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Structures of Three Forms of the Purine Base Precursor 5(4)-Amino-1*H*-imidazole-4(5)-carboxamide (AICA): AICA.C_3H_7OH, AICA.H_2O and $HAICA^+.H_2PO_4^-$

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Abstract

$C_4H_6N_4O.C_3H_7OH$ is monoclinic, space group $P2_1/c$, with $a = 11{\cdot}111$ (4), $b = 6{\cdot}153$ (1), $c = 14{\cdot}904$ (6) Å, $\beta = 105{\cdot}2$ (1)°, $Z = 4$. $C_4H_6N_4O.H_2O$ is monoclinic, space group $P2_1/a$, with $a = 6{\cdot}586$ (5), $b = 9{\cdot}972$ (6), $c = 9{\cdot}499$ (5) Å, $\beta = 91{\cdot}3$ (1)°, $Z = 4$. $C_4H_7N_4O^+.H_2PO_4^-$ is monoclinic, space group $P2_1/c$, with $a = 12{\cdot}238$ (2), $b = 5{\cdot}465$ (1), $c = 12{\cdot}875$ (1) Å, $\beta = 92{\cdot}7$ (1)°, $Z = 4$. The structures were refined to $R = 0{\cdot}091$ for 1363 reflexions, $R = 0{\cdot}055$ for 849 reflexions, and $R = 0{\cdot}071$ for 1215 reflexions respectively. The tautomers AICA.C_3H_7OH (2-propanol) and AICA.H_2O can be distinguished from each other and from the protonated form on the basis of the internal bond angles. The geometry of the $HAICA^+$ cation resembles the corresponding part of the purine nucleotide precursor 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide 5′-(dihydrogen phosphate) (AICAR 5′-P). Similarly the geometry of AICA in AICA.C_3H_7OH resembles the AICA part in the corresponding nucleoside (AICAR). In each molecule the 4-carboxamide moiety is oriented so that a strong intramolecular hydrogen bond is formed to the 5-amino group of the heterocycle.

Introduction

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide 5′-(dihydrogen phosphate) (AICAR 5′-P), synthesized enzymatically in living cells, is a key substance of purine nucleotides (Henderson & Paterson, 1973). To elucidate the formation of such purine nucleotides the molecular structures of their building blocks (precursors), the ambivalent 5(4)-amino-1*H*-imidazole-4(5)-carboxamide (AICA) (Zimmerman, 1979, and references therein), crystallized from two different solvents (2-propanol and water), and a protonated AICA molecule ($HAICA^+.H_2PO_4^-$) have been determined. These structural parameters fit systematically in the picture which has been inferred from the structure determinations of AICAR 5′-P and its nucleoside AICAR (Adamiak & Saenger, 1979). Beyond this, it is worth noting that $HAICA^+.H_2PO_4^-$ is an effective liver regenerating agent (Szepesházi *et al.*, 1978).

First, stable crystals of AICA.H_2O could be obtained which (Kálmán & Simon, 1975), unlike the analogous 5-amino-1*H*-1,2,3-triazole-4-carboxamide (Kálmán, Simon, Schawartz & Horváth, 1974), exhibited the tautomeric form 5-amino-3*H*-imidazole-4-carboxamide (if positions are defined not in relation to the protonated N atoms but in relation to the substituents on the ring; the canonical notation is, however, 4-amino-1*H*-imidazole-5-carboxamide). This phenomenon was mainly attributed to the role of H_2O in forming a complicated hydrogen-bond network with AICA molecules. New, but less stable, crystals of AICA could be obtained from absolute 2-propanol. The structure analysis revealed the co-crystallization of the expected tautomeric form 5-amino-1*H*-imidazole-4-carboxamide with one molecule of 2-propanol per asymmetric unit (hereafter AICA.C_3H_7OH). They are

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bound together by a somewhat simpler bond network than that found in AICA.H_2O. These hydrogen-bond networks together with those of HAICA$^+$.$H_2PO_4^-$ and the analogous 1,2,3-triazole derivatives were recently discussed (Kálmán, Párkányi, Schawartz & Simon, 1978). We now report the three structure determinations and a comparison with the bonding of AICAR and AICAR 5′-P.

