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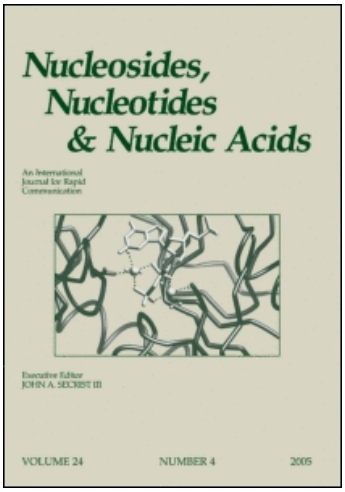

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The X-ray Crystal and Molecular Structure of 5-Amino-1-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl) Imidazole-4-carboxamide

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THE X-RAY CRYSTAL AND MOLECULAR STRUCTURE OF 5-AMINO-1-(2,3:5,6-DI-O-ISOPROPYLIDENE-α-D-MANNOFURANOSYL) IMIDAZOLE-4-CARBOXAMIDE

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Abstract: 5-Amino-1-(2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl) imidazole-4-carboxamide (ADIMIC) crystallizes with six molecules in a hexagonal unit cell of space group $P6_3$. The imidazole ring is closely planar, the furanose ring pucker is O1' endo-C4' exo, and the dioxolane rings are puckered C6' endo-O6' exo and C7' endo-O3' exo. In addition to an intramolecular hydrogen bond from the 5-amino hydrogen to the 4-carboxamide oxygen, a circuit of intermolecular hydrogen bonds links nearly coplanar imidazole rings.

5-Aminoimidazole nucleosides and nucleotides are important intermediates in the de novo biosynthesis of purine nucleotides and, by appropriate ring cyclisation methods, for the general synthesis of a wide variety of purines, purine nucleosides and nucleotides.[1] Moreover, modified imidazoles have considerable potential as anti-viral or anti-tumour agents by inhibition of the de novo pathway. The nucleoside 5-amino-1-(2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl)imidazole-4-carboxamide (ADIMIC), prepared in good yield by reaction[1] of 2,3:5,6-di-O-isopropylidene-D-mannofuranosylamine with ethyl N-(carbamoylcyanomethyl)-formimidate,[2,3] is a valuable intermediate for the synthesis of a wide variety of other imidazole nucleosides including lyxose derivatives.[4] Assignment of the anomeric configuration of ADIMIC and related nucleosides by ^1H n.m.r. chemical shifts raises some apparent contradictions with empirical rules. Thus, whereas the H 1' resonance for α-ADIMIC is singlet,[3] in accordance with expectation from the Karplus equation[5] (as modified for furanose systems) as providing evidence for

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trans H1'-H2' (and hence for α-mannose), it resonates at lower field than the β anomer, in contravention of an empirical rule[6] that the cis anomer resonates downfield of the trans. It is also of interest that the difference ($\Delta\delta$) in chemical shifts for endo- and exo-isopropylidene methyl groups is very small for both α- and β-ADIMIC. For ribosides, $\Delta\delta < 0.15$ for α-anomers and > 0.15 for β-anomers[7] and one might have expected the reverse for 2,3-O-isopropylidenemannosides. Crystal structures of rather few of these compounds have been determined. We report here the single-crystal X-ray analysis of α-ADIMIC, confirming the anomeric assignment and revealing a three-fold chain of intermolecular hydrogen bonds linking imidazole rings in a hexagonal cell.

EXPERIMENTAL

Following separation from the β-anomer by methanol-chloroform elution on a silica-gel column, ADIMIC crystallized from methanol and was recrystallized by slow evaporation from ethanol to yield long colourless needles. Photographic X-ray measurements gave preliminary dimensions for a hexagonal unit cell with systematic absences appropriate to space group $P6_3$. Diffractometrically determined cell dimensions (from 25 reflections with $9^\circ<\theta<12^\circ$ are $a = b = 21.743(3)$, $c = 6.944(1)$ Å. Other crystal data for $C_{16}H_{24}N_4O_6$ are $M_r = 368.4$, $V = 2843.0(2)$ Å^3, $Z = 6$, $F(000) = 1176$, $D_o = 1.27(1)$ (NaI flotation), $D_x = 1.29$ g cm^{-3}; $\mu(MoK_\alpha)$ 0.75 cm^{-1}.

