Stereochemistry of Nucleic Acids and Their Constituents. XXVIII. The Crystal and Molecular Structure of N^2-Dimethylguanosine. A Transfer Ribonucleic Acid Rare Nucleoside Located at the Junction of the Anticodon and Dihydrouridine Arms[1a]

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Abstract: The crystal structure of N^2-dimethylguanosine, a minor constituent of tRNA located at the junction of the anticodon and dihydrouridine arms, has been determined by direct methods. The nucleoside crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions $a = 6.927$ (1), $b = 11.792$ (2), and $c = 16.362$ (2) Å; $D_{obsd} = 1.558$ g cm^{-3} and $D_{calcd} = 1.547$ g cm^{-3} for $Z = 4$. The estimated standard deviations in bond distances and bond angles for the nonhydrogen atoms are 0.005 Å and 0.3°, respectively. The molecule is in the syn conformation with a χ_{CN} value of $-103.9°$. The sugar moiety exhibits $^2T_3$ puckering, and the conformation about the C(4′)–C(5′) bond is gauche–trans. While there is no base pairing, there is extensive intermolecular hydrogen bonding between the base and sugar moieties. Screw related bases stack over each other such that the N-2 dimethylamine groups interact extensively with adjacent pyrimidine rings.

Modified nucleosides[2] are found in all transfer RNA molecules, and are usually located in nonhelical regions. By far the most common modification of nucleosides involves methylation of either the base or ribose moiety. There is evidence now that the tRNA molecules in tumorous cells possibly exist in a hypermethylated state *in vivo* due to increased methylase activity.[3,4] The introduction of alkyl groups on bases usually results in increased association.[5-8] N(1), N(2), and N(7) derivatives of guanosine are present as minor components in most tRNA's. N^2-Dimethylguanosine (DMG) is found in nine[9-18] of the 25 tRNA molecules sequenced to date. It occurs exclusively at the junction between the anticodon and dihydrouridine helical segments as the eighth nucleoside component on the 5′ side of the anticodon triplet (Figure 1). It is always adjacent to cytidine on the 5′ side and either cytidine, adenosine, or pseudouridine on the 3′ side. In the tRNA's not containing DMG it is replaced by either of the two purines, adenosine or guanosine. In recent studies of 16S and 23S ribosomal RNA, although 6 different methylated nucleosides were found in the former and 11 in the latter, DMG was not found in either species.[19] Solution spectral studies have shown that N^2-dimethylguanine exhibits slightly more enhanced stacking interaction than guanine with cytosine and adenine.[20] As well as effecting base stacking, dimethylation of N(2) of guanine will effect hydrogen bonding since the normal Watson–Crick base pairing is precluded. In order to determine what effect methylation of the N(2) position of guanosine has on hydrogen bonding, base stacking, and molecular conformation, a single-crystal X-ray analysis of DMG was undertaken. Just as single-crystal diffraction studies of the common nucleic acid constituents have contributed to the understanding of the stereochemistry of nucleic acids and polynucleotides it can be expected that structural analyses of minor nucleotides[21] will be particularly useful in the conformational studies of tRNA molecules. We have previously reported the crystal structures of

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two other alkylated nucleic acid constituents, *viz.* Δ^2-isopentenyl-2-methylthioadenine[22] and puromycin dihydrochloride pentahydrate,[23] the latter being an N^6-dimethyladenosine derivative.

Experimental Section

Crystals of the nucleoside were obtained by slow evaporation o an aqueous ethanol solution. The material crystallized in the orthorhombic system, and the space group is $P2_12_12_1$ as indicated by the systematic absences: $h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$, and $00l$, $l = 2n + 1$. The unit cell parameters determined from measurements on a manual diffractometer were found to be a = 6.927 (1), b = 11.792 (2), and c = 16.362 (3) Å. The measured density of 1.558 g cm^{-3} by flotation in $CHCl_3$–EtBr agrees well with the calculated value of 1.547 g cm^{-3} for four N^2-dimethylguanosine molecules in the unit cell.

Intensity data were collected by the stationary crystal–stationary counter technique on a General Electric XRD-6 diffractometer using Ni–Co balanced filters for Cu Kα radiation. In the range of measurement ($2\theta_{max}$ = 100°) 1176 reflections were sampled. The data were corrected for Lorentz and polarization factors, and $\alpha_1 - \alpha_2$ splitting when appropriate. A correction based on the anisotropy of transmission of the X-ray beam as a function of the angle ϕ for a reflection at $\chi = 90°$ was also applied.

