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Structure and Stereochemistry of Nucleic Acid Components and Their Reaction Products. III.[1a] Crystal Structure of the Potassium Salt of *N*-(Purin-6-ylcarbamoyl)-L-threonine. Possible Role of Hypermodified Bases Adjacent to Anticodon in Codon–Anticodon Interaction

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Abstract: The crystal structure of the potassium salt of *N*-(purin-6-ylcarbamoyl)-L-threonine, a hypermodified base adjacent to anticodons in tRNAs responding to the codons beginning with adenine, has been accurately determined using X-ray diffraction techniques and refined to an R of 0.057 for 1894 reflections. The crystals are monoclinic, space group $P2_1$, with cell constants a = 15.289 (2) Å, b = 6.410 (1) Å, c = 8.815 (1) Å, β = 105.9°, and Z = 2. The hydrogen atoms were located from electron-density difference maps; they indicate a possible coexistence of N(9)–H and N(7)–H tautomers in the crystal. The N^6 substituent is distal (*trans*) to the imidazole ring, forming an intramolecular hydrogen bond N(threonine)—H - - -N(1) of adenine. This conformation of the N^6 substituent is typical of ureidopurines and blocks the two sites N(6)–H and N(1) of adenine that are normally utilized for complementary base pairing in the double helical regions of nucleic acids; the internal hydrogen bonding further enhances the shielding of N(1). This blocking of N(6)–H and N(1) may be important in enhancing the single-stranded conformation of the anticodon loops of tRNA and in preventing the modified adenosine adjacent to the anticodon from taking part directly in codon–anticodon interaction through the complementary base pairing. The conjugated ureidopurine moiety is stacked in a head-to-tail fashion in planes 3.2 Å apart. The C^α and C^β atoms of threonine are nearly in the plane through the ureidopurine moiety; the bulky carboxyl and methyl groups are pointing in opposite directions from this plane and do not interfere with the close stacking. All polar hydrogens take part in hydrogen bonding; in addition, there are two short C—H - - -O contracts. There is little self association of amino acid or nucleic acid moieties through hydrogen bonding; any interaction by way of hydrogen bonding or stacking between these two moieties is minimal. The four water molecules, exhibiting variable hydrogen bonding geometries, are linked to one another and to the threonine and adenosine residues. The K^+ ion has a sixfold coordination. the torsion angles (χ) about the C^α–C^β bond for O^γ and C^γ atoms with respect to N are respectively 54.5 and −67.1°; this conformation of the threonine side chain is different from those observed previously. The carboxyl group is twisted with respect to the nitrogen about the C^α–C' bond by Ψ = 154.2°, similar to what is commonly found in amino acids.

The ureidopurine derivative *N*-(purin-6-ylcarbamoyl)-L-threonine (PCT) was isolated and characterized from the total tRNA of yeast.[2] Subsequently, it was shown that PCT occupies a position adjacent to the 3′ end of the anticodon in several tRNAs which respond to the codons beginning with adenine (A).[3] Other such nucleic acid bases as N^6-(Δ^2-isopentenyl)adenine (IPA), its 2-methylthio analog (2-MT-IPA), etc., have been found in an analogous position in several tRNAs whose codons begin with uracil (U).[4] As a part of the macromolecule, these components appear to be involved in acceptor as well as transfer activity of tRNA[5] while as free bases some of them act as cytokinins.[6] Although PCT did not show any such cytokinin activity when assayed using tobacco and soyabean systems, some of its analogs did exhibit excellent activity.[7] In order to understand the role of these hypermodified components in tRNA and also to learn about the stereochemical requirements for cytokinin activity, we undertook X-ray crystallographic and

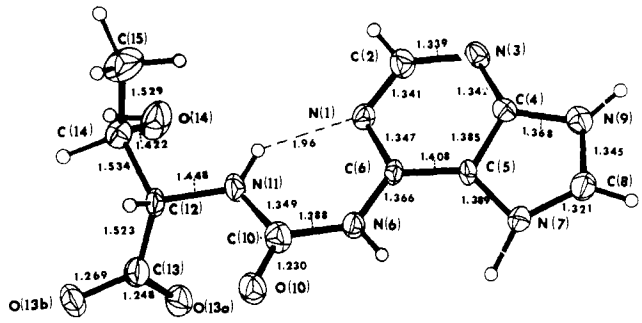

Figure 1. Absolute configuration and conformation of PCTK. The bond distances are in Å. Their average esd is 0.007 Å. This figure and the following ones were drawn using the ORTEP program. The N(7)–HN(7) and N(9)–HN(9) bonds are shown as broken in all these diagrams to indicate possible tautomerism.

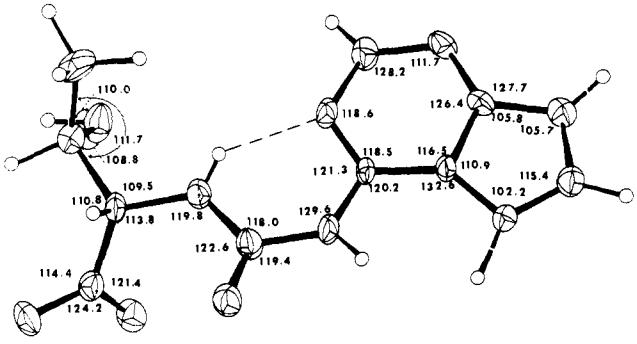

Figure 2. Bond angles in PCTK. The average esd in the bond angles is 0.4°.

chemical investigations of these bases and some of their analogs having cytokinin and antitumor activity. This paper describes the results on the potassium salt (PCTK) of PCT and provides information on the conformation of the anticodon loops of tRNA and the base pairing and base stacking interactions of modified nucleosides; it also sheds some light on the role of this modified nucleoside in tRNA.

