Crystal and Molecular Structure of a Tricyclic Purine Intermediate. 3-Methyl-3*H*-imidazo[2,1-*i*]purine-8(7*H*)-one

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Abstract: N^6-Glycyl-9-methyladenine, when subjected to rearrangement conditions, undergoes a facile transformation into a cyclic intermediate. The structure of this key intermediate has now been established by X-ray diffraction as well as by chemical methods as 3-methyl-3*H*-imidazo[2,1-*i*]purine-8(7*H*)-one. Crystals of this tricyclic purine intermediate are monoclinic, space group $P2_1/c$ with cell constants $a = 7.376$ (3), $b = 10.968$ (3), $c = 10.169$ (4) Å, $\beta = 101.52$ (5)°, $Z = 4$. Using a GE XRD-6 diffractometer, a total of 1771 reflections were measured to the limit $2\theta = 160°$ for the Cu sphere. The complete structure was determined directly by using Sayre's relation and refined by using the least-squares method to an R of 0.047. The tricyclic purine intermediate molecule is nearly planar. The major interaction between the molecules involves parallel stacking. The packing of the molecules exhibits different degrees of overlap with each other in successive planes and the stacking distance ranges from 3.4 to 3.5 Å. Weak C–H···O and N–H···O interactions seem to be present.

In the course of the structure elucidation of a minor nucleoside occurring in tRNA of bacterial and mammalian tissues, several N^6-(α-aminoacyl)adenines were prepared.[2] The study on the chemistry of these compounds led to the realization that the naturally occurring nucleoside was a novel ureido nucleoside, N-[9-(β-D-ribofuranosyl-9H-purin-6-yl)carbamoyl]L-threonine.[3]

From the stability studies on N^6-(α-aminoacyl)-adenines, it is now obvious that if these compounds occurred as part of tRNA or in a free state, they would require special methods of isolation. Under the usual conditions of isolation, the N^6-(α-aminoacyl)adenines would undergo rearrangement to tricyclic purines or hydrolysis to adenines.[2]

Even though N^6-(α-aminoacyl)adenines, tricyclic purines, or their rearrangement products, N-(6-purinyl) amino acids, have not yet been detected in tRNA,[4] they still represent important biochemical compounds since they undergo facile rearrangement under conditions similar to those in physiological systems.

N^6-Glycyl-9-methyladenine (**1**) (see Figure 1), a model for N^6-(α-aminoacyl)adenosines, when subjected to rearrangement conditions undergoes a facile transformation into a cyclic intermediate, established as 3-methyl-3*H*-imidazo[2,1-*i*]purine-8(7*H*)-one[5] (**2**) (Figure 1).

This key intermediate, when heated in water or base, opened up to give 9-methyladenine-1-acetic acid (Figure 1), which in turn rearranged into N-[6-(9-methylpurinyl)]glycine. The structure of this key intermediate has now been established by X-ray diffraction as well as by chemical synthesis.[5]

The mechanism studies[6] using labeled N^6-(^{15}N-glycyl)adenine have shown that the compound **1** undergoes a ring opening with the incorporation of the labeled nitrogen of glycine into the cyclic compound at the N^1 position of adenine.

The present paper deals mainly with the results of the X-ray diffraction studies on this tricyclic purine intermediate.

Initial X-ray diffraction studies were carried out using crystals of tricyclic purine hydrobromide. This study clearly established the structure of the intermediate as 3-methyl-3*H*-imidazo[2,1-*i*]purine-8(7*H*)-one.[7] However, these crystals yielded very poor X-ray data and hence, the structural parameters of this molecule could not be refined accurately. Crystals of the tricyclic purine intermediate base yielded excellent X-ray data and X-ray studies once again showed the chemical structure of the intermediate to be 3-methyl-3*H*-imidazo[2,1-*i*]purine-8(7*H*)-one.

Experimental Section

The tricyclic purine intermediate (herein referred to as TPI) was prepared from N^6-glycyl-9-methyladenine as described by Chheda and Hall.[2] Crystals of TPI, obtained from a water–methanol mixture, are monoclinic and the sytematically absent reflections are: $0k0$ with k odd; $h0l$ with l odd; no absences in hkl. These absences are consistent with the space group $P2_1/c$. The unit cell constants and other crystallographic data of TPI ($C_8H_7N_5O$) are as follows: $a = 7.376$ (3), $b = 10.968$ (3), $c = 10.169$ (4) Å, $\beta = 101.52$ (5)°, $V = 806.09$ Å^3, $\rho_{obsd} = 1.59$ g cm^{-3}, $\rho_{calcd} = 1.56$ g cm^{-3}, $Z = 4$, $\mu = 9.52$ cm^{-1}, Cu K$\alpha_1 = 1.54051$ Å. The unit cell constants were refined from diffractometer data (at $22 \pm 3°$) by a least-squares procedure.