Experimental

The lattice parameters were determined from Weissenberg and refined from Buerger precession photographs. In each case the intensities were collected on a Stoe semi-automatic two-circle diffractometer with Ni-filtered Cu $K\bar{\alpha}$ radiation (Kálmán, Simon, Schawartz & Horváth, 1974). The differences are indicated in each case either in Table 1 or in the following text. No absorption correction was applied.

AICA.C_3H_7OH

The crystals obtained from the solution of AICA in absolute 2-propanol disintegrated rapidly in air. Consequently, the crystal was sealed in a capillary filled with a saturated solution of AICA.C_3H_7OH. The slow deterioration of the crystal was checked by standard reflexions measured after each layer. Rescaling was then performed. The phases for 306 reflexions having $E \geq 1{\cdot}20$ were obtained with *SHELX* (Sheldrick, 1976), giving $R = 0{\cdot}49$ for the non-hydrogen atoms of AICA. A subsequent difference synthesis revealed the heavy atoms of the 2-propanol molecule ($R = 0{\cdot}40$). Anisotropic least-squares refinement of the atomic positions reduced R to 0·128. At this stage the positions of H atoms (except those of methyl H) were located in a difference map. The methyl H positions were generated from assumed geometries. Further anisotropic refinement for the non-hydrogen atoms with two isotropic vibrational parameters for the AICA and the 2-propanol H atoms led to a final R of 0·091 for 1363 reflexions with the weighting scheme $w = k/[\sigma^2(F_o) + gF_o^2]$ (final $k = 46{\cdot}0$, $g = 0{\cdot}0001$).* During this final stage H atoms were riding on the corresponding heavy atoms, which accounts for the unreliably low e.s.d.'s of these atoms.

Table 1. *Crystal and intensity measurement data*

Formula	$C_4H_6N_4O.C_3H_7OH$	$C_4H_6N_4O.H_2O$	$C_4H_7N_4O^+.H_2PO_4^-$
System	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/a$	$P2_1/c$
a (Å)	11·111 (4)	6·586 (5)	12·238 (2)
b (Å)	6·153 (1)	9·972 (6)	5·465 (1)
c (Å)	14·904 (6)	9·499 (5)	12·875 (1)
β (°)	105·2 (1)	91·3 (1)	92·7 (1)
V (Å^3)	983·28	623·59	860·13
D_c (Mg m^{-3})	1·256	1·533	1·728
Z	4	4	4
D_m (Mg m^{-3})	–	1·53	–
Crystal mount	b axis	a axis	b axis
Layers	$h0l$–$h6l$	$0kl$–$6kl$	$h0l$–$h5l$
2θ scan rate (° min^{-1})	1	1	1
$\Delta\omega$	2°	2·5° if $2\theta > 20°$ 4° if $2\theta < 20°$	$\Delta\omega = f(\theta)$*
Time for each background (s)	30	Calculated	30
$\theta_{\max}$ (°)	65	65	75
λ (Å)	1·5418	1·5418	1·5418
Number of independent reflexions	1538	849	1606
Number of observed reflexions	1363	849	1215
$R_{\rm obs}$	0·091	0·055	0·071
$R_{\rm tot}$	0·096	0·055	0·075

* $\cos\left(\frac{\Delta\omega}{2}\right) = \dfrac{\sin^2\theta\cos\left(\frac{\Delta\omega_{\min}}{2}\right) - \sin^2\theta}{\sin^2\theta - \sin^2\mu}$, where $\Delta\omega_{\min} = 2°$; this function was kindly provided by Mr Cs Kertész.

AICA.H_2O

Suitable crystals were obtained from an aqueous solution of HAICA$^+$.$H_2PO_4^-$ neutralized with $NaHCO_3$. Owing to a failure in the electronics of the diffractometer no background measurement could be performed. Instead, it was detected with care at six different 2θ values from which a correction curve was developed. After rescaling the E values in two groups ($k + l = 2n$ and $k + l = 2n + 1$, respectively) the phase problem was solved by *MULTAN* with 183 reflexions having $E \geq 1{\cdot}30$. The E map computed from the set with the best figure of merit gave the positions of all non-hydrogen atoms ($R = 0{\cdot}22$). The structure was refined by block-diagonal least-squares calculations with the weighting scheme $w = (4{\cdot}0 + F_o + 0{\cdot}01F_o^2)^{-1}$ to $R = 0{\cdot}08$. Prior to this, the O and N atoms of the carboxamide moiety were distinguished by studying the bridgehead distances of the potential hydrogen-bond network.