Experimental Section

A synthetic sample of PCT[8] was used as the starting material to prepare the potassium salt of PCT by treating 5 mmol of PCT with 5 mmol of KOH (1 *N*) and the solution was evaporated to dryness. PCTK was crystallized as a tetrahydrate ($C_{10}H_{11}N_6O_4K \cdot 4H_2O$) from a 1:3 mixture of propanol and water. The unit cell constants were refined (and their standard deviations estimated) by a least-squares refinement of the 2θ values of 30 reflections at large 2θ angles, where the peaks from Cu $K\alpha_1$ and Cu $K\alpha_2$ could be distinguished. Intensity data were collected from two different crystals; one set of data was slightly superior to the other set. The final results obtained from the better set of data are used for the discussion of the molecular parameters. The relevant cell data are given in Table I. Complete three-dimensional intensity data (2015 nonequivalent reflections to the limit $2\theta = 164°$ for the Cu sphere) were measured on a GE XRD5 diffractometer by the stationary crystal-stationary counter technique[9] using a 5° take-off angle. Balanced Ni–Co Ross filters were used for the monochromatization. The intensities of 1894 reflections had twice the background value in that ($\sin\theta/\lambda$) range and were used for the structural refinement. The crystals used for the data collection were mounted with the b* axis along the ϕ axis of the goniostat and had the dimensions 0.28 × 0.08 × 0.10 mm. The intensities were corrected for the Lorentz–polarization and α_1–α_2 correction factors. The difference in absorption as a function of ϕ was measured for the axial reflections and was used for correcting approximately the anisotropy of absorption.

Phase Determination. The basis of the phase determination procedure is the multisolution technique.[10,11] Three reflections 12 1 2, 0 0 7, and 1 0 7, their $|E|$'s being 3.70, 2.81, and 2.14, respectively, were assigned a phase of zero for defining the origin. Three other reflections, namely 11 1 1, 11 3 2, and 10 3 $\bar{5}$ with their $|E|$'s being 3.27, 3.19, and 3.14, respectively, were chosen as the starting set for the generation of multiple solutions. The solution with the highest figure of merit[11] of 1.065 yielded the phases for 381 $|E|$'s (>1.3). An *E* map was calculated using these phases and the position of all the 25 nonhydrogen atoms were readily located, yielding a trial structure with an *R* value of 0.27.

Table I. Crystal Data for PCTK

Unit-cell dimensions	Crystal 1	Crystal 2
a, Å	15.279 (7)	15.289 (2)
b, Å	6.410 (1)	6.410 (1)
c, Å	8.815 (4)	8.815 (1)
β, deg	105.75 (6)	105.91 (2)
Color: transparent		
Space group: $P2_1$, $Z = 2$		
Systematic absences: $0k0$ with k odd		
$\mu = 32.9$ cm^{-1}		
$D_{obsd} = 1.54$ g cm^{-3}		
$D_{calcd} = 1.56$ g cm^{-3}		
(for a tetrahydrate)		
Temp 22 ± 3°, λ(Cu $K\alpha_1$) = 1.54051 Å		

Refinement of the Structure. The positional and isotropic thermal parameters of the 25 nonhydrogen atoms in PCTK were subjected to several cycles of least-squares refinement (with block-diagonal approximation) until the discrepancy factor *R* ($= \Sigma||F_o| - |F_c||/\Sigma|F_o|$) dropped to 0.11. Additional cycles of refinement with anisotropic thermal parameters reduced the *R* index to 0.088. An electron-density difference map at this stage revealed the locations of ten hydrogens. Inclusion of their positional and isotropic thermal parameters in the least-squares refinement lowered the *R* index to 0.080. The electron-density difference map at this stage did not yield unambiguously the locations of the other nine hydrogens, especially those belonging to the water molecules. Of the ten hydrogens located, one was bonded to N(9) and, somewhat surprisingly, another bonded to N(7); one would expect protonation on either N(9) or N(7) but not on both. In order to settle this problem and to locate the remaining hydrogens unambiguously, a new set of data was collected from another crystal and structural refinement was continued with this new data from this stage on. The parameters of the nonhydrogen atoms were used to start the refinement; the *R* index fell to 0.077. Successive electron-density maps revealed the location of 20 hydrogens (including the one on N(7)). Inclusion of their positional and isotropic thermal parameters reduced the *R* index to 0.057. Refinement was terminated at this point when the shifts of the atomic parameters were a small fraction, of the order of 0.1 for the nonhydrogen atoms and 0.3 for the hydrogen atoms, of the corresponding esd's.

For the block-diagonal approximation, blocks of (9 × 9) and (4 × 4) were used for atoms with anisotropic and isotropic thermal parameters, respectively. The scattering factors and anomalous dispersion corrections for K^+, O, N, and C given by Cromer and Liberman[12a] were used. For the hydrogen atoms, the values given by Stewart, Davidson, and Simpson[12b] were used. The differential synthesis weighting scheme with $w = 1/f_c$, where f_c is the scattering factor of carbon atom, was used for the refinement.

The absolute configuration was determined by the *R*-factor method[13] using the anomalous dispersion of potassium for the Cu $K\alpha$ radiation. The ratio of the *R* factors for the coordinates of the structure shown in Figure 1 and of its mirror image was 0.958, establishing that the structure given in Figure 1 is in the correct absolute configuration.

