Elementary Patterns in Protein-Nucleic Acid Interactions. IV.† Crystal Structure of 3-(Adenin-9-yl)propionamide : 1-Methylthymine (1 : 1) Complex Dihydrate

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As a ternary interaction model between adenine:thymine base pair and carbamoyl group, 3-(adenin-9-yl)-propionamide: 1-methylthymine complex was prepared and its crystal structure was examined. The crystal exhibits a disordered structure, and the structure unit is a monoclinic cell with dimensions $a=11.368(1)$, $b=6.909(1)$, $c=12.708(2)$ Å, and $\beta=114.49(1)°$. The space group is $P2_1$ and the unit cell contains two complexes and four water molecules. The base pairing pattern between adenine and thymine is the Hoogsteen type. The carbamoyl group is hydrogen-bonded to N(A1) of adenine in this base pair, the distance NH···N(A1) being 2.94(2) Å. With two kinds of hydrogen bonds of the carbamoyl group, NH···N(A1) above-mentioned and NH···O(carbamoyl), the 3-(adenin-9-yl)propionamide molecules form a sheet extending perpendicular to the c axis; the base-paired thymine molecules extrude alternately from the sheet. Diffused spots along c* with half integers of l can be interpreted as a stacking disorder of the sheets.

In the studies of the elementary patterns in protein: nucleic acid interactions, we have reported several modes of hydrogen bonding between cytosine and carboxyl group,[1-4] between adenine and indolyl group,[5,6] between adenine and carboxyl group,[7,8] and between adenine and carbamoyl group.[9]

It is well-known that nucleic acid tends to form double strands by the hydrogen bonds between the complementary bases. Rich *et al.* proposed a recognition pattern between the carbamoyl group and base-paired adenine.[10] It is interesting to examine whether some base pair shows special affinity to the carbamoyl group, and where is the preferential binding site of the bases.

We have succeeded in preparing crystals of 3-(adenin-9-yl)propionamide : 1-methylthymine complex as one of the ternary interaction models between purine:pyrimidine base pair and the side chain of amino acid, and an X-ray analysis of the crystal structure has been performed. In this paper, we will report a mode of hydrogen bonding between adenine: thymine base pair and the carbamoyl group, and discuss the capability of the interaction of carbamoyl group with a double-stranded polynucleotides.

Experimental

Equimolar quantities of 3-(adenin-9-yl)propionamide[9] and 1-methylthymine (purchased from Cyclo Chem. Co.) were dissolved in a water–methanol (1:1) solution. Thick plate crystals of the 1:1 complex were obtained after standing the solution for 10 d. Density was measured by flotation in a mixture of cyclohexane and carbon tetrachloride. Preliminary X-ray photographs indicated the space group to be $P2_1$ or $P2_1/m$, but on the upper-layer Weissenberg photographs diffused spots extending along c* appeared at the positions with half-integer of l, as shown in Fig. 1. It apparently suggests the stacking disorder with two kinds of sheets along c. To obtain the crystals without such disorder, we tried crystallization from water-methanol solutions of the adenine and thymine with different molar ratios (1:2, 1:3, 2:1 and 3:1) at different temperatures (2—25 °C), but failed.

A crystal from the solution with 1:1 molar ratio, $0.2\times0.2\times0.05$ mm³ in size, was used for data collection. The intensities for 2767 independent reflexions in the range $4°<2\theta<122°$ were measured on a Rigaku automated four-circle diffractometer with nickel filtered Cu $K\alpha$ radiation ($\lambda=1.54184$ Å). A scan speed was 4° (in 2θ) min^{-1} and a scan width was 1.2° (in ω) plus α_1-α_2 divergence. After every 50 reflexions, five standard reflexions were monitored, the intensities of which showed no significant change. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Only 73 reflexions had no net intensities; the observational threshold value, F_{11m}, was 1.98. The standard deviations were estimated by the equation of $\sigma^2(F_o)=\sigma_P^2(F_o)+qF_o^2$, where q, 8.1×10^{-6}, was derived from the variations of the monitored reflexions.[11]

Crystallographic data are summarized in Table 1.