Structure Determination. The structure was solved by direct methods. Starting with the phases of four reflections used to define the origin and enantiomorph and two phases indicated by Σ_1 relations[24] (see Table I), a basis set of phases for 30 reflections was

Table I. Starting Phases

h	k	l	$\|E\|$	Phase	
4	0	1	4.09	$\pi/2$	origin
0	7	2	3.07	$\pi/2$	
5	1	0	2.20	$\pi/2$	
0	7	9	1.76	$\pi/2$	enantiomorph
0	8	12	3.11	π	Σ_1 indications
2	0	0	2.02	0	

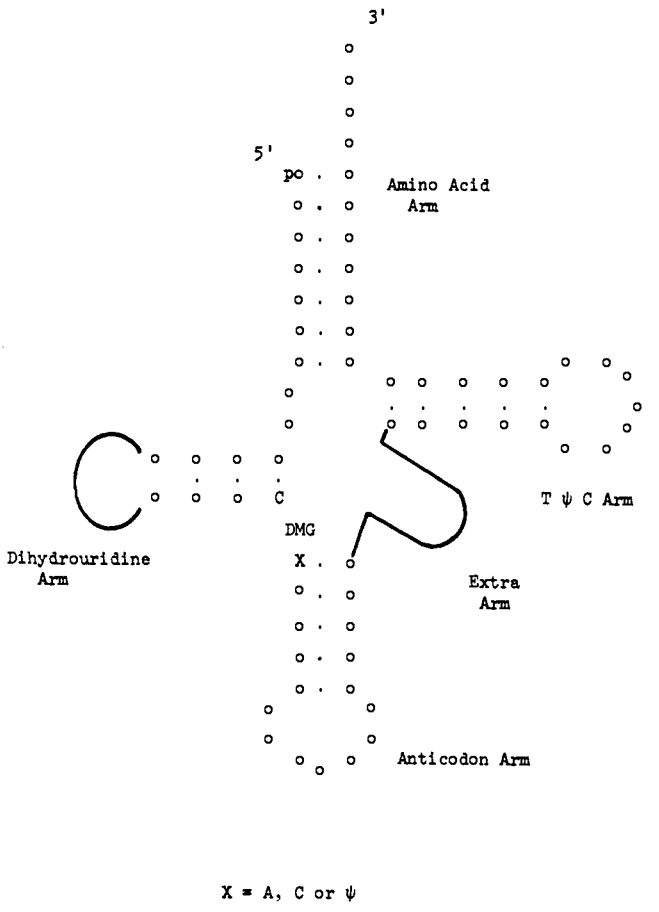

Figure 1. Cloverleaf model of tRNA showing the various arms. DMG is located at the junction of the anticodon arm and the dihydrouridine arm.

determined by employing the structure invariants $\cos(\phi_{h_1} + \phi_{h_2} + \phi_{h_3})$ where $h_1 + h_2 + h_3 = 0$. The cosine invariant values were calculated by means of formulas given by Hauptman, *et al.*[25] These 30 phases were then used in the tangent formula[26] which determined and refined a total of 250 phases. An E map was computed using these phases and a reasonable structure was revealed. However, this turned out to be a false solution and would not refine below an R value of 33%. When the phase development was repeated using a value of 0 instead of π for the 0,8,12 reflection the true structure appeared in the E map with 19 of the 22 nonhydrogen atomic sites among the 22 strongest peaks. The remaining nonhydrogen atoms O(6), C(5′), and O(5′) and hydrogen atoms were located in subsequent difference electron density maps.

Simultaneous with the solution by direct methods, the location of the purine ring was deduced by analyzing the ring–ring vectors in the Patterson map.