Complete three-dimensional intensity data were obtained employing Cu Kα radiation. The stationary crystal–stationary counter technique[8] was used for obtaining the intensities using a 5° take-off angle. A total of 1771 nonequivalent reflections was measured to the limit $2\theta = 160°$ for the Cu sphere, of which 1340 reflections whose intensities were twice the background in that (sin θ/λ) range were considered observable. The crystal used for the data collection had the dimensions $0.2 \times 0.15 \times 0.1$ mm and was mounted with the a^* axis along the ϕ axis of the goniostat. The difference in absorption as a function of ϕ was measured for the axial reflections and was used for correcting approximately anisotropy of absorption. No detailed absorption corrections were carried out, and the data were processed in the usual way.

(1) (a) Center for Crystallographic Research; (b) General Clinical Research Center.

(2) G. B. Chheda and R. H. Hall, *Biochemistry*, 5, 2082 (1966).

(3) (a) G. B. Chheda, R. H. Hall, D. I. Magrath, J. Mozejko, M. P. Schweizer, L. Stasiuk, and R. P. Taylor, *ibid.*, 8, 3282 (1969); (b) M. P. Schweizer, G. B. Chheda, L. Baczynskyj, and R. H. Hall, *ibid.*, 8, 3278 (1969); G. B. Chheda, *Life Sci.*, 8 (Part 2), 979 (1969).

(4) N-(6-Purinyl)aspartic acid was found in the hydrolysis of crude tRNA, however, not in purified tRNA.

(5) G. B. Chheda and R. H. Hall, *J. Org. Chem.*, 34, 3492 (1969).

(6) G. B. Chheda, R. H. Hall, and P. M. Tanna, *ibid.*, 34, 3498 (1969).

(7) R. Parthasarathy and G. B. Chheda, Abstracts of the Summer Meeting of the American Crystallographic Association, Buffalo, N. Y., 1968, p 100.

(8) T. F. Furnas and D. Harker, *Rev. Sci. Instrum.*, 26, 449 (1955).

Phase Determination

The basis of the sign-determination procedure is Sayre's relation[9] which also results from the Σ_2 equation of Hauptman and Karle.[10] From a preliminary listing of the Σ_2 interactions, the signs of three reflections, namely $21\bar{1}$, 356, and $41\bar{2}$—their $|E|$'s being 2.49, 3.82, and 2.71, respectively—which occurred most frequently in the Σ_2 interactions were specified as plus for defining the origin. In addition, four other reflections which also occurred frequently in the Σ_2 interactions were chosen as the starting set for the phase determination; these are $41\bar{3}$, 158, 094, and 210, their $|E|$'s being 2.75, 3.62, 3.99, and 2.30, respectively. The procedure used was to choose a particular set of signs for the four starting reflections, then apply Sayre's relation to these four and the three origin-determining reflections to determine additional signs and to redetermine those already predicted. This process is reiterated until there are no new additions or changes in the input signs. Since four reflections were used in the starting set, $2^4 = 16$ possible sign combinations are possible for the starting phases, thus yielding 16 solutions. To find out which of these 16 solutions is the most probable one, a consistency index c, defined as

$$c = \frac{\langle |E_H \sum_{\substack{H=K+L}} E_K E_L| \rangle_H}{\langle |E_H| \sum_{\substack{H=K+L}} |E_K||E_L| \rangle_H}$$

where $\langle\ \rangle_H$ means the average overall values of H, was calculated for each solution. The program used was written by Long.[11] The highest value for c was 0.8772 for solution 14, the next highest being 0.8352 for solution 13, both predicting 122 positive and 128 negative signs for the 250 reflections included in the iterative procedure. Also, solution 14 converged in three iterative cycles but four cycles were needed for solution 13.

Using the signs from solution 14, which appeared to be more promising, an E map was calculated. This map clearly revealed the positions of all the 14 nonhydrogen atoms. A structure factor calculation showed the R value for this structure to be 0.19.