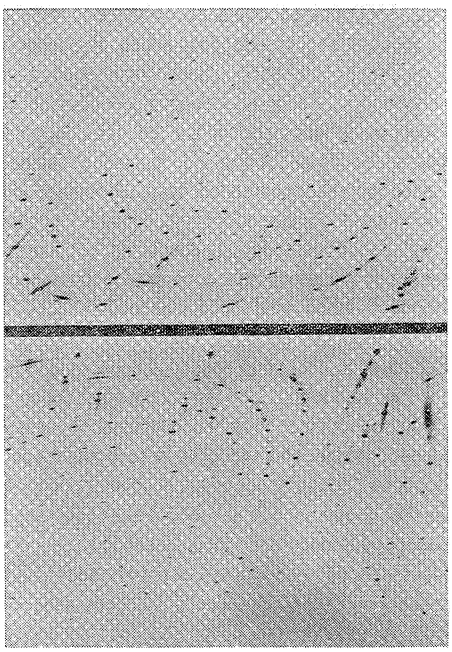

Fig. 1. An hll layer Weissenberg photograph of the title crystal.

Structure Determination and Refinement

Structure determination was unsuccessful on the basis of the space group $P2_1$ and $P2_1/m$. As stated in the

† Part III of this series is Ref. 8.

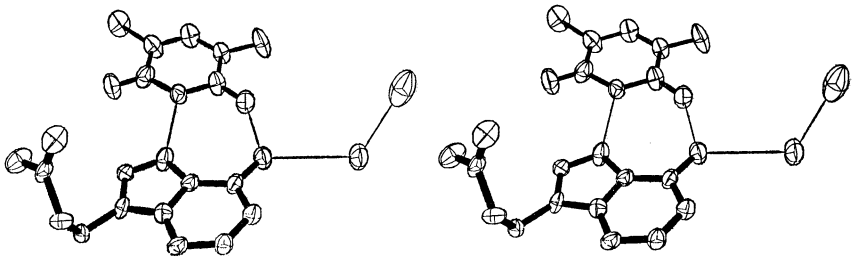

Fig. 2. Stereoview of 3-(adenin-9-yl)propionamide:1-methylthymine complex dihydrate with 50% probability ellipsoids.

Table 1. Crystal data

3-(Adenin-9-yl)propionamide: 1-Methylthymine Complex Dihydrate	
$C_8H_{10}N_6O : C_6H_8N_2O_2 : 2H_2O$	
Space group: $P2_1$	
$a=11.368(1)$ Å	$U=907.0$ (1) Å^3
$b=6.909(1)$ Å	$Z=2$
$c=12.708(2)$ Å	$D_x=1.41$ g cm^{-3}
$\beta=114.49(1)°$	$D_m=1.40$ g cm^{-3}