Structure Refinement. The structure was refined by the full-matrix least-squares method. A Cruickshank[27] type weighting scheme was used in the refinement where the weight $w = 1/(11.278 + 0.0103|F_o| + 0.00003|F_o|^2)^2$. Reflections with $I_0 \leq 1.5\sigma(I_0)$ were considered unobserved and given zero weight; thus, there were 1125 observed reflections. A secondary extinction correction was applied to the strong reflections according to Zachariasen.[28] The nonhydrogen atoms were refined with anisotropic temperature factors while the hydrogen atoms were given fixed isotropic values (B = 3.2 Å^2 for the methyl hydrogens and 1.8 Å^2 for the others). The final weighted and unweighted R ($= \Sigma||F_o| - F_o||/\Sigma|F_o|$) factors are 0.036 and 0.046, respectively, for 1125 observed reflections. The corresponding R values for all 1176 reflections are 0.039 and 0.059. The average shift/σ ratios were 0.07 and 0.11 for the nonhydrogen and hydrogen atom parameters, respectively, with corresponding maximum values of 0.29 and 0.53.

The scattering factors for carbon, nitrogen, and oxygen were taken from Cromer and Waber[29] and those for hydrogen from Stewart, Davidson, and Simpson.[30]

The final positional and thermal parameters together with their esd's are given in Table II. The observed and calculated structure factor amplitudes have been deposited in the microfilm edition of this volume of the journal.[31a] The thermal ellipsods of the atoms projected on the base plane are represented by the drawing[31b] in Figure 2.

Results and Discussion

Bonding. The bond distances and bond angles for the base and the sugar are shown in Figure 3. The average esd's in bond lengths and angles for the non-

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Table II. Positional and Thermal Parameters of Atoms in N^2-Dimethylguanosine[a]

Atom	X	Y	Z	B_{11} or B	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	4408 (5)	2288 (2)	−882 (2)	115 (7)	29 (2)	11 (1)	−9 (4)	0 (3)	−2 (1)
C(2)	4369 (6)	2626 (3)	−70 (2)	77 (9)	37 (3)	12 (1)	0 (4)	−1 (3)	−3 (2)
N(3)	4418 (5)	3699 (2)	149 (2)	112 (7)	35 (2)	10 (1)	−1 (4)	2 (2)	−1 (1)
C(4)	4476 (6)	4431 (3)	−486 (2)	83 (8)	30 (3)	9 (1)	1 (4)	1 (3)	−2 (2)
C(5)	4522 (6)	4168 (3)	−1313 (2)	89 (8)	41 (3)	9 (1)	3 (4)	6 (3)	3 (2)
C(6)	4502 (5)	3022 (3)	−1558 (3)	78 (8)	37 (3)	13 (1)	2 (4)	−5 (3)	−1 (2)
N(7)	4599 (5)	5154 (3)	−1778 (2)	145 (7)	39 (3)	13 (1)	3 (4)	2 (3)	0 (1)
C(8)	4587 (6)	5963 (3)	−1244 (2)	129 (9)	30 (3)	13 (1)	−1 (5)	2 (3)	2 (2)
N(9)	4492 (5)	5588 (2)	−445 (2)	110 (8)	29 (2)	9 (1)	1 (4)	6 (3)	−1 (1)
O(6)	4584 (5)	2629 (2)	−2254 (1)	185 (7)	47 (2)	11 (1)	7 (4)	−4 (2)	−6 (1)
N(2)	4243 (5)	1826 (2)	502 (2)	164 (8)	32 (2)	11(1)	−2 (4)	−2 (3)	3 (1)
C(10)	4297 (7)	2168 (4)	1360 (2)	174 (11)	50 (3)	9 (1)	−24 (5)	2 (3)	0 (2)
C(11)	4404 (7)	621 (3)	331 (3)	147 (11)	37 (3)	23 (2)	−4 (5)	1 (4)	0 (2)
C(1′)	4563 (6)	6330 (3)	273 (2)	104 (8)	28 (3)	11 (1)	5 (4)	2 (3)	1 (2)
C(2′)	3131 (5)	6010 (3)	941 (2)	83 (8)	28 (3)	14 (1)	5 (4)	1 (3)	−1 (2)
C(3′)	4151 (6)	6439 (3)	1708 (2)	111 (8)	38 (3)	10 (1)	6 (4)	4 (3)	−3 (2)
C(4′)	6272 (6)	6205 (3)	1514 (2)	112 (8)	41 (3)	10 (1)	−3 (4)	4 (3)	−4 (2)
C(5′)	6966 (5)	5071 (3)	1780 (2)	114 (8)	43 (3)	14 (1)	−7 (5)	5 (3)	1 (2)
O(1′)	6422 (4)	6247 (2)	628 (1)	91 (6)	59 (2)	12 (1)	−4 (3)	3 (2)	1 (1)
O(2′)	1316 (4)	6502 (2)	787 (2)	96 (6)	44 (2)	21 (1)	1 (3)	7 (2)	3 (1)
O(3′)	3923 (4)	7619 (2)	1812 (2)	140 (7)	49 (2)	26 (1)	16 (3)	1 (3)	−15 (1)
O(5′)	8993 (4)	4926 (2)	1636 (1)	111 (6)	47 (2)	10 (1)	12 (3)	−5 (2)	1 (1)
H(1)	441 (5)	160 (3)	−98 (2)	1.8 (0)					
H(8)	456 (5)	677 (3)	−137 (2)	1.8 (0)					
H(101)	348 (6)	286 (4)	146 (3)	3.2 (0)					
H(102)	371 (6)	156 (3)	166 (3)	3.2 (0)					
H(103)	548 (6)	236 (3)	157 (2)	3.2 (0)					
H(111)	332 (6)	38 (4)	−8 (2)	3.2 (0)					
H(112)	571 (6)	50 (3)	8 (2)	3.2 (0)					
H(113)	419 (6)	24 (3)	75 (2)	3.2 (0)					
H(1′)	428 (6)	707 (3)	11 (2)	1.8 (0)					
H(2′)	296 (5)	515 (3)	95 (2)	1.8 (0)					
H(3′)	382 (5)	600 (3)	218 (2)	1.8 (0)					
H(4′)	718 (5)	679 (3)	177 (2)	1.8 (0)					
H(5′)	621 (5)	446 (3)	152 (2)	1.8 (0)					
H′(5′)	678 (5)	503 (3)	239 (2)	1.8 (0)					
H(O2′)	57 (5)	608 (3)	103 (2)	1.8 (0)					
H(O3′)	294 (5)	765 (3)	199 (2)	1.8 (0)					
H(O5′)	958 (5)	483 (3)	208 (2)	1.8 (0)					