Refinement of the Structure

The atomic coordinates and thermal parameters were refined by several cycles of least squares, employing a block diagonal approximation. Blocks of (9×9) and (4×4) were employed for atoms with anisotropic and isotropic thermal parameters, respectively. Five cycles of refinement, using individual isotropic thermal parameters, reduced the R value to 0.13. This was followed by eight cycles of refinement, using individual anisotropic thermal parameters, reducing the R value to 0.09. A difference electron density map at this stage clearly revealed the locations of all the seven hydrogen atoms. Four cycles of refinement, in which the positional and individual isotropic thermal parameters of the hydrogen atoms were also allowed to vary, brought the R index to 0.047. None of the shifts in the final cycle was greater than one-tenth of the standard deviations for the nonhydrogen atoms and one-fifth the standard deviations for the hydrogen atoms. The refinement was considered to be complete. The final atomic and thermal parameters and their standard deviations, as obtained directly from the inverse of the block-diagonal matrix, are listed in Tables I and II. A list of the ob-

(9) D. Sayre, *Acta Crystallogr.*, 5, 60 (1952).
(10) H. Hauptman and J. Karle, "Solution of the Phase Problem I. The Centrosymmetric Crystal," A. C. A. Monograph No. 3, Polycrystal Book Service, Brooklyn, N. Y., 1953.
(11) R. E. Long, Ph.D. Dissertation, University of California, Los Angeles, Calif., 1965.

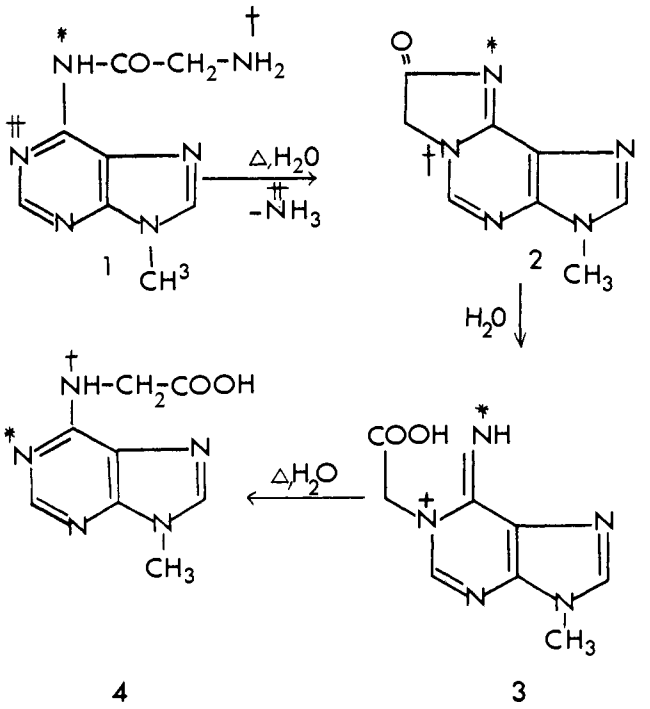

Figure 1. The figure shows the conversion of N^6-glycyladenine (**1**) into *N*-(6-(9-methylpurinyl))glycine (**4**) through the tricyclic purine intermediate **2** and 9-methyladenine-1-acetic acid (**3**). The nitrogens are marked with †, *, †† in order to show their path during the rearrangement.

Table I. Coordinates and Thermal Parameters[a]

	x	y	z	b_{11}
O	1214 (2)	1357 (2)	9753 (2)	338 (5)
N(1)	4206 (2)	5692 (2)	11944 (2)	186 (4)
C(2)	4456 (3)	6878 (2)	11873 (2)	175 (5)
N(3)	3676 (2)	7374 (2)	10653 (2)	174 (4)
N(4)	1964 (2)	6501 (2)	8583 (2)	208 (5)
C(5)	1317 (3)	5449 (2)	8092 (2)	183 (5)
N(6)	1528 (2)	4395 (2)	8817 (2)	141 (4)
C(7)	860 (3)	3184 (2)	8356 (2)	167 (5)
C(8)	1514 (3)	2445 (2)	9640 (2)	189 (6)
N(9)	2499 (2)	3179 (2)	10638 (2)	186 (4)
C(10)	2461 (3)	4295 (2)	10132 (2)	129 (4)
C(11)	3191 (3)	5404 (2)	10691 (2)	136 (4)
C(12)	2870 (3)	6426 (2)	9880 (2)	133 (4)
C(13)	3682 (4)	8676 (2)	10270 (2)	307 (8)