previous section, diffused spots appeared at the positions with half-integer of l, but the spreads of these spots were rather small. If these spots were regarded to be Bragg reflexions, the space group should be $P2_1/c$. Values of l for all normal spots became even and those for diffused ones were odd. On the basis of the space group $P2_1/c$, however, the analysis by the use of the MULTAN 74 Programme[12] was not straightforward. As E values of reflexions with odd l's were much less than those with even l's, the former reflexions were not included in the data set for phase determinations, if the normal criterion for the magnitudes of E was applied. So, we prepared a starting data set by picking up the largest 30 reflexions in each parity group. An E map with the fifth lowest R value revealed a reasonable molecular skeleton. Successive refinement of the structural parameters, however, was not successful in getting a reasonably low R value. Therefore, we tried to modify the refinement process from the view of rather special character of the present crystal including some stacking disorder along the c axis. As will be described in the later section, the molecules related by 2_1 symmetry form a sheet parallel to the ab plane by the hydrogen bonds. If such a sheet is represented by P, the stacking mode in the space group $P2_1/c$ is $P\bar{P}\bar{P}P\cdots$, where $\bar{P}$ stands for an inversed sheet. The unit cell for P contains equivalent positions x, y, z, and $\bar{x}$, $1/2+y$, $\bar{z}$, and that for $\bar{P}$ $\bar{x}$, $\bar{y}$, $\bar{z}$ and x, $1/2-y$, z (the unit cell dimensions are those given in Table 1). Therefore, a reasonable model of disorder was constructed by putting the stacking mode PP$\cdots$ or $\bar{P}\bar{P}\cdots$ into the alternate P's and $\bar{P}$'s. Intensity profiles of the diffused spots on $h1l$ Weissenberg photographs were measured with a microdensitometer (SAKURA PDM-5) and interpreted on such a disordered model by the use of Wilson's equation.[13] The probability α of finding P after P was estimated to be 0.16 from half-value width of a diffused spot (2,1,3/2), after correction for spot size. Low value of α means that the major part of the crystal consists of the $P2_1/c$ domains. So, intensities can be approximately expressed as a sum of the intensity from the $P2_1/c$ domains and that from the $P2_1$ domains. Refinement on such approximation is equivalent to the improvement of the structural parameters and w in the equation:

$$F = K[wF_P+(1-w)F_{\bar{P}}],$$

Table 2. Fractional coordinates and isotropic temperature factors

The B values accompanied with $\langle\ \rangle$ are the equivalent isotropic temperature factors calculated from anisotropic thermal parameters using the equation $B=8\pi^2(U_1+U_2+U_3)/3$, where U_1, U_2, and U_3 are the principal components of mean square displacement matrix $\boldsymbol{U}$. Values in $\langle\ \rangle$ are anisotropicity defined by $(\sum(B-8\pi^2Ui)^2/3)^{1/2}$. The e.s.d.'s in ( ) refer to last decimal places.

Atom	x	y	z	B/Å^2
N(A1)	0.6478(8)	0.166(2)	0.5857(7)	2.8⟨8⟩
C(A2)	0.564(1)	0.167(2)	0.473(1)	3.0⟨7⟩
N(A3)	0.4344(8)	0.184(2)	0.4280(7)	2.7⟨8⟩
C(A4)	0.393(1)	0.208(2)	0.5130(9)	2.8⟨3⟩
C(A5)	0.4702(9)	0.207(2)	0.6320(8)	2.6⟨7⟩
C(A6)	0.603(1)	0.186(2)	0.668(1)	2.9⟨8⟩
N(A6)	0.6899(7)	0.190(2)	0.7803(7)	3.6⟨17⟩
N(A7)	0.3931(7)	0.240(4)	0.6921(6)	3.3⟨19⟩
C(A8)	0.2745(8)	0.253(4)	0.6109(8)	2.9⟨11⟩
N(A9)	0.2685(6)	0.244(4)	0.4996(6)	2.5⟨13⟩
C(A11)	0.1535(9)	0.263(4)	0.3899(8)	2.6⟨7⟩
C(A12)	0.114(1)	0.058(2)	0.335(1)	3.1⟨9⟩
C(A13)	0.064(1)	−0.068(3)	0.409(1)	3.2⟨20⟩
N(A13)	0.1066(8)	−0.256(4)	0.4322(8)	3.7⟨16⟩
O(A13)	−0.0199(8)	0.001(2)	0.4383(7)	4.3⟨18⟩
N(T1)	0.3505(8)	0.247(4)	1.0715(7)	4.9⟨33⟩
C(T1M)	0.233(1)	0.215(5)	1.101(1)	7.0⟨56⟩
C(T2)	0.326(1)	0.255(4)	0.9551(9)	4.1⟨18⟩
O(T2)	0.2195(6)	0.250(4)	0.8778(6)	6.4⟨52⟩
N(T3)	0.4361(7)	0.263(4)	0.9340(6)	3.1⟨9⟩
C(T4)	0.562(1)	0.262(4)	1.0175(9)	3.5⟨17⟩
O(T4)	0.6519(6)	0.270(4)	0.9865(6)	4.7⟨27⟩
C(T5)	0.5801(9)	0.260(4)	1.1343(7)	3.2⟨17⟩
C(T5M)	0.716(1)	0.269(5)	1.2266(9)	5.6⟨43⟩
C(T6)	0.474(1)	0.245(4)	1.1570(8)	4.0⟨16⟩
O(W1)	1.0719(7)	−0.242(4)	0.9350(6)	6.7⟨40⟩
O(W2)	0.9731(7)	0.140(2)	0.8638(7)	5.8⟨37⟩