[a] Positional parameters of heavy atoms are $\times 10^4$; positional parameters of hydrogen atoms are $\times 10^3$; anisotropic thermal parameters are $\times 10^4$; the anisotropic temperature factor is of the form $\exp[-(h^2B_{11} + \ldots + 2hkB_{12} + \ldots)]$; standard deviations refer to the least significant digits.

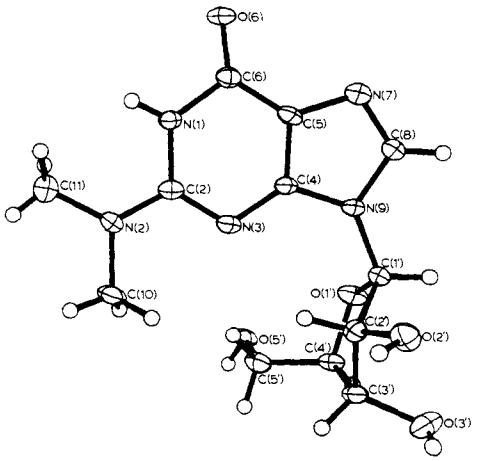

Figure 2. The thermal vibration ellipsoid of the nonhydrogen atoms is DMG, and atom numbering.

hydrogen atoms are 0.005 Å and 0.3°, respectively. It is of interest to compare the molecular dimensions of the modified guanine base in N^2-dimethylguanosine with those of the guanine moiety in the common nucleoside. The comparison will be limited to guanosine dihydrate (GDH), which has two independent molecules in the unit cell, because the crystal structure of this nucleoside has also been determined with high precision.[32] In general, the bond distances and angles of the guanine moieties agree with each other within experimental error. The largest differences are in the N(1)–C(2) bond length which is 1.338 Å in DMG while it is 1.370 Å in molecule 1 and 1.365 Å in molecule 2 of GDH, and in the N(1)–C(2)–N(3) (122.5 *vs.* 124.4 and 124.1°, respectively) and C(2)–N(3)–C(4) (113.9 *vs.* 111.6 and 111.9°, respectively) bond angles. It may be noted that the methylation of the amino group has had little effect on the C(2)–N(2) bond distance which is 1.332 Å in DMG, and 1.338 and 1.347 Å in molecules 1 and 2, respectively, of GDH. The average N(2)–CH_3 bond distance of 1.458 Å is in good agreement with the values found for other *N*-dimethyl groups conjugated to aromatic systems, *e.g.*, 1,2,3-trisdimethylcyclopropenium perchlorate.[33]