A difference synthesis revealed the positions of all H atoms. Further refinement with anisotropic vibrational parameters for non-hydrogen atoms and isotropic for H resulted in a final R of 0·055 for 849 reflexions.* The final structure factor table was computed with *SHELX*.

HAICA$^+$.$H_2PO_4^-$

Crystals were obtained as described by Schawartz & Hornyák (1971). The structure was solved by *SHELX* with 275 reflexions having $E \geq 1{\cdot}20$. All non-hydrogen atoms were located from the E map with $R = 0{\cdot}39$. However, the structure based on these atoms could not be refined because one of the atoms attached to the imidazole ring turned out to be wrong. After taking another maximum, isotropic and anisotropic refine-

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* Lists of structure factors and anisotropic thermal parameters for the three compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35349 (27 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Positional parameters* (×10⁴) *and* B_{eq} (Å²) *for* AICA.C_3H_7OH *with e.s.d.'s in parentheses*

	x	*y*	*z*	B_{eq}
N(1)	1949 (5)	133 (7)	4555 (3)	3·7 (2)
C(2)	1592 (6)	−1932 (9)	4317 (4)	3·9 (3)
N(3)	1214 (5)	−2955 (7)	4963 (3)	3·5 (2)
C(4)	1341 (5)	−1426 (8)	5673 (3)	3·0 (3)
C(5)	1793 (5)	508 (8)	5424 (4)	3·1 (3)
C(6)	917 (5)	−1845 (9)	6503 (3)	3·0 (3)
O(7)	1080 (4)	−480 (6)	7149 (3)	3·1 (2)
N(8)	344 (5)	−3725 (7)	6536 (3)	4·1 (3)
N(9)	2113 (5)	2418 (7)	5874 (4)	4·2 (3)
O(10)	2776 (3)	2106 (5)	8343 (2)	5·7 (2)
C(11)	4880 (7)	3105 (11)	8967 (6)	9·4 (5)
C(12)	4025 (6)	1584 (10)	8363 (6)	8·4 (4)
C(13)	4299 (7)	−711 (11)	8421 (7)	12·5 (6)
H(1)	2216 (5)	1306 (7)	4225 (3)	6·2 (7)
H(2)	1642 (6)	−2609 (9)	3635 (4)	6·2 (7)
H(81)	74 (5)	−4385 (7)	5976 (3)	6·2 (7)
H(82)	42 (5)	−4278 (7)	6975 (3)	6·2 (7)
H(91)	1755 (5)	3447 (7)	5549 (4)	6·2 (7)
H(92)	1702 (5)	2656 (7)	6311 (4)	6·2 (7)
H(10)	2277 (3)	1031 (5)	8153 (2)	15·2 (8)
H(111)	5849 (7)	2915 (11)	8973 (6)	15·2 (8)
H(112)	4773 (7)	2817 (11)	9657 (6)	15·2 (8)
H(113)	4579 (7)	4735 (11)	8751 (6)	15·2 (8)
H(12)	4215 (6)	1847 (10)	7697 (6)	15·2 (8)
H(131)	5239 (7)	−1274 (11)	8487 (7)	15·2 (8)
H(132)	3667 (7)	−1541 (11)	7850 (7)	15·2 (8)
H(133)	4040 (7)	−1046 (11)	9057 (7)	15·2 (8)

Table 3. *Positional parameters* (×10⁴, *for* H ×10³) *and* B_{eq} (Å²) *for* AICA.H_2O *with e.s.d.'s in parentheses*