Table 3. Hydrogen bond distances and angles of 3-(adenin-9-yl)propionamide: 1-methylthymine complex dihydrate

Standard deviations are given in parentheses. * and † indicate PP̄ and PP junctions, respectively.

	l/Å		ϕ/°
N(A1)···N(A13)[a]	2.94(2)	C(A8)-N(A7)···N(T3)	120(1)
N(A13)···O(A13)[e]	2.80(2)	C(T2)-N(T3)···N(A7)	116(1)
N(A6)···O(W2)	2.96(2)	C(T4)-N(T3)···N(A7)	119(1)
O(T2)···O(W2)[h]	2.83(2)	C(T4)-O(T4)···N(A6)	137(1)
O(T4)···O(W1)[g]	2.88(3)*	C(T4)-O(T4)···O(W1)[g]	144(1)*
N(T3)···N(A7)	2.91(2)	C(T4)-O(T4)···O(W1)[c]	145(1)†
O(T4)···N(A6)	2.88(2)	N(A6)···O(T4)···O(W1)[g]	75(1)*
O(T4)···O(W1)[c]	2.87(3)†	N(A6)···O(T4)···O(W1)[c]	76(1)†
O(W1)···O(W2)[g]	2.90(2)*	N(A6)···O(W2)···O(W1)[g]	74(1)*
O(W1)···O(W2)	2.86(2)	N(A6)···O(W2)···O(W1)[c]	74(1)†
O(W1)···O(W2)[i]	2.93(2)†	O(T4)···O(W1)[c]···O(W2)	105(1)†
		O(T4)···O(W1)[g]···O(W2)	106(1)*
	ϕ/°	O(T4)···O(W1)[g]···O(W2)[g]	114(1)*
		O(T4)[i]···O(W1)···O(W2)	108(1)†
C(A13)-O(A13)···N(A13)[b]	154(1)	O(W1)[g]···O(W2)···O(W1)	98(1)*
C(A13)-N(A13)···O(A13)[e]	121(1)	O(W1)[c]···O(W2)···O(W1)	100(1)†
C(A13)-N(A13)···N(A1)[f]	115(1)	O(W2)···O(W1)···O(W2)[g]	82(1)*
O(A13)[e]···N(A13)···N(A1)[f]	121(1)	O(W2)···O(W1)···O(W2)[i]	110(1)†
C(A2)-N(A1)···N(A13)[a]	101(1)	N(A6)···O(W2)···O(T2)[d]	153(1)
C(A6)-N(A1)···N(A13)[a]	136(1)	N(A6)···O(W2)···O(W1)	116(1)
C(A6)-N(A6)···O(W2)	125(1)	O(T2)[d]···O(W2)···O(W1)	89(1)
C(A6)-N(A6)···O(T4)	130(1)	C(T2)-O(T2)···O(W2)[h]	134(2)
O(T4)···N(A6)···O(W2)	104(1)	O(T2)[d]···O(W2)···O(W1)[c]	113(1)†
C(A5)-N(A7)···N(T3)	136(1)	O(T2)[d]···O(W2)···O(W1)[g]	114(1)*

Symmetry codes

(a) $1-x$, $1/2+y$, $1-z$, (b) $-x$, $1/2+y$, $1-z$, (c) $2-x$, $1/2+y$, $2-z$, (d) $1+x$, y, z, (e) $-x$, $-1/2+y$, $1-z$, (f) $1-x$, $-1/2+y$, $1-z$, (g) $2-x$, $-y$, $2-z$, (h) $-1+x$, y, z, (i) $2-x$, $-1/2+y$, $2-z$.