The bond distances and angles in the ribose moiety are in agreement with the values generally found[34,35] in

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nucleosides and nucleotides having C(2′) endo puckering. The puckered carbon atom C(2′) is involved in the largest exocyclic and the smallest endocyclic bond angles: C(3′)–C(2′)–O(2′) = 115.0° and C(1′)–C(2′)–C(3′) = 101.9°.

The average C–H, N–H, and O–H bond distances of 0.99, 0.84, and 0.84 Å, respectively, are close to the values usually found in X-ray determinations.

Base. The least-squares plane through the nine atoms of the purine base (plane I in Table III) indicates

Table III. Least-Squares Planes and Deviation of the Atoms from the Planes for the Base[a]

Atoms	Plane I	Plane II	Plane III
N(1)	0.009*	0.004*	0.015
C(2)	0.004*	0.004*	0.002
N(3)	−0.014*	−0.008*	−0.021
C(4)	−0.003*	0.004*	−0.007*
C(5)	0.000*	0.003*	0.004*
C(6)	−0.003*	−0.007*	0.006
N(7)	−0.004*	0.001	0.000*
C(8)	−0.002*	0.010	−0.004*
N(9)	0.014*	0.027	0.007*
O(6)	−0.035	−0.043	−0.019
C(1′)	−0.053	−0.033	−0.068
N(2)	0.041	0.039	0.037
C(10)	−0.031	−0.028	−0.043
C(11)	−0.094	−0.102	−0.092
Rms Δ	0.008	0.005	0.005
σ(rms Δ)	0.004	0.004	0.004

[a] The asterisk indicates atoms included in calculation of the plane. Equations of the planes are: plane I, $-0.999x + 0.022y - 0.031z = -2.956$; plane II, $-0.999x + 0.026y - 0.029z = -2.943$; plane III, $-0.999x + 0.019y - 0.036z = 2.961$.

that the base is not strictly planar. Atoms N(3) and N(9) are displaced most from this plane. Similar deviations from planarity are observed in many of the other purine bases in nucleosides and nucleotides[23,36] and the bases themselves.[37] In DMG the exocyclic atoms O(6) and C(1′) are displaced 0.035 and 0.053 Å, respectively, on one side of the plane and N(2) is displaced 0.041 Å on the opposite side. The dihedral angle between the pyrimidine ring (plane II) and the imidazole ring (plane III) is only 0.6°. The dimethylamine group, N(2), C(10), and C(11), is twisted at an angle of approximately 6° with respect to the base plane. The bonding to N(2) shows some pyramidal character, N(2) being displaced 0.08 Å from the plane through C(2), C(10), and C(11).

Ribose. The displacements of atoms from several planes through the ribose moiety are given in Table IV. Atom C(2′) is displaced most from the five-atom plane (plane IV) and lies on the same side as C(5′) and atom C(3′) shows the next largest displacement from this plane and lies on the opposite side as C(5′). Hence, the sugar exhibits the twist (*T*) conformation $^2T_3$ [C(2′) endo, C(3′) exo[35,38]], which is one of the preferred modes of puckering for ribose rings. A conformational analysis of syn nucleosides has already shown that as a rule the C(2′) endo puckering is highly preferred in comparison to the alternative C(3′) endo puckering.[39]