	x	*y*	*z*	B_{eq}
N(1)	1321 (4)	1515 (3)	4037 (2)	2·7 (1)
C(2)	1477 (5)	2703 (3)	3398 (3)	2·7 (1)
N(3)	1813 (4)	2587 (2)	2030 (2)	2·5 (1)
C(4)	1898 (4)	1216 (3)	1718 (3)	2·3 (1)
C(5)	1578 (5)	591 (3)	2989 (3)	2·4 (1)
C(6)	2308 (5)	651 (3)	347 (3)	2·5 (1)
O(7)	2477 (4)	−592 (2)	214 (2)	3·1 (1)
N(8)	2521 (5)	1495 (3)	−727 (3)	3·4 (1)
N(9)	1608 (5)	−776 (3)	3303 (3)	3·2 (1)
O(10)	6100 (4)	−963 (3)	3501 (2)	4·1 (1)
H(2)	136 (5)	361 (4)	385 (4)	1·3 (7)
H(3)	200 (7)	337 (5)	141 (5)	3·6 (10)
H(81)	268 (8)	116 (6)	−167 (5)	5·0 (12)
H(82)	226 (8)	249 (5)	−66 (5)	4·1 (11)
H(91)	79 (7)	−101 (5)	415 (5)	3·9 (11)
H(92)	144 (7)	−133 (5)	249 (5)	4·1 (11)
H(101)	695 (8)	−114 (5)	431 (5)	5·4 (13)
H(102)	460 (9)	−110 (6)	365 (6)	5·8 (14)

ment reduced *R* to 0·09. At this stage the H atoms were located from a difference synthesis. All H atoms were riding on the heavy atoms; therefore, the e.s.d.'s for these atoms are underestimated. The refinement was terminated at $R = 0{\cdot}071$ for 1215 observed reflexions.*

Table 4. *Positional parameters* (×10⁴) *and* B_{eq} (Å²) *for* $HAICA^+.H_2PO_4^-$ *with e.s.d.'s in parentheses*

	x	*y*	*z*	B_{eq}
N(1)	2560 (4)	3296 (9)	3584 (4)	3·7 (2)
C(2)	2073 (5)	2998 (11)	4485 (4)	3·6 (3)
N(3)	2501 (4)	1169 (8)	4975 (4)	3·4 (2)
C(4)	3326 (4)	124 (10)	4387 (4)	3·2 (2)
C(5)	3338 (6)	1531 (13)	3506 (5)	3·4 (3)
C(6)	4000 (5)	−1961 (10)	4653 (5)	3·5 (2)
O(7)	4698 (4)	−2608 (8)	4017 (4)	4·7 (2)
N(8)	3868 (4)	−3155 (11)	5526 (4)	3·9 (2)
N(9)	3978 (5)	1393 (13)	2676 (4)	5·3 (3)
P(10)	8930 (1)	2389 (3)	3043 (1)	3·0 (1)
O(11)	9797 (4)	1256 (9)	3831 (4)	4·0 (2)
O(12)	8835 (3)	5091 (8)	3424 (3)	3·9 (2)
O(13)	7852 (3)	1182 (8)	3158 (3)	3·8 (2)
O(14)	9330 (3)	2285 (7)	1949 (3)	3·4 (2)
H(1)	2330 (4)	4910 (9)	3030 (4)	7·2 (2)
H(2)	1320 (5)	4100 (11)	4640 (4)	7·2 (2)
H(3)	2370 (4)	60 (8)	5780 (4)	7·2 (2)
H(81)	4462 (4)	−4709 (11)	5634 (4)	7·2 (2)
H(82)	3663 (4)	−2870 (11)	6375 (4)	7·2 (2)
H(91)	4592 (5)	290 (13)	2860 (4)	7·2 (2)
H(92)	4198 (5)	3061 (13)	2485 (4)	7·2 (2)
H(11)	9800 (3)	−1000 (8)	3600 (3)	7·2 (2)
H(12)	9800 (4)	5600 (9)	3500 (4)	7·2 (2)

The final *k* and *g* in the weighting scheme $w = k/\sigma^2(F_o + gF_o^2)$ were 1·0 and 0·02 respectively.

A bonded H-atom scattering factor was employed (Stewart, Davidson & Simpson, 1965) with complex neutral scattering factors for the remaining atoms (Cromer & Mann, 1968; Cromer & Liberman, 1970). All calculations were performed on an ODRA 1305 computer at the Computer Centre of Chinoin Factory. The final atomic coordinates are given in Tables 2, 3 and 4, bond distances and angles in Tables 5 and 6. A common atom-numbering scheme for the three structures is shown in Fig. 1.