Discussion of the Structure

The final positional and thermal parameters for nonhydrogen atoms are given in Table II and those for hydrogen atoms in Table III. The observed and calculated structure factors will be deposited (see paragraph at end of paper regarding supplementary material). The bond lengths and angles involving nonhydrogen atoms are illustrated in Figures 1 and 2. Bond distances and angles involving the hydrogen atoms fall in the usual range for X-ray determinations. The

Table II. Positional and Thermal Parameters ($\times 10^4$)[a]

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
K	2810 (1)	7500 (3)	9910 (1)	26 (0)	192 (3)	73 (1)	2 (1)	9 (1)	−31 (4)
O(W1)	4316 (3)	9871 (8)	9859 (4)	29 (2)	246 (13)	62 (5)	34 (8)	25 (5)	52 (14)
O(W2)	2085 (4)	3810 (12)	11073 (6)	53 (3)	386 (20)	110 (7)	−67 (14)	32 (7)	−12 (23)
O(W3)	1011 (3)	8496 (8)	9872 (6)	46 (2)	180 (13)	180 (9)	32 (9)	89 (8)	91 (18)
O(W4)	76 (3)	5139 (8)	8196 (6)	29 (2)	194 (12)	134 (7)	39 (8)	15 (6)	10 (16)
O(10)	3449 (2)	4124 (8)	8776 (4)	24 (2)	203 (11)	64 (4)	−6 (8)	31 (4)	−27 (14)
O(13a)	2251 (3)	38 (7)	7286 (5)	27 (4)	166 (10)	107 (7)	35 (8)	53 (5)	57 (14)
O(13b)	1162 (3)	1739 (8)	8008 (5)	25 (12)	203 (12)	126 (6)	10 (8)	74 (5)	62 (15)
O(14)	1380 (2)	2174 (9)	3766 (5)	21 (2)	268 (15)	92 (5)	−7 (9)	−4 (4)	−72 (16)
N(1)	3963 (2)	3916 (8)	4372 (4)	14 (1)	110 (9)	54 (5)	−7 (7)	2 (4)	−15 (13)
N(3)	5081 (3)	4043 (8)	2907 (5)	26 (2)	139 (11)	64 (5)	−5 (8)	38 (5)	−5 (14)
N(6)	4368 (2)	4066 (8)	7157 (4)	13 (2)	144 (10)	49 (3)	−3 (8)	5 (4)	−22 (14)
N(7)	6326 (2)	4060 (8)	6987 (5)	15 (2)	145 (11)	63 (5)	−5 (8)	9 (4)	27 (14)
N(9)	6624 (3)	4220 (8)	4626 (5)	19 (2)	151 (11)	62 (5)	−3 (8)	30 (5)	7 (14)
N(11)	2783 (3)	3803 (3)	6159 (5)	12 (2)	160 (12)	68 (5)	−14 (8)	22 (4)	−12 (14)
C(2)	4233 (3)	3925 (10)	3048 (6)	20 (2)	125 (12)	75 (6)	−17 (9)	21 (6)	−6 (17)
C(4)	5699 (3)	4101 (9)	4319 (5)	21 (2)	107 (11)	56 (6)	−1 (9)	27 (5)	4 (15)
C(5)	5522 (3)	4011 (9)	5777 (5)	10 (2)	114 (11)	65 (6)	−2 (8)	18 (5)	−2 (15)
C(6)	4601 (3)	3989 (8)	5770 (5)	11 (2)	85 (10)	68 (6)	3 (8)	20 (5)	−5 (15)
C(8)	6947 (3)	4204 (10)	6206 (6)	16 (2)	163 (14)	69 (6)	6 (9)	14 (6)	0 (17)
C(10)	3514 (3)	4008 (9)	7419 (6)	19 (2)	116 (11)	78 (6)	4 (9)	37 (6)	4 (16)
C(12)	1885 (3)	3581 (9)	6388 (6)	10 (2)	159 (14)	79 (7)	−4 (8)	19 (5)	6 (16)
C(13)	1768 (3)	1610 (9)	7276 (6)	15 (2)	151 (12)	56 (6)	3 (8)	17 (5)	−9 (15)
C(14)	1167 (3)	3689 (11)	4787 (6)	17 (2)	198 (16)	63 (6)	8 (10)	6 (6)	30 (18)
C(15)	1123 (5)	5856 (14)	4047 (10)	36 (3)	243 (21)	166 (12)	34 (14)	7 (10)	183 (29)

[a] $T_F = \exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$. Estimated standard deviations in parentheses.

Table III. Positional Parameters ($\times 10^3$) for the Hydrogen Atoms

	x	y	z
H(1W1)	460 (4)	980 (10)	909 (6)
H(2W1)	403 (6)	1141 (17)	955 (11)
H(1W2)	187 (7)	258 (24)	1024 (12)
H(2W2)	170 (4)	319 (11)	1189 (8)
H(1W3)	87 (7)	936 (21)	900 (13)
H(2W3)	73 (5)	858 (14)	1055 (9)
H(1W4)	38 (7)	398 (21)	788 (12)
H(2W4)	38 (4)	630 (11)	871 (7)
HC(2)	376 (3)	368 (9)	212 (6)
HN(6)	479 (3)	427 (9)	797 (5)
HN(7)	613 (13)	441 (37)	806 (23)
HC(8)	751 (3)	455 (14)	674 (9)
HN(9)	699 (5)	459 (13)	401 (9)
HN(11)	296 (3)	369 (10)	536 (6)
HC(12)	177 (5)	525 (14)	695 (8)
HC(14)	59 (5)	335 (15)	500 (9)
HO(14)	83 (7)	115 (19)	344 (12)
HC(15a)	170 (6)	609 (15)	355 (10)
HC(15b)	98 (5)	716 (16)	486 (9)
HC(15c)	66 (7)	573 (19)	300 (12)