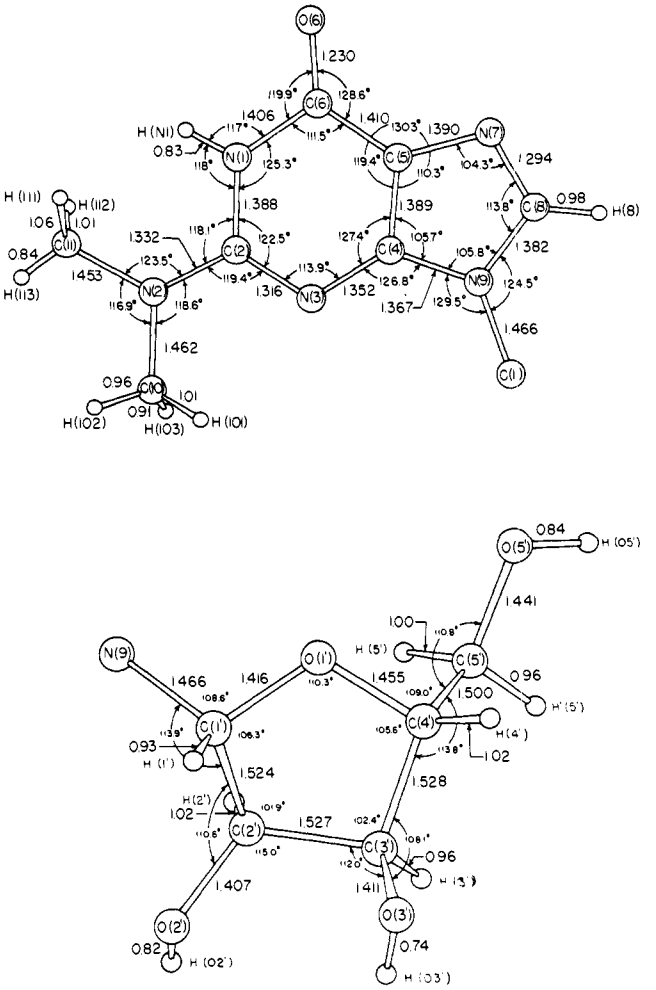

Figure 3. Bond distances and bond angles in the base and ribose components of DMG.

Table IV. Least-Squares Planes for the Ribose[a]

Atoms	Plane IV	Plane V	Plane VI	Plane VII
C(1′)	0.152*	−0.028*	−0.083*	0.000*
C(2′)	−0.222*	−0.555	0.048*	−0.393
C(3′)	0.209*	0.025*	−0.525	0.202
C(4)	−0.118*	−0.041*	−0.052*	0.000*
O(1′)	−0.021*	0.044*	0.086*	0.000*
C(5′)	−1.711	−1.307	1.263	−1.288
Rms Δ	0.161	0.036	0.069	0.000
σ(rms Δ)	0.004	0.004	0.004	0.004

[a] An asterisk indicates atoms included in calculation of the plane. Equations of the planes are: plane IV, $-0.042x + 0.999y - 0.036z = 7.151$; plane V, $0.138x + 0.990y - 0.015z = 7.848$; plane VI, $0.111x - 0.986y - 0.1212 = -6.984$; plane VII, $0.058x + 0.998y + 0.0392 = 9.647$.

The structure determination of DMG has further supported this rule.

The conformation about the C(4′)–C(5′) bond is gauche–trans[35,40] with ϕ_{OO}[40] = 64.9° and ϕ_{OC} = −177.5°. The 5′ hydroxy bond is in an anti conformation, the H–O(5′)–C(5′)–C(4′) torsion angle being 121°. In contrast, those purine nucleosides in the syn conformation which have an O(5′)–H···N(3) intra-

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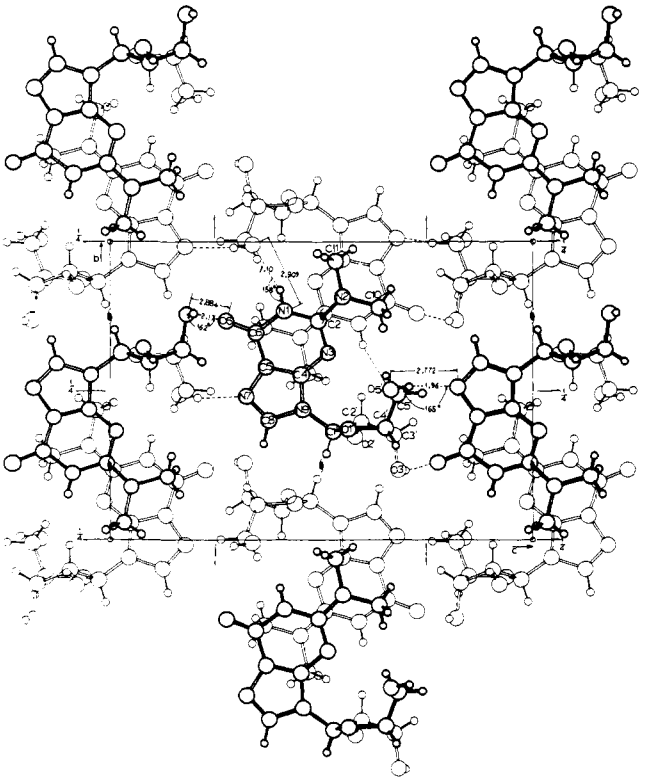