b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
50 (2)	126 (2)	−50 (5)	−18 (6)	10 (3)
69 (2)	55 (2)	−5 (5)	−7 (4)	−17 (3)
72 (2)	64 (2)	−20 (6)	−23 (6)	−33 (4)
54 (2)	70 (2)	−29 (4)	42 (5)	−21 (3)
57 (2)	61 (2)	−18 (5)	−10 (5)	11 (3)
67 (2)	56 (2)	−13 (6)	−12 (5)	16 (4)
53 (2)	48 (2)	−17 (4)	−8 (4)	−2 (3)
55 (2)	65 (2)	−30 (5)	2 (5)	−12 (3)
62 (2)	82 (3)	−1 (6)	21 (6)	−5 (4)
54 (2)	63 (3)	7 (5)	−3 (4)	−33 (3)
57 (2)	48 (2)	14 (5)	15 (4)	3 (3)
53 (2)	49 (2)	7 (5)	6 (5)	10 (3)
52 (2)	60 (2)	7 (5)	14 (5)	−5 (3)
50 (2)	112 (3)	52 (7)	74 (8)	−14 (4)

[a] TF = $\exp -(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)$. Values $\times 10^4$; standard deviations given in parentheses refer to the last digit.

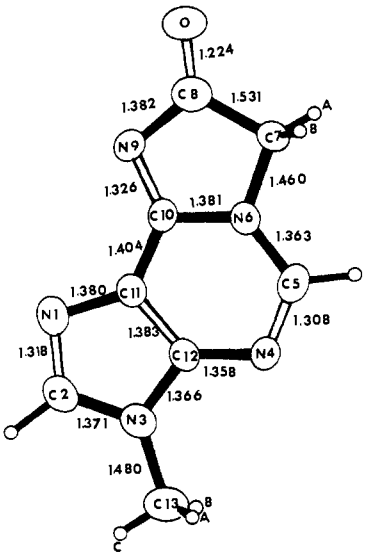

Figure 2. Bond distances in ångströms.

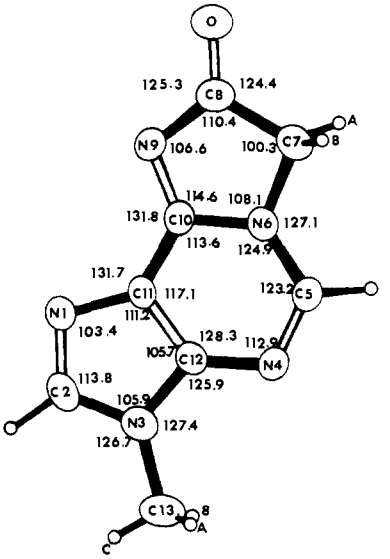

Figure 3. Bond angles in degrees.

served and calculated structure factors has been deposited with NAPS–ASIS as document no. 01097 ($2.00 for microfiche, $5.00 for photocopies).

Table II. Coordinates ($\times 10^3$) and Thermal Parameters for Hydrogen Atoms

	x	y	z	$B(\times 10^2)$
H(2)	507 (5)	742 (3)	1270 (4)	244
H(5)	66 (5)	538 (3)	709 (3)	466
H(7A)	−45 (3)	319 (2)	808 (2)	167
H(7B)	144 (3)	284 (2)	752 (2)	293
H(13A)	480 (5)	875 (4)	959 (4)	913
H(13B)	250 (5)	892 (3)	995 (3)	565
H(13C)	417 (5)	908 (3)	1103 (3)	539

The observations were weighted according to the scheme of Evans,[12] and the refinement was carried out by minimizing $[(|F_{obsd}| - 1/k|F_{calcd}|)^2]$. Reflections too weak to be observed were given zero weight during the refinement and for the R-index calculation. Atomic scattering factors for C, N, and O atoms were those presented in International Tables for X-Ray Crystallography.[13] For the hydrogen atoms, the values given by Stewart, Davidson, and Simpson[14] were used. The final value of the "goodness of fit" $(\Sigma\omega(|F_{obsd}| - |F_{calcd}|)^2/(m - n))$ is 1.44.