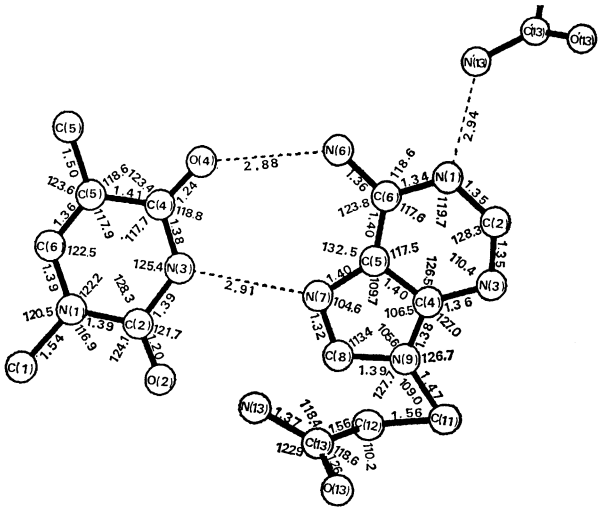

Fig. 3. Atomic numbering and bond distances (l/Å) and angles (ϕ/°) in 3-(adenin-9-yl)propionamide:1-methylthymine complex.

Numbers for the atoms in 3-(adenin-9-yl)propionamide and 1-methylthymine should be prefixed by A and T, and methyl carbon atoms, C(1) and C(5), should be read C(T1M) and C(T5M), respectively. E.s.d's for the bond distances and angles are 0.03 Å and 1.2—2.1°, respectively.

where F_P and $F_{\bar{P}}$ are structure factors for P and $\bar{P}$, respectively, and K scale factor. The value of w is related to the volume fraction W of the $P2_1/c$ domain by equation

$$(1-W)/W = \pm(1-2w)/2\sqrt{w(1-w)}.$$

The parameters were refined by the full-matrix least-squares method. The quantity minimized was $\Sigma\omega(|F_o|-|F_c|)^2$, where $\omega=1/(\sigma^2(F_o))$. As the adenine-thymine pair lies near the plane at $y=1/4$, the matrix became ill-conditioned. In order to resolve such difficulty, only F_P was differentiated in the least-squares calculations. The R value converged to 0.091. The maximum shift of parameters in the last cycle was 0.1σ for C, N, and O atoms. From the final w of 0.763, the volume fraction of the $P2_1/c$ domains was estimated to be 0.62, which is compatible to the expectation from the value of α.

Atomic scattering factors used were taken from "International Tables for X-Ray Crystallography."[14] The final atomic parameters are listed in Table 2.[15]

Results and Discussion

Molecular Structure. Figure 2 gives stereoscopic view of 3-(adenin-9-yl)propionamide:1-methylthymine complex dihydrate. Bond distances and angles are shown in Fig. 3, together with the atomic numbering

TABLE 4. DEVIATIONS OF ATOMS FROM THE LEAST-SQUARES PLANES

Plane 1: carbamoyl plane, Plane 2: adenine plane, Plane 3: thymine plane.

Deviations l/Å					
Plane 1		Plane 2		Plane 3	
C(A12)*	−0.007	N(A1)*	0.024	N(T1)*	0.002
C(A13)*	0.024	C(A2)*	0.013	C(T2)*	0.007
N(A13)*	−0.008	N(A3)*	−0.029	N(T3)*	0.001
O(A13)*	−0.009	C(A4)*	−0.021	C(T4)*	−0.017
C(A11)	1.055	C(A5)*	−0.029	C(T5)*	0.027
		C(A6)*	−0.001	C(T6)*	−0.020
		N(A7)*	0.006	C(T1M)	−0.151
		C(A8)*	−0.006	O(T2)	−0.029
		N(A9)*	0.043	O(T4)	−0.016
		N(A6)	0.044	C(T5M)	0.082
		C(A11)	0.101		

* Atoms included in the calculations of the least-squares plane.