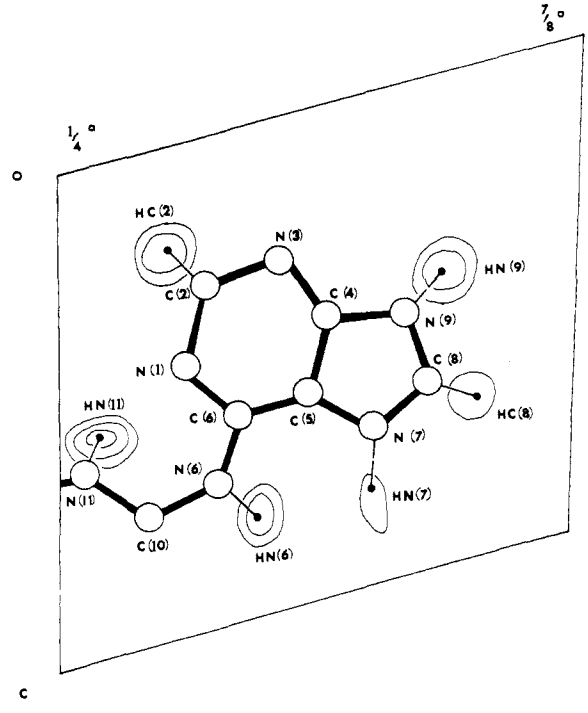

Figure 3. A composite of the electron-density map showing possible protonation of N(7). The contours are at intervals of 0.3 e A^{-3}.

average esd's in the bond distances and angles involving nonhydrogen atoms are 0.007 Å and 0.4°, respectively.

(a) Protonation and Tautomerism of the Nucleic Acid Base. The chemical structure of PCTK consists of the nucleic acid component adenine connected to the amino acid threonine through a ureido linkage bridging the N(6) of adenine and the amino nitrogen of threonine. Since the potassium salt was used, the carboxyl group of threonine will be ionized, carrying a negative charge. The adenine moiety will be expected to be protonated on N(9) or N(7). The electron-density difference map readily yielded the locations of all hydrogens, showing peaks corresponding to hydrogens on both N(9) and N(7); this could be interpreted in terms of a distribution of two tautomeric forms of adenine, if the peaks in the difference map were not artifacts. A composite of the electron-density difference maps is given in Figure 3. There were other background peaks of the same height as the peak near N(7). These background peaks were distributed around the potassium and made no stereochemical sense. Inclusion of the parameters of the hydrogen on N(7) in the least-squares refinement (with the occupancies of the hydrogens on N(9) and N(7) adjusted according to the peaks in the difference maps to 0.7 and 0.3) indicated a reasonable thermal parameter (B = 0.75 $Å^2$) for the hydrogen on N(7). In view of these results, it was felt that the presence of N(9)–H and N(7)–H tautomers has to be considered in further discussions of the molecular properties of PCTK.

(b) Bond Distances and Angles. The dimensions of the adenine moiety are in general agreement with the values usually found for the neutral base (N(1) not protonated). Substitution at N(6) seems to result in a slightly longer C(6)–N(6) bond (Table IV), compared to the corresponding bond

Table IV. Effect of Substitution at N(6) on C(6)–N(6) Bond Lengths (Å)

N^6 substituted		N^6 unsubstituted	
N^6-(Δ^2-Isopentenyl)-2-methylthioadenine[14a]	1.342	Adenosine[17]	1.332
6-Histaminopurine dihydrate[15]	1.351	Adenine N^1-oxide–sulfuric acid complex[18]	1.310
N^6-(Δ^2-Isopentenyl)adenine[16]	1.340	3′-*O*-Acetyladenosine[19]	1.336
PCTK	1.366	3′-AMP[20]	1.319
Puromycin[22]	1.317	5′-Methylene analog of cyclic 3′,5′-AMP[21]	1.320

Table V. Effect of Protonation of N(7) on N(7)–C(8) Bond Lengths (Å)

Protonated at N(7)		Not protonated	
Purine[24]	1.327, 1.337	N^6-(Δ^2-Isopentenyl)-2-methylthioadenine[14]	1.305
6-Histaminopurine dihydrate[15]	1.344	Adenosine[17]	1.308
Adenine N^1-oxide–sulfuric acid complex[18]	1.333	N^6-(Δ^2-Isopentenyl)adenine[16]	1.311
6-Mercaptopurine[25]	1.346	3′-*O*-Acetyladenosine[19]	1.314
6-Mercaptopurine[26]	1.352		

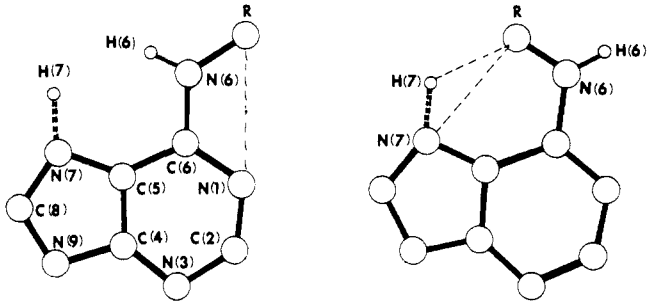

Figure 4. Illustrates how the preferred orientation of the N^6 substituent is a result of the steric hindrance from N(7) to the substituent. The H(6) · · · N(7) distance observed in PCTK is 2.71 Å.

in unsubstituted adenines. Puromycin[22] with a dimethyl substituent on N(6) seems to be an exception.

Since the protonation of N(7) is a possibility, as indicated in the discussion of the structure refinement, a study of the dimensions of the protonated and unprotonated bases was carried out. Though it has been observed[23] that the ring angle at the site of protonation increases by 2 to 4°, it is not clear what the (average) value whould be when there is partial protonation (due to the distribution of protonation at two sites, namely N(7) and N(9)). Besides the ring angle, another parameter which seems to be sensitive to the study of protonation at N(7) in purines is the N(7)–C(8) bond distance. A survey of recent literature shows that the N(7)–C(8) bond in the N(7)-protonated purines is significantly longer than in unprotonated purines (Table V). The N(7)–C(8) bond of 1.321 Å in PCTK does not rule out partial protonation at N(7). Since the evidence of protonation at N(7) is not clear cut, we decided to study whether the protonation at N(7) will make any stereochemical sense in the packing of molecules; the results of this study are discussed in the sections on coordination and hydrogen bonding.