Discussion of the Structure

The bond distances and angles in the molecule are shown in Figures 2 and 3, respectively. The average C–H distance is 1.02 Å with an esd of 0.03 Å. The bond distances and angles in the adenine residue of TPI are in general agreement with those found in the adenine and purine residues of AUP,[15,16] 5′-AMP,[17] 3′-AMP,[18] 1-methylthymine, 9-methyladenine,[19] 9-methyladenine,[20] deoxyadenosine monohydrate,[21] purine,[22] 8-azaguanine monohydrate,[23] and hypoxanthine hydrochloride monohydrate.[24] A summary of the bond lengths in purines is given by Sletten and Jensen[24] and in adenines and substituted adenines by Ringert.[25] The formation of the third ring in TPI does not seem to have a marked influence on the angles subtended at atoms C(10) and N(6) (C(6) and N(1) in the purine numbering).

The TPI molecule is nearly planar, the maximum deviations from the plane occurring for the two substituents O and C(13) (see Table III). The atoms comprising the adenine residue are nearly planar (Table III) with C(13) being displaced most from the plane. The bending of the purine ring around the C(4)–C(5) bond (in the purine numbering, but C(11)–C(12) for the TPI molecule) found in other structures[23] involving purine residues does not seem to occur in this structure.

Thermal Libration

The thermal motions of four groups of atoms were analyzed to check whether the individual anisotropic thermal motions of the atoms in each group could be explained in terms of rigid-body librations. The four groups of atoms are: (I) the molecule as a whole; (II) the atoms O, N(6), C(7), C(8), N(9), and C(10); (III) the atoms N(4), C(5), N(6), C(10), C(11), and C(12); (IV) the atoms N(1), N(2), N(3), C(11), C(12), and C(13). The method and program used were those developed by Schomaker and Trueblood.[26]

The rms differences between the observed and calculated u_{ij}'s are, respectively, 0.7655, 0.0014,

(12) H. T. Evans, *Acta Crystallogr.*, **14**, 489 (1961).
(13) "International Tables of X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, 1962, pp 202–203.
(14) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 42, 3175 (1965).
(15) Abbreviations used are: adenosine 5′-phosphate, 5′-AMP; adenosine 3′-phosphate, 3′-AMP; β-adenosine-2′-β-uridine 5′-phosphate, AUP. See M. Sundaralingam, *Acta Crystallogr.*, **21**, 495 (1966).
(16) E. Shefter, M. Barlow, R. A. Sparks, and K. N. Trueblood, *ibid.*, *B*, **25**, 895 (1969).
(17) J. Kraut and L. H. Jensen, *ibid.*, **16**, 79 (963).
(18) See Sundaralingam, ref 15.
(19) K. Hoogsteen, *Acta Crystallogr.*, **16**, 28 (1963).
(20) R. F. Stewart and L. H. Jensen, *J. Chem. Phys.*, **40**, 2071 (1964).
(21) D. G. Watson, D. J. Sutor, and P. Tollin, *Acta Crystallogr.*, **19**, 111 (1965).
(22) D. G. Watson, R. M. Sweet, and R. E. Marsh, *ibid.*, **19**, 573 (1965).
(23) J. Sletten, E. Sletten, and L. H. Jensen, *ibid.*, *B*, **24**, 1692 (1968).
(24) J. Sletten and L. H. Jensen, *ibid.*, *B*, **25**, 1608 (1969).
(25) H. Ringert, Thesis, Karolinska Institute, S-10401 Stockholm, 1969, pp 9–17.
(26) V. Schomaker and K. N. Trueblood, *Acta Crystallogr. B*, **24**, 63 (1968).

Table III. Equations of Planes

	$lx + my + nz = d$				Rms deviation, Å
	l	m	n	d	
1. Entire molecule	0.9331	−0.1803	−0.3112	−4.236	0.033
2. Adenine residue	0.9344	−0.1682	−0.3141	−4.182	0.021
3. N(1), C(2), N(3), C(11), C(12)	0.9330	−0.1625	−0.3211	−4.208	0.004
4. N(4), C(5), N(6), C(10), C(11), C(12)	0.9337	−0.1777	−0.3109	−4.201	0.006
5. N(6), C(7), C(8), N(9), C(10)	0.9318	−0.1923	−0.3077	−4.238	0.012

Deviation of atoms from planes[a] Å × 10^3

	1	2	3	4	5
O	**−69**	−122	−167	−98	−49
N(1)	**38**	**16**	**3**	24	6
C(2)	**10**	**0**	**0**	1	−37
N(3)	**−14**	**−17**	**−3**	−23	−72
N(4)	**14**	**10**	29	**1**	−38
C(5)	**22**	**−9**	21	**6**	−18
N(6)	**14**	**−9**	−15	**−6**	**−10**
C(7)	**24**	**−8**	−24	0	**15**
C(8)	**−21**	**−64**	−96	−46	**−16**
N(9)	**13**	**−26**	−58	−9	**11**
C(10)	**18**	**−10**	−26	**−1**	**0**
C(11)	**23**	**3**	**−5**	**7**	−9
C(12)	**5**	**−4**	**5**	**−8**	−43
C(13)	**−76**	−67	36	−82	−153

[a] Boldface numbers indicate the atoms used in calculating the plane.