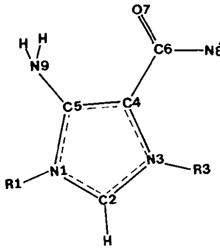

Fig. 1. A schematic drawing of the AICA molecules with uniform atomic numbering. *R*1 and *R*3 represent H atoms or a lone pair of electrons (–) as follows:

	R_1	*R*3
AICA.C_3H_7OH	H	–
AICA.H_2O	–	H
$HAICA^+.H_2PO_4^-$	H	H.

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* See deposition footnote.

Table 5. *Bond distances* (Å) *with e.s.d.'s in parentheses*

The corresponding values for AICAR and AICAR 5′-P are also presented.

	AICA.- C_3H_7OH	AICA.- H_2O	HAICA$^+$.- $H_2PO_4^-$	AICAR	AICAR 5′-P
N(1)–C(2)	1·350 (7)	1·336 (4)	1·339 (7)	1·384 (5)	1·350 (7)
N(1)–C(5)	1·371 (5)	1·370 (4)	1·362 (9)	1·369 (5)	1·383 (8)
C(2)–N(3)	1·308 (6)	1·328 (3)	1·281 (7)	1·299 (6)	1·308 (8)
N(3)–C(4)	1·395 (5)	1·400 (4)	1·411 (7)	1·402 (5)	1·406 (8)
C(4)–C(5)	1·380 (7)	1·379 (4)	1·371 (8)	1·381 (6)	1·376 (8)
C(4)–C(6)	1·457 (5)	1·450 (4)	1·439 (8)	1·437 (6)	1·455 (9)
C(5)–N(9)	1·354 (7)	1·395 (4)	1·356 (8)	1·355 (5)	1·342 (7)
C(6)–O(7)	1·254 (6)	1·251 (4)	1·261 (8)	1·255 (5)	1·239 (8)
C(6)–N(8)	1·328 (7)	1·332 (4)	1·316 (8)	1·333 (6)	1·343 (8)
P(10)–O(11)			1·561 (5)		
P(10)–O(12)			1·562 (5)		
P(10)–O(13)			1·489 (4)		
P(10)–O(14)			1·514 (4)		

Table 6. *Bond angles* (°) *with e.s.d.'s in parentheses*

The corresponding values for AICAR and AICAR 5′-P are also presented.

	AICA.- C_3H_7OH	AICA.- H_2O	HAICA$^+$.- $H_2PO_4^-$	AICAR	AICAR 5′-P
C(2)–N(1)–C(5)	107·8 (7)	104·7 (4)	108·6 (9)	107·3 (3)	108·9 (5)
N(1)–C(2)–N(3)	112·8 (8)	112·6 (5)	109·5 (9)	111·5 (4)	109·6 (5)
C(2)–N(3)–C(4)	104·2 (7)	107·5 (4)	109·8 (8)	106·0 (3)	108·4 (5)
N(3)–C(4)–C(5)	110·4 (7)	104·4 (4)	104·6 (8)	109·2 (3)	107·0 (5)
N(3)–C(4)–C(6)	122·3 (7)	125·4 (4)	127·6 (8)	123·6 (4)	127·9 (6)
C(5)–C(4)–C(6)	127·0 (7)	130·3 (5)	127·8 (9)	127·2 (4)	125·0 (6)
N(1)–C(5)–C(4)	104·7 (7)	110·9 (5)	107·5 (10)	105·9 (3)	106·1 (5)
N(1)–C(5)–N(9)	122·2 (8)	120·2 (5)	121·9 (10)	123·7 (4)	124·1 (5)
C(4)–C(5)–N(9)	133·0 (8)	128·8 (5)	130·5 (11)	130·4 (4)	129·7 (6)
C(4)–C(6)–O(7)	121·3 (7)	119·6 (5)	117·8 (9)	121·1 (4)	118·3 (6)
C(4)–C(6)–N(8)	116·8 (7)	117·9 (5)	120·3 (9)	117·4 (4)	118·6 (6)
O(7)–C(6)–N(8)	121·9 (8)	122·5 (5)	122·0 (10)	121·5 (4)	123·1 (6)
O(11)–P(10)–O(12)			103·3 (4)		
O(11)–P(10)–O(13)			109·8 (4)		
O(11)–P(10)–O(14)			110·5 (4)		
O(12)–P(10)–O(13)			108·0 (4)		
O(12)–P(10)–O(14)			111·1 (4)		
O(13)–P(10)–O(14)			113·8 (4)		