The amino acid, threonine, is attached to the nucleic acid base through a ureido link. The bond distances and angles agree well with the dimensions of amino acid obtained in other studies on compounds containing threonine moiety.[27] The exception is the C(12)–N(11) (C^α–N) distance of 1.448 Å; the shortening of the C^α–N bond arises due to the sp^2 character for the nitrogen N(11). The carboxyl group is, as expected, ionized, and the molecular geometry is in agreement with this conclusion.

One would expect the two C(sp^2)–N(sp^2) bonds in the ureido group to be equal, but it turns out that the C(10)–N(6) bond nearer to the base is significantly longer (by 0.04 Å) than the C(10)–N(11) bond. This situation is true not only in PCTK but also in PCGK and PCTR[28] and in an analogous ureido link in N^1-(N-methylcarbamoyl)-N^3-methyl-5,6-dihydrouracil.[1a] In these cases, the C(sp^2)–N(sp^2) bond nearer to the base is longer than the farther one by 0.07, 0.09, and 0.11 Å, respectively.

The least-squares plane through the nine atoms of the base (Table VI plane 1) was calculated and it shows that the ureido link and the C^α atom of threonine C(12) are approximately in this plane through adenine. The ureido group (plane 2) and the carboxyl group (plane 3) are planar to the limits of accuracy of our data.

(c) Conformation of the Molecule. The N^6 substituent is "distal" (trans) to the imidazole ring. In unsubstituted adenines, N(6) carries two hydrogens, one cis and the other trans with respect to the imidazole ring. When one of these hydrogens is substituted, the substituent will be cis or trans to the imidazole ring due to the partial double bond character of the C(6)–N(6) bond. Steric repulsion from N(7) will constrain the substituent to be away from N(7), *i.e.*, to be distal to the imidazole ring. Due to this steric repulsion (see Figure 4), the trans or distal conformation will be preferred in all monosubstituted adenines. This generalization is supported from our own studies on PCTK, PCGK, and PCTR[28] and by other studies on isopentenyl-adenine (IPA),[16] its 2-methylthio derivative (2-MT-IPA),[14] N^6-histaminopurine,[15] and N^6-methyladenine.[29] If N(7) is protonated, as in N^6-histaminopurine, and possibly in PCTK, the trans or distal conformation of the N^6 substituent is all the more favorable. The consequences of this distal conformation are discussed later.

C(10) is twisted out of the plane of the base by a small amount. The pertinent torsion angles are N(1)–C(6)–N(6)–C(10) = 2.7° and C(5)–C(6)–N(6)–C(10) = −178.2°.

As seen from Figure 1, C(10) is distal to the imidazole ring. The oxygen O(10) can occur cis or trans to the base. If the oxygen O(10) were trans to the base, as found in the present structure, only the hydrogen H(11) (and not the bulky threonine residue) on N(11) can be between N(11) and N(1). This orientation around the C(6)–N(6) bond leads to the formation of an intramolecular hydrogen bond to N(1) (see the discussion on hydrogen bonding). This additional energy stabilizes the trans conformation of O(10) with respect to the base about the C(10)–N(6) bond. Thus, it is seen that the distal conformation of the ureido group on N(6) influences the conformation of the molecule about the N(6)–C(10) and C(10)–N(11) bonds. A more detailed analysis of the conformation of ureidopurines has been carried out and will be published elsewhere.

(d) Conformation of Threonine Moiety. The anomalous

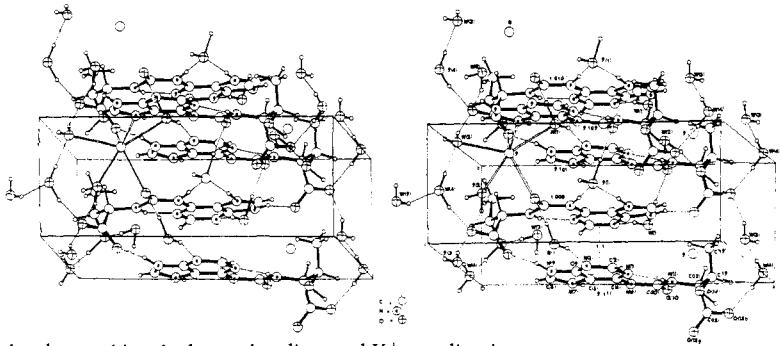

Figure 5. A stereo view of the molecular stacking, hydrogen bonding, and K^+ coordination.

Table VI. Least-Squares Planes[a]

Plane	Atoms	l	m	n	d, Å	rms, Å
1	N(1)C(2)N(3)C(4)C(5)C(6)N(7)C(8)N(9)	−0.032	0.999	−0.020	2.293	0.026
2	C(6)N(6)C(10)O(10)N(11)	−0.048	0.996	−0.082	1.87	0.005
3	C(12)C(13)O(13a)O(13b)	−0.474	−0.343	0.811	−5.813	0.004
4	N(1)C(6)N(6)C(10)N(11)	−0.048	0.998	−0.050	2.059	0.018

Atoms	Plane 1	Atoms	Plane 1	Atoms	Plane 2	Atoms	Plane 3	Atoms	Plane 4
N(1)	−0.010*	N(6)	−0.115	C(6)	0.005*	N(11)	−0.569	N(1)	0.020*
C(2)	0.021*	HN(6)	−0.23	N(6)	−0.008*	C(12)	−0.002*	C(6)	−0.023*
N(3)	0.007*	HN(7)	−0.22	C(10)	0.002*	C(13)	0.007*	N(6)	0.002*
C(4)	−0.005*	HN(9)	−0.22	O(10)	0.003*	O(13a)	−0.003*	C(10)	0.020*
C(5)	0.020*	C(10)	−0.142	N(11)	−0.002*	O(13b)	−0.002*	N(11)	−0.019*
C(6)	−0.031*	O(10)	−0.239					HN(11)	−0.08
N(7)	0.029*	N(11)	−0.045						
C(8)	−0.009*	HN(11)	0.05						
N(9)	−0.021*	C(12)	0.030						