0.0011, and 0.0008 Å^2 for the four groups of atoms. The u_{ij}'s observed and u_{ij}'s derived from the rigid-body libration for the first group of atoms do not fit as well as the corresponding quantities for the groups II, III, and IV.

The maximum amplitude of libration for the groups II, III, and IV, are, respectively, 6.8, 15.0, and 5.1°; the corresponding principal axes of libration are nearly in the plane of the TPI molecule. The minimum amplitudes of libration for the three groups range from 2.2 to 2.5°, with the corresponding principal axes all being nearly normal to the plane of TPI molecule.

The bond distances, after correction for thermal librations, involving atoms in group III which has the maximum libration, are given in Table IV. It is seen that

Table IV. Bond Distances Corrected for Thermal Libration

	Corrected	Uncorrected
N(4)–C(12)	1.360	1.358
N(4)–C(5)	1.324	1.308
C(5)–N(6)	1.384	1.363
N(6)–C(10)	1.383	1.381
C(10)–C(11)	1.421	1.404
C(11)–C(12)	1.404	1.383

this correction for thermal libration is significant and, in some cases, is as large as 0.02 Å. In spite of the large correction for thermal libration, only the uncorrected distances were used for the discussion because of the uncertainty as to the proper model to use for making such corrections and because no such correction seems to have been applied in the analyses of many other purine structures with which our structure could be compared.

Packing and Intermolecular Distances

The major interaction between the molecules seems to involve parallel stacking of the rings; this stacking is shown in Figures 4 and 5. Recent investigations have suggested that the dominating force of interaction in solutions between nucleic acid constituents involves parallel stacking of purine and pyrimidine bases.[27] Similar conclusions have also been arrived at for solids.[28]

The structure of the TPI crystals seems to be held mainly by the stacking forces and other van der Waals interactions. The molecules exhibit differing degree of overlap with each other in successive planes; molecules A (see Table V for the explanation of the symbols

Table V

Plane	Position[a]	Translation
A	4	$0\bar{1}1$
B	3	$00\bar{1}$
C	4	001
D	3	$01\bar{1}$
E	1	000
F	2	012
G	3	000
H	4	$1\bar{1}2$
I	3	010
J	4	102
K	1	$0\bar{1}0$

[a] The equivalent positions are: 1 = x, y, z; 2 = $\bar{x}, \bar{y}, \bar{z}$; 3 = $x, \frac{1}{2} - y, \frac{1}{2} + z$; 4 = $\bar{x}, \frac{1}{2} + y, \frac{1}{2} - z$.

A, B, C, etc.), which are at 3.5 Å from the plane through molecules B, stack in such a way that maximum overlap occurs for the six-membered rings. Also, atoms of differing electronegativity lie above one another. Simi-

(27) S. I. Chan, B. W. Bangerter, and H. H. Peter, *Proc. Nat. Acad. Sci. U. S.*, 55, 720 (1964); S. I. Chan, M. P. Schweizer, P. O. P. Ts'o, and G. K. Helmkemp, *J. Amer. Chem. Soc.*, 86, 4182 (1964); T. N. Solie and J. A. Schellman, *J. Mol. Biol.*, 33, 61 (1968); P. O. P. Ts'o and S. I. Chan, *J. Amer. Chem. Soc.*, 86, 4176 (1964); P. O. P. Ts'o, J. S. Melvin, and A. C. Olsen, *ibid.*, 85, 289 (1963).

(28) C. E. Bugg, V. T. Thewalt, and R. E. Marsh, *Biochem. Biophys. Res. Commun.*, 33, 436 (1968).

