)
C(6)–N(6)–C(11)–C(12)	±103.6 (4)
N(6)–C(11)–C(12)–C(13)	±143.6 (4)
C(11)–C(12)–C(13)–C(14)	±1.4 (7)
C(11)–C(12)–C(13)–C(15)	+179.6 (5)

[a] The chirality for molecule A (Figure 4, Table II) is defined by the upper signs on the torsion angles and for the enantiomorph A′ by the lower signs.

may be attributed to hydrogen–hydrogen repulsions which arise in the observed conformation of this overcrowded group (Figure 1). The uncorrected bond distances, N–C, C–C, and C=C, all are shorter than the expected values of 1.47, 1.53, and 1.34 Å. However, these apparent deviations are attributed to effects of thermal motion, the upper bound on the corrected value being, for example, 1.56 Å for the C(13)–C(14) bond length.

The bond lengths and angles in the adenine moiety are similar to the values found in 3′-*O*-acetyladenosine[23] and related neutral adenine derivatives. The variations in bond distances, which show a maximum difference of 0.018 Å, are associated with the presence of different substituents on N-9 and N-6. Bond distances and angles involving hydrogen atoms are in the usual range. These ranges and the mean values are listed in Table V.

Table V. Bond Distances and Angles Involving Hydrogen Atoms

	Range	Mean	Esd
C–H bonds	0.86–1.11 Å	0.96 Å	0.04 Å
N–H bonds	0.78–0.85 Å	0.81 Å	0.03 Å
C–C–H angles (tetrahedral)	107–120°	112°	2°
N–C–H angles (tetrahedral)	107–110°	108°	1°
S–C–H angles (tetrahedral)	112–114°	113°	2°
H–C–H angles (tetrahedral)	89–113°	106°	2°
C–N–H angles (trigonal)	117–130°	122°	1°
C–C–H angles (trigonal)	115–118°	117°	1°
N–C–H angles (trigonal)	120–126°	123°	1°

The Molecular Packing and Hydrogen Bonding. The hydrogen-bonding scheme is shown in Figure 4. The purine bases are joined across inversion centers by hydrogen-bond pairs, N(6)–H···N(7) and N(9)–H···N(3), so as to form continuous ribbons extending along the *b* direction. Both hydrogen atoms bonded covalently to nitrogen atoms participate in hydrogen bonding. Clearly, this scheme requires that the molecules exist in the N(9)–H tautomeric form rather than in the N(7)–H form. The angular displacements of H-6 and H-9 from the lines, N(6)–N(7) and N(9)–N(3), are equal within the limits of error. The N(9)–N(3) length of 2.88 Å is typical of those hydrogen bonds linking purine rings.[24] The longer N(6)–N(7) length of 2.99 Å apparently results from the comparatively large number of close nonbonding distances between the isopentenyl and adenine residues of adjacent hydrogen-bonded molecules.

The two side groups in the conformations observed in the crystal shield site N-1 from involvement in hydrogen bonding.

The arrangement of hydrogen-bonded ribbons in the crystal is shown in Figure 3. The purine rings in ribbons which are displaced by lattice translations along the *a* direction exhibit parallel stacking typical of nucleic acid constituents in other crystal structures,[25] as shown in Figure 5. Extensive annular overlap of the bases does not occur here; rather, the bases superimpose along the molecular edges formed by the chains of six atoms N-9 through C-10, as shown in Figure 6. The closest interatomic distances between overlapping atoms of adjacent chains are 3.59 ± 0.05 Å. Other close contacts between these ribbons (Figure 5) are the purine–thiomethyl separation, N(3)···H(101), and the purine–isopentenyl separation, N(7)···H(112), which equal the sum of the van der Waals radii, 1.5 for nitrogen and 1.2 Å for hydrogen.[26] The isopentenyl and thiomethyl groups form a hydrophobic zone about the plane $z = {}^1/_2$, as shown in Figure 3. Isopentenyl groups from ribbons related by translations $(a + c)$ interleave at *b* periodicity along the ribbons, and their terminal methyl groups (C-14) interlock loosely with adjacent thiomethyl groups from related ribbons. This structural feature apparently contributes appreciably to the cohesive interactions in the hydrophobic zones. The distance between parallel isopentenyl groups is about 3.8 Å, or van der Waals separation. Figures 5 and 6 show all closest interatomic distances between ribbons; these exceed van der Waals separations, except those noted above. Within the ribbons (Figure 4) the only anomalous contact is the exceptionally short separation of 2.38 Å between N-1 and H-111, which is considered to be a forced nonbonding contact resulting from the requirements of hydrogen bonding and parallel stacking of purine and isopentenyl residues.

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