Discussion

As shown by the least-squares planes (Table 7), in each structure the imidazole ring is fairly planar and makes a dihedral angle with the planar $CONH_2$ moiety of 7·6, 3·7 and 1·0° respectively. The geometry of the carboxamide group is nearly identical in these three structures and in those of AICAR and AICAR 5′-P. The differences in the C(4)–C(6)–O(7) [and consequently in the C(4)–C(6)–N(8)] angles can be attributed to the strength of the characteristic intramolecular N(9)–H···O(7) bonds. The strongest found in HAICA$^+$.$H_2PO_4^-$ is accompanied by the smallest C(4)–C(6)–O(7) angle. The corresponding multiple bonds of the aromatic imidazole ring are identical in each structure within experimental error. The greatest deviations are found in the C(2)–N(3) bonds. The somewhat longer C(5)–N(9) in AICA.H_2O can be attributed to the acceptor role of N(9) in a relatively strong hydrogen bond formed with the water molecule. The different positions of the *endo* (tautomeric) and the additional (by protonation) H atoms have, however, a significant effect on the values of the internal bond angles. The 1*H* tautomers AICA.C_3H_7OH and AICAR have nearly identical internal bond angles, while those of the 3*H*-AICA.H_2O differ from them. Similarly, the corresponding endocyclic bond angles in HAICA$^+$.$H_2PO_4^-$ and AICAR 5′-P agree within experimental error. Consequently, as in the 1*H* and 2*H* tautomers of the analogous 1,2,3-triazoles (Párkányi, Kálmán, Argay & Schawartz, 1977) the bond-angle inequalities enable us to distinguish between the 1*H* and $3H$ tautomeric forms. Similar inequalities have been observed for the desmotropes (*i.e.* stable tautomers crystallized from different solvents) of 2-methylthio-5,5-diphenyl-2-imidazolin-4-one (MTDPI) (Lempert, Nyitrai, Zauer, Kálmán, Argay, Duisenberg & Sohár, 1973) and for 5-(3,3-dimethyl-1-triazenyl)-imidazole-4-carboxamide (DTIC) (Freeman & Hutchinson, 1979) in the asymmetric unit of which both tautomers are present simultaneously. The four inequalities are summarized in Table 8. It is worth noting that the lone-pair-induced (Gillespie, 1963) alterations of the bond angles at N(1) and N(3) are accompanied by somewhat more pronounced changes of the angles at the adjacent C(5) and C(4) in the opposite direction. This effect seems to be balanced at the midway atom C(2), at which the bond-angle pairs are:

	$1H$	$3H$
AICA	112·8 (8)°	112·6 (5)°
DTIC	113·2 (3)	112·4 (3)
MTDPI	117·3 (4)	115·8 (3).

On protonation of the imidazole ring this angle is considerably closed in both the HAICA$^+$ cation and the zwitterion AICAR 5′-P to 109·5 (9) and 109·6 (5)° respectively. In these rings the angles at the hetero-atoms assume almost the same value, indicating that the lone-pair effect no longer exists.

Table 7. *Equations of planes in the form $AX + BY + CZ = D$, where X, Y and Z are orthogonal coordinates* (Å)

Plane (1): N(1), C(2), N(3), C(4) and C(5)

AICA.C_3H_7OH: $0\cdot8597X - 0\cdot3135Y + 0\cdot4070Z = 2\cdot9701$
AICA.H_2O: $0\cdot9814X + 0\cdot0010Y + 0\cdot1920Z = 1\cdot5011$
HAICA$^+$.$H_2PO_4^-$: $0\cdot6557X + 0\cdot6056Y + 0\cdot4508Z = 5\cdot0793$

The maximum deviation of atoms forming the planes is 0·002 (5) Å.

Plane (2): C(4), C(6), O(7) and N(8)

AICA.C_3H_7OH: $0\cdot7922X - 0\cdot4235Y + 0\cdot4395Z = 3\cdot3824$
AICA.H_2O: $0\cdot9770X + 0\cdot0637Y + 0\cdot2034Z = 1\cdot5910$
HAICA$^+$.$H_2PO_4^-$: $0\cdot6537X + 0\cdot5970Y + 0\cdot4650Z = 5\cdot1526$

The maximum deviation of atoms forming the planes is 0·006 (6) Å.