Dihedral angles between the planes ϕ/°

No.	2	3
1	69.2(6)	70.8(7)
2		10.8(5)

system, and the geometries of hydrogen bonds in Table 3. The displacements of atoms from the least-squares planes of adenine, thymine and carbamoyl moieties are given in Table 4.

The dimensions of 3-(adenin-9-yl)propionamide in the present complex are in good agreement with those in the crystal of 3-(adenin-9-yl)propionamide.[9] The N(A6) atom is almost on the purine ring plane and the C(A11) atom deviates by 0.1 Å from it. The conformation of the ethyl chain with the carbamoyl group is different from that of 3-(adenin-9-yl)propionamide. In the present crystal the torsion angle of N(A9)–C(A11)–C(A12)–C(A13) and C(A11)–C(A12)–C(A13)–N(A13) are 78.1 and −135.1°, respectively, while in 3-(adenin-9-yl)propionamide they are −170.0 and 173.3°.

In 1-methylthymine, the C(T4)–O(T4) bond is longer than C(T2)–O(T2). Such difference is also found in 1-methylthymine:9-methyladenine complex.[16] The methyl carbon atoms, C(T1M) and C(T5M), deviate by 0.15 and 0.08 Å from the pyrimidine plane, respectively.

Crystal Structure. As seen in Fig. 3, the adenine and thymine moieties form a pair through the two hydrogen bonds between N(A6) and O(T4) and between N(A7) and N(T3), their distances being 2.88(2) and 2.91(3) Å, respectively. This pattern is the "Hoogsteen" pairing found in 1-methylthymine:9-methyladenine complex.[16] The purine and pyrimidine planes are twisted to each other by 10.8(5)°, as commonly observed in the other Hoogsteen base pairs.[16,17] Such a twisting is favourable to relieve the bending of hydrogen bonds.

The crystal structure viewed along the b axis is shown in Fig. 4. The carbamoyl group branching from the adjacent base pair related by 2_1 around (1/2, y,1/2) is hydrogen-bonded to the adenine moiety; in the NH···N(A1) hydrogen bond, the NH···N(A1) distance is 2.94(2) Å and the dihedral angle between the carbamoyl group and the adenine moiety is 106.7(6)°. The adenine moieties in the molecules connected by this hydrogen bond are, at the same time, stacked to form a molecular column around the 2_1 axis at $x=1/2$ and $z=1/2$. The remaining carbamoyl hydrogen atom participates in hydrogen bond to the carbamoyl group, the O(A13) atom in the complex related by 2_1 around (0,y,1/2) being an acceptor. This hydrogen bond links the molecular columns to form a sheet parallel to the ab plane.

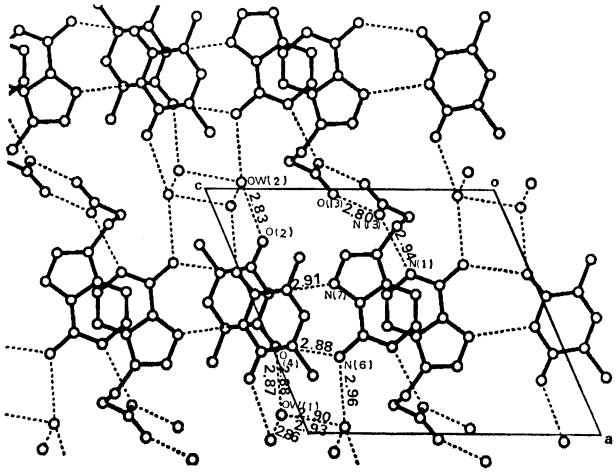

Fig. 4. Crystal structure of 3-(adenin-9-yl)propionamide : 1-methylthymine complex dihydrate projected along the b axis.
In hydrogen bond distances (l/Å) doubly indicated, the upper one corresponds to the value in the PP̄ junction and the lower one in the PP junction.