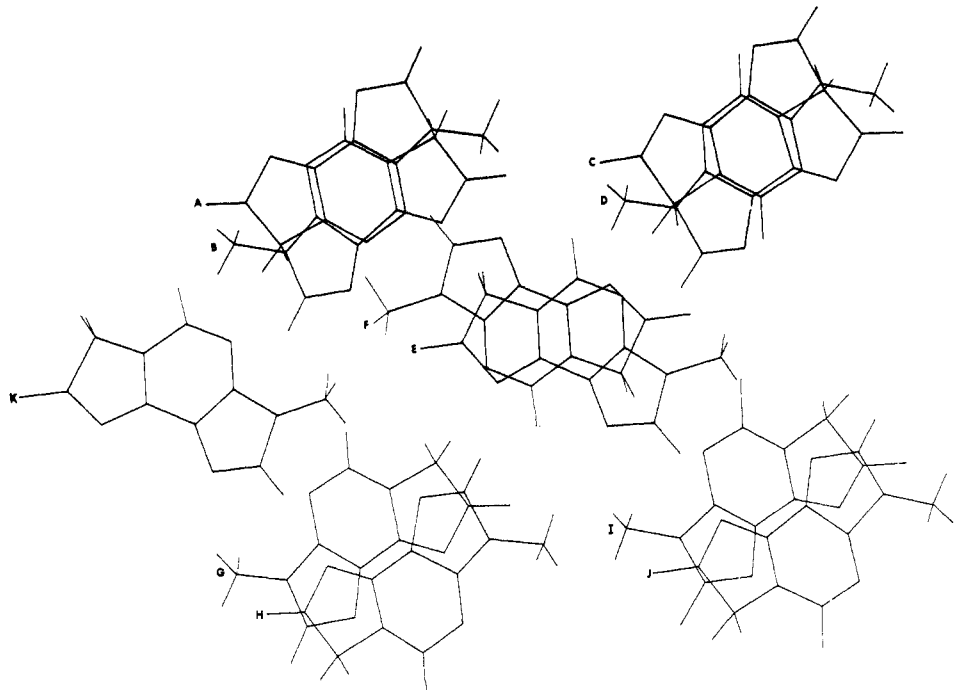

Figure 4. Stacking and overlapping of the bases. The view direction is nearly normal to the plane of the molecules.

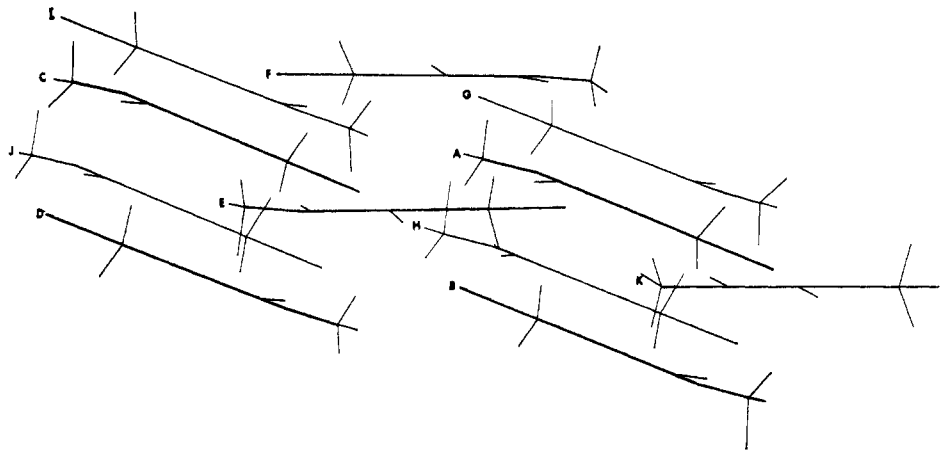

Figure 5. Stacking of the bases viewed on edge.

lar remarks apply for molecules C and D. Molecules E and F are in planes 3.5 Å apart and stack in such a way that the hydrogen atom, H(7a), of one molecule fits into the dimple at the center of the five-membered ring consisting of atoms 1, 2, 3, 12, and 11 of the second molecule. Molecules G and H, as well as I and J, which are in planes 3.4 Å apart are stacked so that there is only partial overlapping of the six-membered rings. The degree of overlap does not seem to influence greatly the stacking distance. Partial rather than complete overlap seems to be an important mode of packing in this structure as well as in other structures of nucleic acid constituents.[29]

There is a short C–H···O contact involving C(5), which is 3.27 Å (Table VI) from the oxygen, O. The H(5)···O distance of 2.35 Å together with the C(5)–H(5)···O angle of 147° suggest that a weak C–H···O bond may be present,[30] but Donohue's[31] reservations about such a system must be kept in mind.

Similar interactions have been observed in a number of recent studies: 3′-AMP,[18] AUP,[16] L-azetidine-2-carboxylic acid.[32] N(9) has a short contact with C(2) (Table VI); the angle of 156° for the C(2)–H(2)···N(9) suggest that a weak C–H···N interaction may be present, but again, Donohue's reservations should be noted.