Angles between planes (1) and (2): 7·6, 3·7 and 1·0°.

To summarize, as shown by the three stable pairs of imidazole tautomers (AICA, DTIC and MTDPI) the energy difference between these pairs is not significant. However, only the $1H$ tautomer of AICA fits in the process of forming purine nucleosides and nucleotides. It retains its endo- and exocyclic geometries in AICAR. Similarly, the protonated HAICA$^+$ retains its geometry in the nucleotide AICAR 5′-P. Accordingly, the water-induced $3H$ form of AICA (its lone pair is blocked by a strong hydrogen bond formed with a water molecule) suggests the hypothesis that the linkage between AICA and the sugar residue is formed in an aprotic enzymatic process. It is even more probable that AICAR is built up from the more suitable HAICA$^+$ cation in proper media.

The characteristic intramolecular hydrogen bond formed between the vicinal 5-amino and 4-carboxamide moieties (Table 9) is sustained throughout these structures. This hydrogen bond, as claimed also by Adamiak & Saenger (1979), has to be broken in an enzymatic reaction in order to create the optimal geometry; *i.e.* 180° rotation of the carboxamide moiety, to the ring closure producing hypoxanthine or guanine.

Geometry of the $H_2PO_4^-$ *anion in* HAICA$^+$.$H_2PO_4^-$

In the infinite hydrogen-bonded $H_2PO_4^-$, helices formed around the 2_1 axes have a mean bond length of 1·532 (5) Å in accord with the predicted value (Kálmán, 1971) for non-corrected P—O distances. The mean bond angle is 109·4 (4)°. Within these mean values the individual bond lengths and angles are in accordance with the function (bridging or terminal) of the O atoms.

Table 9. *Intramolecular* N(9)—H···O(7) *hydrogen bonds*

	N···O	H···O	∠NH···O
AICA.C_3H_7OH	3·04 Å	2·49 Å	120°
AICAR	2·96	2·47	126
AICA.H_2O	3·01	2·40	121
AICAR 5′-P	2·82	2·19	144
HAICA$^+$	2·90	2·17	129

Table 8. *Endocyclic bond angles* (°) *for the* $1H$ *and* $3H$ *tautomers of* AICA *and two other imidazoles* (DTIC *and* MTDPI)

	AICA				DTIC				MTDPI			
	$1H$		$3H$	Δ	$1H$		$3H$	Δ	$1H$		$3H$	Δ
N(1)	107·8 (7)	>	104·7 (4)	3·1	106·4 (3)	>	104·7 (3)	1·7	108·9 (4)	>	106·3 (3)	2·6
N(3)	104·2 (7)	<	107·5 (4)	3·3	104·2 (3)	<	107·0 (3)	2·8	105·1 (4)	<	108·8 (3)	3·7
C(4)	110·4 (7)	>	104·4 (4)	6·0	110·3 (3)	>	106·1 (3)	4·2	110·0 (4)	>	105·3 (3)	4·7
C(5)	104·7 (7)	<	110·9 (5)	6·2	105·9 (3)	<	109·8 (3)	3·9	98·7 (4)	<	103·7 (2)	5·0

Table 10. *Distances* (Å) *and angles* (°) *for possible intra- and intermolecular hydrogen-bond contacts*