As shown in Fig. 5, the molecular sheets are joined along the direction of c by the alternate stacking of the 1-methylthymine molecules extruded perpendicular to the sheets. Although there are two kinds of stacking in PP and PP̄ junctions, the spacings are almost the same. In the latter junction, however, the N(A6) atom at $1-x$, $-y$, $2-z$ is close to the C(T1M) atom, the distance being 3.13(3) Å.

In addition, there are two different hydrogen bonding patterns for PP and PP̄ junctions. In both junctions, the water oxygen atoms, O(W1) and O(W2), are hydrogen bonded to O(T4) and O(T2), respectively, and the O(W2) atom is an acceptor of hydrogen bond from N(A6) of adenine moiety. In PP junction, two water molecules are connected by hydrogen bonds, to form a chain around the 2_1 axis at $x=0$, and $z=1$. In PP̄ junction, the hydrogen bonding scheme between waters is a loop around the inversion centre. There is no significant difference in hydrogen bond distances and angles between the two junctions.

Interaction between Carbamoyl Group and Adenine:Thymine Base-pair. In the present model crystal, it is found that the carbamoyl group interacts with the Hoogsteen base pair of adenine and thymine through the hydrogen bond between the adenine N(A1) and the car-

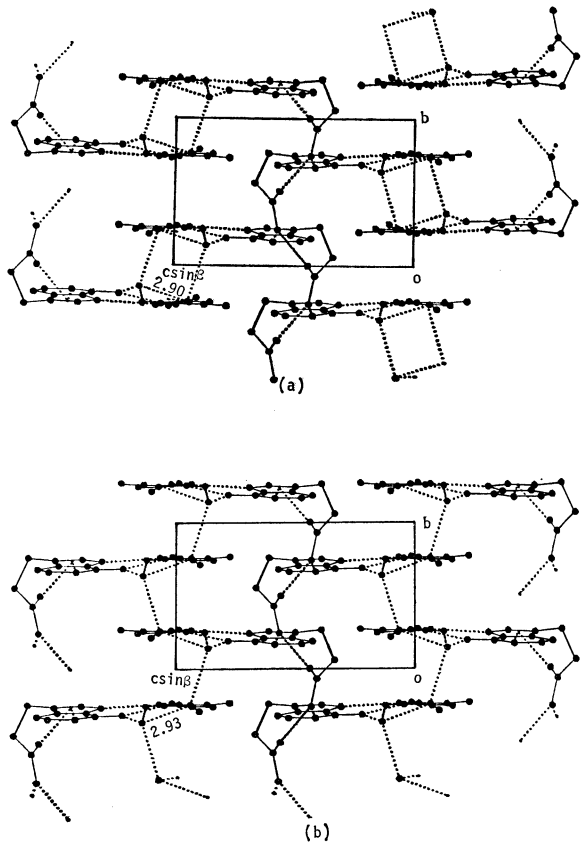

Fig. 5. Crystal structure of 3-(adenin-9-yl)propionamide : 1-methylthymine complex dihydrate projected along the a axis.
(a) $P\bar{P}$ junction and (b) PP junction.

bamoyl N(A13) atoms, as shown in Fig. 3. For adenine: thymine pair in Hoogsteen type, the carbamoyl group seems to have a preferential interaction with adenine.

To examine whether the present mode is possible in the protein:nucleic acid interaction, we need geometrical data of the Hoogsteen base pair in the nucleic acids. This type of base pair has been found to occur actually between Uracil 8 and Adenine 14 in tRNA,[18-20] though it is reversed. Model building by computer graphics[21] proves that the observed interaction geometry can be incorporated into $tRNA^{Phe}$ [22] at Adenine 14, with minor adjustment. It is indicated that ethidium bromide[23] and magnesium ion[24] bind to tRNA in the vicinity of this pair. Enzymes involved in protein synthesis would also possibly interact with this region. If glutamine or asparagine residue in the protein would participate in such an interaction, the carbamoyl group might combine to tRNA in a mode shown in Fig. 3.

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