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Table VI. The Shortest Intermolecular Distances (in Å)

O–C(5)	4	01̄1	3.270	C(2)–H(7A)	2	012	2.97
N(1)–N(6)	2	112	3.390	C(2)–H(7B)	2	112	2.98
C(2)–N(4)	3	010	3.292	C(2)–H(13A)	3	010	2.81
C(2)–N(9)	4	102	3.350	N(3)–H(7A)	2	012	2.99
N(3)–N(9)	2	112	3.396	N(3)–H(2)	3	01̄1	3.37
N(4)–C(2)	3	01̄1	3.292	N(4)–H(2)	3	01̄1	2.87
N(4)–C(7)	4	001	3.162	N(4)–H(7A)	4	001	2.60
C(11)–C(11)	2	112	3.374	N(4)–H(7B)	4	001	2.93
O–H(5)	4	01̄1	2.35	C(5)–C(7)	4	001	3.27
O–H(13B)	1	01̄0	2.82	C(8)–H(13A)	2	112	2.98
O–H(13A)	2	112	2.88	C(8)–H(7B)	3	000	2.95
O–H(13B)	2	012	2.83	N(9)–N(3)	2	112	3.40
N(1)–H(7A)	2	012	3.03	N(9)–H(13A)	2	112	2.94
N(1)–H(13A)	3	010	2.71	N(9)–H(7B)	3	000	2.47
N(1)–H(13C)	4	1̄12	2.80	N(9)–H(2)	4	1̄12	2.46

modified version of the Gaentzel, Sparks, and Trueblood ACA Old Program #317), a general program for Fourier summation by Dr. S. T. Rao, the Sayres relation by Dr. R. E. Long (ACA(New) #2). We are grateful to the following agencies for financial assistance: National Institutes of Health, Grants No. GM-15787 and AM-3942, and the National Science Foundation, Grant No. GB-8690.

Radical Cyclization during Autoxidation of 5-Hexenylmagnesium Bromide[1]

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Abstract: No cyclization to cyclopentylmethanol occurs in the reaction of 5-hexenylmagnesium bromide with *t*-BuOOMgCl. The amount of cyclization observed during the autoxidation of 5-hexenylmagnesium bromide increases markedly as the O_2 concentration in the solution is decreased. These observations are consistent with a radical chain mechanism in which cyclization of 5-hexenyl radicals competes with their reaction with oxygen but appears to rule out any simple bimolecular reaction between Grignard reagent and oxygen.

The autoxidation of Grignard reagents to magnesium salts of alcohols is generally considered

$$2RMgX + O_2 \longrightarrow 2ROMgX \quad (1)$$

$$RMgX + O_2 \longrightarrow ROOMgX \quad (2)$$

$$ROOMgX + RMgX \longrightarrow 2ROMgX \quad (3)$$

to follow the two-step path originally proposed by Porter and Steele,[3] since the intermediate hydroperoxides may be obtained in good yield (30–90% for aliphatic Grignard reagents) if the Grignard reagent is added slowly to oxygen-saturated solvents at −78°.[4] The second step, reaction 3, apparently involves a simple nucleophilic attack on oxygen (perhaps *via* the rearrangement of an intermediate complex in which oxygen is coordinated with the magnesium) and is observed in the reaction of organometallics with a variety of peroxide derivatives.[4]

The first step, reaction 2, can either be formulated as a simple insertion or a radical chain. In their initial study, Walling and Buckler could find no evidence for a chain process, since diphenylamine, a good autoxidation inhibitor, did not decrease hydroperoxide yields, and butyraldehyde, which is readily autoxidized, did not interfere with the reaction or undergo cooxidation. Subsequently, however, rearrangements typical of radical processes have been observed to accompany autoxidations of certain Grignard reagents and have been taken as evidence for the radical chain path. Thus 3,3-diphenylallylcarbinylmagnesium bromide yields appreciable amounts of cyclopropyldiphenylmethanol on autoxidation, but only open-chain products on carbonation.[5] Similarly 3,5-hexadienylmagnesium bromide gives some 1- and 3-cyclopropylallyl alcohol on autoxidation, but no cyclized products on carbonation.[5] Finally, 5-hexenylmagnesium bromide on autoxidation gives approximately 25% cyclopentylmenthanol but little or no cyclization in other reactions.[6] The cyclization is evidently not reversible, since autoxidation of

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