[a] The equation to the plane is $lX + mY + nZ = d$; X, Y, and Z are Cartesian coordinates along a, b and c^*. l, m, and n are the direction cosines. Atoms used to define the plane are marked by an asterisk.

dispersion of potassium for the Cu Kα radiation permitted the determination of the absolute configuration of threonine; as expected, it had the L configuration or 1*S* 2,*R* using the sequence rule of Cahn, Ingold, and Prelog.[30]

The conformation of threonine moiety found in this structure is different from the one observed in the crystal structures of L-threonine[27a] and L-threonyl L-phenylalanine *p*-nitrobenzyl ester HBr.[27b] There are three possible locations for a γ atom for the staggered conformation about the C^α–C^β bond; these may be denoted as I, II, and II corresponding to torsion angles[31] χ = 0, 60, and −60° (300°). Threonine contains two γ atoms, namely O^γ (O(14)) and C^γ (C(15)). For threonine, there are three possible pairs of positions for the two γ atoms; these pairs of positions may be labeled as (I, III), (III, II), and (II, I); the first and second positions refer to the locations occupied by the O^γ and C^γ atoms, respectively. Looking along the C^α–C^β (C(12)–C(14)) bond, the hydroxyl group is located between the amino nitrogen and the carboxyl group; the relevant torsion angles (χ) are respectively 54.5 and −67.1° (292.9°) for the O^γ and C^γ atoms. These values correspond to the pairs of positions (I, III) and are different from the (III, II) positions calculated to be most favorable energetically[32] and observed in the structure of L-threonine and L-threonyl L-phenylalanine-*p*-nitrobenzyl ester HBr.

The amino nitrogen is 0.57 Å away from the plane through the carboxyl group (Table VI). The torsion angle corresponding to the twist of the carboxyl group is 154.2° similar to the angle of 156° found in the structure of L-threonine.

(e) **Hydrogen Bonding.** The molecular stacking, hydrogen bonding, and potassium coordination are illustrated in the stereo view (Figure 5). The distances and angles involved in the hydrogen bonding are given in Table VII.

The conformation of the substituent on N(6) orients the amino nitrogen in such a way that an intramolecular hydrogen bond is formed from N(11)–H(11) of threonine to the N(1) of adenine, resulting in the formation of a planar (see Table VI for planes) six-membered ring. The formation of such intramolecular hydrogen bonding is well known in organic compounds[33] and has also been observed in a derivative of nucleic acid component N^1-(*N*-methylcarbamoyl)-N^3-methyl-5,6-dihydrouracil).[1a] The consequences of this intramolecular hydrogen bond are discussed later.

There are two polar hydrogens on the base, one on N(6) and the other distributed mostly on N(9) and to a small extent on N(7), if we do not ignore possible protonation of N(7). HN(6) is hydrogen bonded to O(W1) (see Figure 5 and Table VII). The hydrogen HN(9) is hydrogen bonded to the oxygen O(13a) of the carboxyl group of a neighboring molecule. The hydrogen on N(7) points directly at the water oxygen O(W1) and forms a hydrogen bond to it. If we ignore the possible protonation of N(7), it is not involved in any hydrogen bonding. N(3) partakes in a hydrogen bond to O(W1).

The four water molecules take part in 11 hydrogen bonds. The eight hydrogens of the water molecules are all involved in hydrogen bonding; in addition O(W4) accepts the hydrogen from O(14), and O(W1) accepts two hydrogens, one from N(6) and the other from N(7). The surroundings of each water molecule are illustrated in Figure 5; the water molecules exhibit a variable environment, both in the number and orientation of the coordinating atoms.

There are two C—H - - -O contacts; one from C(2) to O(W2) and another from C(8) to O(14) (see Table VII) which may be interpreted as weak C—H- - -O hydrogen bonds.[34a] Though similar short contacts have been found in the structures of several nucleic acid components, Donohue's[34b] reservations about such systems must be kept in mind.

Table VII. Hydrogen Bonds and C—H---O Contacts

D---H···A			D--H, Å	D···A, Å	H···A, Å	D—H···A, deg	A in position		
O(W1)	H(1W1)	N(3)	0.90	2.883	2.01	163	$1 - x$	$-1/2 + y$	$2 - z$
O(W1)	H(2W1)	O(10)	1.08	3.067	1.99	174	x	$1 + y$	z
O(W2)	H(1W2)	O(13b)	1.07	2.994	2.04	147	x	y	z
O(W2)	H(2W2)	O(14)	1.12	3.050	1.96	163	x	y	$1 + z$
O(W3)	H(1W3)	O(13b)	0.92	2.699	1.88	147	x	$1 + y$	z
O(W3)	H(2W3)	O(W4)	0.84	2.886	2.11	154	$\bar{x}$	$1/2 + y$	$2 - z$
O(W4)	H(1W4)	O(13b)	0.96	2.773	1.86	160	x	y	z
O(W4)	H(2W4)	O(W3)	0.93	2.775	1.85	176	x	y	z
O(14)	H(O14)	O(W4)	1.04	2.745	1.82	145	$\bar{x}$	$-1/2 + y$	$1 - z$
N(6)	H(N6)	O(W1)	0.83	2.888	2.06	171	$1 - x$	$-1/2 + y$	$2 - z$
N(7)	H(N7)	O(W1)	1.09	3.234	2.14	175	$1 - x$	$1/2 + y$	$1 - z$
N(9)	H(N9)	O(13a)	0.91	2.769	1.86	174	$1 - x$	$1/2 + y$	$1 - z$
N(11)	H(N11)	N(1)	0.83	2.703	1.96	149	x	y	z
C(2)	H(2)	O(W2)	0.94	3.269	2.48	141	x	y	$-1 + z$
C(8)	H(8)	O(14)	0.83	3.184	2.52	133	$1 - x$	$1/2 + y$	$1 - z$

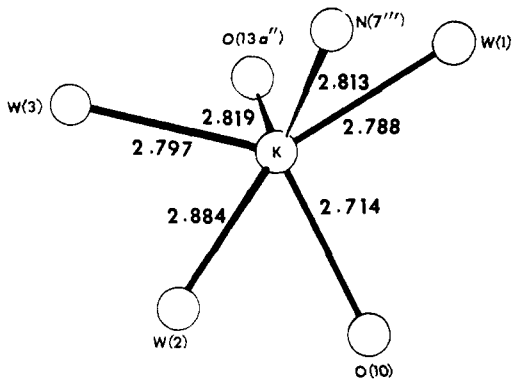

Figure 6. The sixfold coordination of the K^+ ion. The arrangement of the coordination may be described in terms of a distorted octahedron.