Figure 4. The a axis projection of the crystal structure of DMG showing the intermolecular hydrogen bonding (see also Table VI) and the base stacking pattern.

molecular bond exhibit the gauche–gauche conformation about the C(4′)–C(5′) bond, and a gauche torsion angle of about +60° for H–O(5′)–C(5′)–C(4′).[39]

The torsion angles about the ribose ring bonds are: $\tau_0 = -15.6$, $\tau_1 = 32.4$, $\tau_2 = -35.9$, $\tau_3 = 27.7$, and $\tau_4 = -7.9°$. These can most simply be expressed in terms of the pseudorotation parameters:[41] the phase angle $P = 173.7°$ and the amplitude of puckering $\tau_m = -36.9°$. Other conformational angles of interest are given in Table V.

Table V. Some Torsion Angles[a]

Atoms	Torsion angle, deg
C(8)–N(9)–C(1′)–C(2′)	138.0 (4)
C(4)–N(9)–C(1′)–O(1′)	70.5 (5)
C(4)–N(9)–C(1′)–C(2′)	−47.7 (5)
N(9)–C(1′)–C(2′)–C(3′)	151.9 (3)
N(9)–C(1′)–O(1′)–C(4′)	−138.5 (3)
O(2′)–C(2′)–C(3′)–O(3′)	−40.0 (4)
C(1′)–O(1′)–C(4′)–C(5′)	114.7 (3)
C(2′)–C(3′)–C(4′)–C(5′)	−91.9 (4)

[a] Standard deviations are given in parentheses and refer to the least significant digits.

Glycosyl Torsion Angle. The torsion angle χ_{CN}[42] about the glycosyl bond N(9)–C(1′) is −103.9°, corresponding to the syn conformation of the base relative to the sugar. This value is the smallest value found so far for a syn nucleoside, and is probably due to steric interactions between the C(10) methyl and the C(5′) methylene groups. Circular dichroism spectral studies[43] have shown that DMG prefers the syn conformation in solution also. Guanosine[32] itself exists in both the syn and anti conformations in the same unit cell and the anti conformation in solution.[43] It appears that in general the guanosine system prefers the syn conformation.

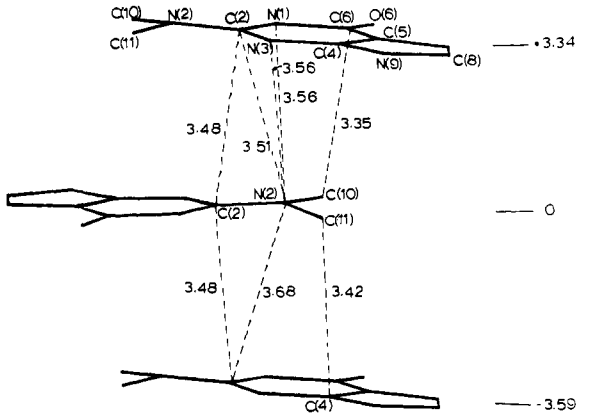

Figure 5. The closest approaches between adjacent bases in the stacked column of bases.

Hydrogen Bonding. Figure 4 shows the hydrogen bonding viewed down the a axis. The hydrogen bond distances and angles are also given in Table VI. There is neither any intramolecular hydrogen bonding nor interbase hydrogen bonding in this structure. The only interribose hydrogen bond O(2′)–H···O(5′) involves molecules related by a translation along the a axis forming an infinite chain parallel to the axis. Atom O(5′) is involved in three hydrogen bonds, twice as an acceptor and once as a donor. N(2) does not participate in hydrogen bonding due to the presence of the two methyl groups, while N(3) is shielded from hydrogen bonding by the close approaches of H(2′) (2.37 Å), H(5′) (2.70 Å), H(101) (2.43 Å), and H(103) (2.85 Å).