	$D\cdots A$	$H\cdots A$	$\angle D\text{–}H\cdots A$
(*a*) AICA.C_3H_7OH			
O(10)–H(10)···O(7)$[1-x, -\frac{1}{2}+y, 1\frac{1}{2}-z]$	2·737 (7)	1·957 (7)	150·0 (10)
N(1)–H(1)···O(10)$[1-x, -y, 1-z]$	2·804 (7)	1·870 (7)	162·7 (10)
N(9)–H(91)···N(3)$[x, 1+y, z]$	3·199 (6)	2·398 (6)	161·8 (9)
N(8)–H(81)···N(3)$[-x, -1-y, 1-z]$	3·184 (6)	2·374 (6)	148·7 (9)
N(8)–H(81)···N(3)$[x,y,z]$	2·802 (6)	2·379 (6)	108·5 (9)
N(9)–H(92)···O(7)$[x,y,z]$	3·042 (6)	2·493 (6)	120·0 (9)
(*b*) AICA.H_2O			
O(10)–H(101)···N(1)$[1-x, -y, 1-z]$	2·910 (4)	1·96 (5)	180 (5)
O(10)–H(102)···N(9)$[x,y,z]$	2·966 (4)	2·02 (5)	155 (5)
N(3)–H(3)···O(7)$[\frac{1}{2}-x, \frac{1}{2}+y, -z]$	2·847 (4)	1·90 (5)	161 (5)
N(8)–H(81)···O(10)$[1-x, -y, -z]$	2·857 (4)	1·94 (5)	157 (5)
N(8)–H(82)···O(7)$[\frac{1}{2}-x, \frac{1}{2}+y, -z]$	2·945 (4)	1·97 (5)	163 (5)
N(9)–H(91)···N(1)$[-x, -y, 1-z]$	3·298 (4)	2·30 (5)	175 (5)
C(2)–H(2)···O(10)$[-\frac{1}{2}+x, \frac{1}{2}-y, z]$	3·261 (4)	2·37 (5)	147 (5)
N(9)–H(92)···O(7)$[x,y,z]$	3·008 (4)	2·40 (5)	121 (5)
(*c*) HAICA$^+$.$H_2PO_4^-$			
O(12)–H(12)···O(14)$[2-x, \frac{1}{2}+y, \frac{1}{2}-z]$	2·610 (6)	1·541 (6)	142·5 (9)
O(11)–H(11)···O(14)$[2-x, -\frac{1}{2}+y, \frac{1}{2}-z]$	2·638 (6)	1·607 (6)	132·8 (9)
N(1)–H(1)···O(13)$[1-x, \frac{1}{2}+y, \frac{1}{2}-z]$	2·769 (7)	1·685 (7)	152·8 (10)
N(3)–H(3)···O(13)$[1-x, -y, 1-z]$	2·777 (7)	1·711 (7)	161·5 (10)
N(8)–H(81)···O(7)$[1-x, -1-y, 1-z]$	2·948 (8)	1·834 (8)	171·3 (11)
N(8)–H(82)···O(13)$[1-x, -y, 1-z]$	2·967 (8)	2·181 (7)	123·3 (11)
N(9)–H(91)···O(7)$[x,y,z]$	2·897 (8)	2·174 (8)	129·1 (11)
N(9)–H(92)···O(7)$[1-x, \frac{1}{2}+y, \frac{1}{2}-z]$	2·830 (8)	2·438 (8)	103·2 (11)

Intermolecular hydrogen bonding

Since the three-dimensional hydrogen-bond networks of the three AICA forms have already been reported in detail along with those of the analogous 1,2,3-triazoles (Kálmán, Párkányi, Schawartz & Simon, 1978) only the distances and angles for possible hydrogen-bonded contacts are presented (Table 10).

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The Stereochemistry of 3′-*N*-Substituted 3′-Deoxyadenosines

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Abstract

The crystal structures of three 3′-*N*-substituted 3′-deoxyadenosines have been determined. The antitumor agent from *Helminthosporium* s.p. 215, 3′-amino-3′-deoxyadenosine (I), crystallizes in the monoclinic space group $P2_1$, with $a = 11{\cdot}925\ (3)$, $b = 10{\cdot}302\ (2)$, $c = 4{\cdot}752\ (1)$ Å, $\beta = 100{\cdot}52\ (2)°$, $Z = 2$; 3′-cyclobutylamino-3′-deoxyadenosine (II) crystallizes in the orthorhombic space group $P2_12_12_1$, with $a = 11{\cdot}392\ (2)$, $b = 18{\cdot}434\ (2)$, $c = 7{\cdot}992\ (1)$ Å, $Z = 4$; and the oxazolidine (III) of 3′-(*N*-benzyl-*N*-methylamino)-3′-deoxyadenosine crystallizes in the orthorhombic space group $P2_12_12_1$, with $a = 9{\cdot}927\ (2)$, $b = 22{\cdot}401\ (4)$, $c = 7{\cdot}743\ (1)$ Å, $Z = 4$. The structures were refined to $R = 0{\cdot}034$, 0·057, and 0·044 for 1108,

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