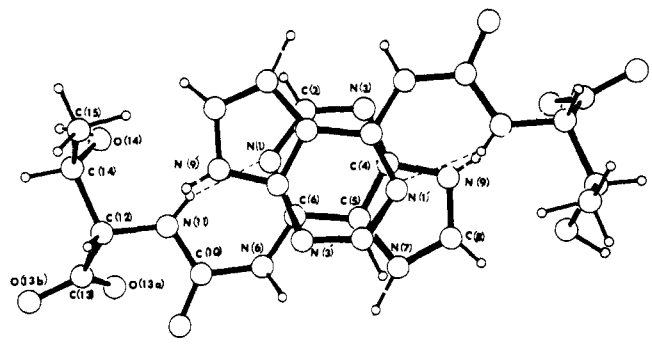

Figure 7. Stacking of the bases viewed along the twofold screw axis, which is practically normal to the plane of the base (see Table V). The 2_1-screw axis passes close to the center of the six-membered ring of adenine.

(f) Coordination of K^+ Ion. The K^+ ion is coordinated (see Figure 6) to six ligands; these are three water oxygens, the keto oxygen O(10) on the ureido group, O(13a) of the carboxyl, and N(7), if we disregard possible protonation of N(7). The arrangement of this sixfold coordination around K^+ can be described in terms of a distorted octahedron.

Protonation of N(7) will place the hydrogen on N(7) at a distance of only 2.35 Å to K^+, a somewhat surprisingly short contact distance. This raises the following questions: can hydrogen atoms be coordinated to cations or can a hydrogen bond occur in the edge of a coordination polyhedron around a cation? Templeton[35] has suggested the unlikelihood of hydrogen bonds in polyhedral edges. Recent X-ray studies (see Table 5 of Baur)[36] and neutron studies,[37] however, have indicated that a coordination polyhedron *can* contain a hydrogen bond with cation-H distances shorter than cation-O distances, though it does not mean that the hydrogen atom is coordinated to the cation.

A protonation on N(7) will result in a formal positive charge on N(7), giving rise to a repulsive and energetically unfavorable N(7)- -K contact. On the other hand, the formation of the N(7)—HN(7)- - -O(W1) hydrogen bond might be able to compensate for this energetically unfavorable contact.

(g) Base Stacking. The crystal structure is stabilized by an extensive network of hydrogen bonds, the coordination around potassium, and stacking and extensive overlapping of the bases almost on top of one another in a head-to-tail fashion in planes 3.2 Å apart (Figures 7 and 8).

The plane of the ureidopurine moiety (for planes, see Table VI) is very nearly normal to the 2_1-screw axis, which passes close to the center of the six-membered ring. The six-membered rings overlap almost on top of each other and to a small extent on the five-membered rings. The ureido groups do not participate in this stacking. The bulky threonine groups take up such a conformation that the hydrophobic methyl group and the polar carboxyl and hydroxyl groups point in opposite directions of the plane through the base; this orientation of the threonine moiety does not interfere with the base stacking; in fact, the hydrogen bonding of one molecule of N(9) to O(13a) of another molecule stacked on top of it contributes energetically to molecular association.

The stacked rings associate more closely than what has been usually observed.[38] Short distances between atoms in the two overlapping parts of the rings are given in Table VIII. Some of these short contacts are significantly less than the accepted minimal van der Walls interatomic contacts[39] (3.4 Å for C- -C, 3.2 Å for C- -N, 3.1 Å for C- -O).

Conclusion

(a) Role of Hypermodified Bases in tRNA. The hypermodified bases adjacent to the 3′ end of the anticodons appear to be involved in acceptor as well as transfer activity of tRNA. Studies dealing with the modification or removal of the base adjacent to the anticodon suggest that this hypermodified nucleoside is needed for the binding of tRNA to ribosome-mRNA complex, but it *is* not essential to the charging of the tRNA.[5] Removal of the base Y adjacent to the anticodon of yeast $tRNA^{Phe}$ changes its coding properties.[40] Binding studies[40] show that unmodified and modified $tRNA^{Phe}$ cannot occur next to each other on the two binding sites of a ribosome. These results have been interpreted in terms of a change in the conformation of the anticodon loop on removal of the hypermodified base, changing the orientation of the "Wobble" base relative to the other bases in the anticodon.

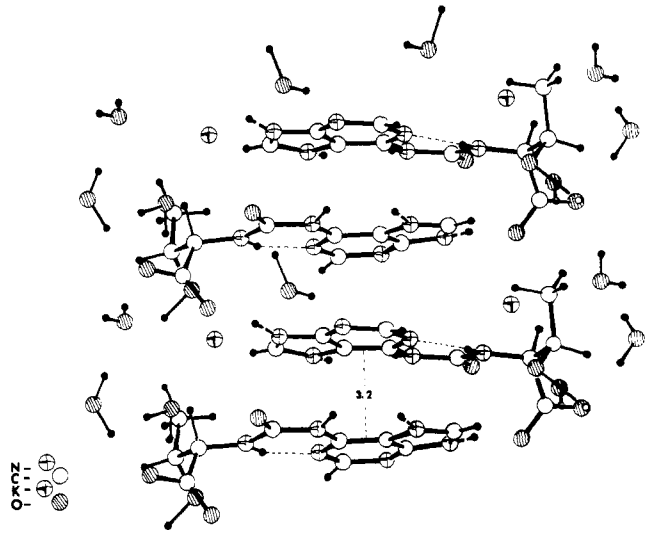

Figure 8. Stacking of the bases seen edgewise. Note how the bulky threonine residues do not interfere with the stacking.