Base Stacking. Figure 4 also shows the base stacking as viewed down the a axis. Screw related bases with their planes perpendicular to the a axis stack in infinite columns such that the dimethylamine groups lie over pyrimidine rings in a head-to-tail fashion. Adjacent bases are inclined 4.6° with respect to each other. The interplanar distances between the centers of the pyrimidine rings are alternately 3.34 and 3.59 Å (Figure 5); each nucleoside is involved in N(1)–H···O(5′) hydrogen bonds with the two molecules above and below it. The shorter N(2)–base interactions may be partly responsible for the slightly pyramidal nature of N(2) mentioned previously. While the type of base stacking[44] in which polar groups stack over π systems is most common, the head-to-tail stacking found in DMG allows for greater interaction between adjacent bases. The base stacking found in guanosine dihydrate is also quite extensive; however, the manner of stacking is different from that of DMG. In the former structure there is extensive overlap between entire purine rings with little N(2) involvement, while in DMG the imidazole rings do not participate in stacking, but the N(2)

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Table VI. Hydrogen Bond Lengths and Angles

Bond A–H···B	Symmetry[a] code for B	Distance, Å A···B	Distance, Å A–H	Distance, Å H···B	Angle, deg A–H–B
N(1)–H···O(5′)	I	2.901	0.83	2.10	158
O(2′)–H···O(5′)	II	2.824	0.82	2.01	173
O(3′)–H···O(6)	III	2.884	0.74	2.17	162
O(5′)–H···N(7)	IV	2.772	0.84	1.96	165

[a] Symmetry code: I, $-1/2 + x$, $1/2 - y$, $-z$; II, $1 + x$, y, z; III, $1/2 - x$, $1 - y$, $1/2 + z$; IV, $1\,1/2 - x$, $1 - y$, $1/2 + z$.

dimethyl group plays a predominant role in stacking interactions.

Interactions between guanine derivatives in aqueous solution have been found to be unusually strong.[45–47] Hypochromism values from uv spectral studies and fluorescence and phosphorescence emission spectral studies on model dinucleoside compounds containing N^2-dimethylguanine or guanine or adenine linked to adenine or cytosine through a trimethylene bridge instead of the sugar–phosphate backbone indicate that the stacking interactions in solution between N^2-dimethylguanine and adenine or cytosine is greater than those between guanine and adenine or cytosine.[20] These results suggest that the intimate stacking observed in the crystal may also occur in solution and that the N(2) dimethyl group is implicated in the increased stacking. It should be pointed out that the stacking patterns observed in Figure 4 could serve as a reasonable model for the association of dimethylguanosine molecules in solution.

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The Stereochemical Basis of Anticonvulsant Drug Action. IV.[1a] The Crystal and Molecular Structure of Trihexyphenidyl[1b]

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Abstract: The molecular structure of trihexyphenidyl (α-cyclohexyl-α-phenyl-1-piperidinepropanol) has been elucidated as part of a series of conformational determinations of anticonvulsant drugs in order to investigate stereochemical bases for drug action. Crystals of trihexyphenidyl are monoclinic with cell dimensions $a = 31.059 \pm 0.004$, $b = 5.713 \pm 0.002$, and $c = 21.889 \pm 0.004$ Å; $\beta = 112.67 \pm 0.02°$; space group $C2/c$. Crystal data were collected on an automated diffractometer and the structure was solved by the symbolic addition procedure. Refinement was by least squares to an R value of 0.051. The molecule has stereochemical features in common with other anticonvulsants which have demonstrated clinical or laboratory efficacies against grand mal epilepsy. These stereochemical similarities are analyzed and discussed, and may account for the ability of chemically different drugs to block grand mal seizures.

Trihexyphenidyl (α-cyclohexyl-α-phenyl-1-piperidinepropanol) (I) is a pharmacological agent which has been widely used in the treatment of the symptoms of Parkinsonism. Its effects resemble those of atropine, and it is generally believed that it acts by blocking acetylcholine at certain cerebral synaptic sites.[3a] The potency of trihexyphenidyl and related drugs against nicotine-induced tremors and electroencephalographic abnormalities in animals has recently led to successful trials of the drug as an anticonvulsant,

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