Our structural studies[41] shed some light on the role of modified components in codon–anticodon interaction and in maintaining the integrity of the single stranded conformation of the anticodon loop. The conformation of the molecule in which the substituent on N(6) is "distal" to the imidazole ring and the intramolecular hydrogen bonding to N(1) block the two sites N(6)–H and N(1) of adenine that are utilized for the "Watson–Crick" base pairing postulated for the double helical regions of nucleic acids[42] but will allow "Hoogsteen" [43] or "reverse Hoogsteen" [44] base pairing. The "distal" conformation is preferred for all N^6 substituted adenines, thereby rendering them unable to take part in the "Watson–Crick" base pairing, an important modification of the function of the base achieved by its chemical modification. This inability to base pair according to the "Watson–Crick" scheme is one common feature shared by all modified bases that are known to occur adjacent to the anticodon;[45] these substances are the base Y, PCTR, methyl-PCTR, 1-methylinosine, 1-methylguanosine, 2-methyladenine, 6-methyladenine, and isopentenyladenine and its 2-methylthio derivative. These results suggest that the role of modified nucleosides in the anticodon loops of tRNA may be twofold: (i) to prevent any misreading of the codons by bases adjacent to (and on the 3′ end of) the anticodons; (ii) to promote the single stranded conformation of the anticodon loops of tRNA. Fuller and Hodgson[46] suggested that misreading of the codons *may* be prevented due to the chemical modification of the nucleoside adjacent to the anticodons. Our results clearly show that the modified adenines adjacent to the anticodons *cannot* take part in codon recognition, if codon recognition is achieved through the "Watson–Crick" pairing[47] as is normally believed. The inability of the modified nucleosides to base pair according to the "Watson–Crick" scheme has been observed in polymer–polymer and polymer–monomer binding studies and commented upon by several investigators,[48] especially by Miles and coworkers. The impaired base pairing will contribute to the observed reduced binding (by one order of magnitude) of tetramers complementary to anticodons plus the adjacent base on the 3′ end compared to the binding of tetramers complementary to anticodons plus the adjacent base on the 5′ end.[49] In addition, there is an inherent asymmetry in the binding of complementary tetramers even in cases when there is no hypermodified adenine adjacent to anticodons.[49] These results seem to indicate that the modified nucleoside adjacent to the anticodon may be considered as important as the three anticodon bases in codon recognition processes.

Table VIII. Short Contacts Due to Stacking

Atom 1 (x,y,z)	Atom 2 (1−x, ½+y, 1−z)	Distance, Å	Atom 1 (x,y,z)	Atom 2 (1 − x,−½ +y,1−z)	Distance, Å
N(1)	N(7)	3.321	C(6)	N(3)	3.367
N(1)	N(9)	3.330	C(6)	C(4)	3.165
N(1)	C(4)	3.287	N(6)	N(3)	3.333
N(1)	C(5)	3.252	N(7)	C(2)	3.399
N(1)	C(8)	3.306	N(11)	N(9)	3.206
C(2)	C(5)	3.305	N(11)	HN(9)	2.73
C(2)	N(7)	3.232			
N(3)	N(6)	3.305			
C(4)	C(6)	3.307			
C(5)	N(1)	3.371			

(b) Correlation of the Structure of Ureidopurines to Their Cytokinin Activity. PCT, its glycine analog PCG, and other amino acid analogs do not exhibit cytokinin activity, although some of its analogs containing hydrocarbon chain and *o*-halophenylureidopurines are very active.[7] Dyson, *et al.*,[7] have discussed the structure–activity relationship of these compounds in terms of their three-dimensional model structures and electronic rearrangements. They have explained the lack of activity of PCT by the inability of exogenous PCT to reach the active site. Additional contribution to the inactivity of PCT as a cytokinin can be suggested from our results. From extensive chemical work, it is known that any substitution on N(1) of adenine results in a total loss or a drastic reduction of cytokinin activity.[50] PCT contains an intramolecular hydrogen bond between N(1) and the hydrogen on N(11). The hydrogen on N(11) is held in this orientation by a series of conjugated systems of bonds and hence is not free to move away from N(1). This hydrogen, which forms the intramolecular hydrogen bond to N(1) and is held in this position by other constraints, may be likened to a substitution on N(1) causing a loss of activity. A comparison of the three-dimensional structure of N^6-(Δ^2-isopentenyladenine)[16] and its 2-methylthio analog,[14] which are cytokinin active, with the structures of PCTK and PCGK,[41] which are not active, suggests that the above hypothesis regarding the effective substitution of N(1) is not unreasonable. Structural studies on the most potent cytokinin of the ureido series, *o*-chlorophenylureidopurine, are in progress and should shed more light on this structure–activity relationship of ureidopurines.

(c) PCTK Crystal Structure. A Model for the Interaction of Protein and Nucleic Acid Components. In this structure, there is only minimal interaction by way of hydrogen bonding or association of hydrophobic groups of the nucleic acid and protein components. The stacking of the bases dominates the nonpolar interactions while the hydrogen bonding to water and K^+-ion coordination dominate the polar interactions. The methyl groups are not in a hydrophobic environment but are embedded in a hydrophilic cavity. There is no contact between adjacent methyl groups or from methyl groups to the stacked bases. The structure of puromycin[22] exhibits interaction of aromatic side chains with adenine moiety. Such interactions may be expected in other aromatic amino acid analogs of PCT; structural studies on several of these analogs are in progress in our laboratory.

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Supplementary Material Available. A listing of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-8087.

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