Intensity data were collected for the θ range 1.5-25° from a crystal of dimensions 0.4 x 0.1 x 0.2 mm with graphite-monochromated Mo K_α radiation ($\lambda = 0.7107$ Å) on an Enraf-Nonius CAD 4F diffractometer (w/θ scan; scan width 0.70 + 0.35 tan θ). From a total of 4374 reflection measurements, 1819 unique reflections were obtained, of which 1389 with $I > 2\sigma(I)$ were used in the structure analysis. During the collection, no significant intensity decay was apparent.

The structure was solved by direct methods (MULTAN 78[8]) and parameters were refined on CRYSTALS[9] by blocked-matrix least squares. Positional parameters were refined in one block; a second block contained the scale factor, anisotropic temperature factors for the C, N, O atoms (Cromer and Mann[10] scattering factors) and separate but common isotropic temperature factors for each kind of H atom (Stewart et al scattering factors). Positions of hydrogen atoms in the four methyl groups were located by slant-plane difference Fourier (ΔF) sections and positions of other H atoms by ΔF syntheses. Methyl H-atom positions were restrained at C-H = 1.00(2) Å and H-C-H = 109.5 (2.5)°. For the final refinement cycle, with three coefficients 79.4, 110.1 and 33.0 in the Chebyshev polynomial for $\langle w\Delta F^2\rangle$ distribution[12], the converged $R = 0.036$ and $R_w = 0.042$. A final ΔF synthesis showed only randomly distributed peaks within ±0.15e Å^{-3}.

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TABLE 1 Fractional atomic positional coordinates (x 10^4) with e.s.d.s in parentheses and equivalent isotropic thermal parameters ($Å^2$ x 10^2)

Atom	x/a	y/b	z/c	U(ISO)*
N(1)	5712(1)	5791(1)	2054(7)	342
N(3)	4607(1)	5287(2)	3208(8)	431
N(5)	5823(2)	6812(2)	420(8)	472
N(6)	3618(2)	5764(2)	2652(8)	432
O'(1)	6876(1)	6456(1)	3263(7)	398
O'(2)	7074(1)	5417(1)	527(7)	398
O'(3)	7661(1)	5675(1)	3328(7)	429
O'(5)	7249(1)	6911(1)	7350(7)	517
O'(6)	8451(1)	7504(2)	7028(8)	599
O(6)	4456(1)	6724(1)	1081(7)	495
C(2)	5182(2)	5244(2)	3103(8)	418
C(4)	4763(2)	5899(2)	2190(8)	339
C(5)	5441(2)	6212(2)	1482(7)	325
C(6)	4267(2)	6158(2)	1928(8)	360
C'(1)	6448(2)	5977(2)	1809(8)	366
C'(2)	6571(2)	5343(2)	1933(8)	366
C'(3)	6946(2)	5438(2)	3863(8)	380
C'(4)	6877(2)	6027(2)	4840(8)	379
C'(5)	7441(2)	6462(2)	6317(8)	440
C'(6)	8175(2)	6970(2)	5576(9)	543
C'(7)	7642(2)	5385(2)	1481(8)	419
C'(8)	7475(3)	4623(3)	1329(9)	606
C'(9)	8317(2)	5860(3)	417(10)	646
C'(10)	7880(2)	7585(2)	7357(8)	521
C'(11)	7826(3)	8138(3)	6536(13)	922
C'(12)	7967(3)	7738(3)	9792(11)	717

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RESULTS AND DISCUSSION

Table 1 gives the atomic positional co-ordinates and equivalent isotropic thermal parameters. Figure 1 shows the structure and atom numbering for a molecule of ADIMIC and Figure 2 shows how the molecule packs around the three-fold crystallographic axis in the crystal. Three almost coplanar imidazole rings are linked by a chain of three intermolecular hydrogen bonds between the carboxamide groups with an intermolecular O...H distance of 2.13 Å. The imidazole ring is highly planar; the substituent carboxyl group and amino nitrogen substituent are also in this plane to within 0.07 Å and the C1' of the sugar to within 0.16 Å. The carboxamide substituent lies essentially in the imidazole plane, with torsion angles C5-C4-C6-O6 and N3-C4-C6-N6 - 3° and C5-C4-C6-N6 and N3-C4-C6-O6 177°. There is an intramolecular hydrogen

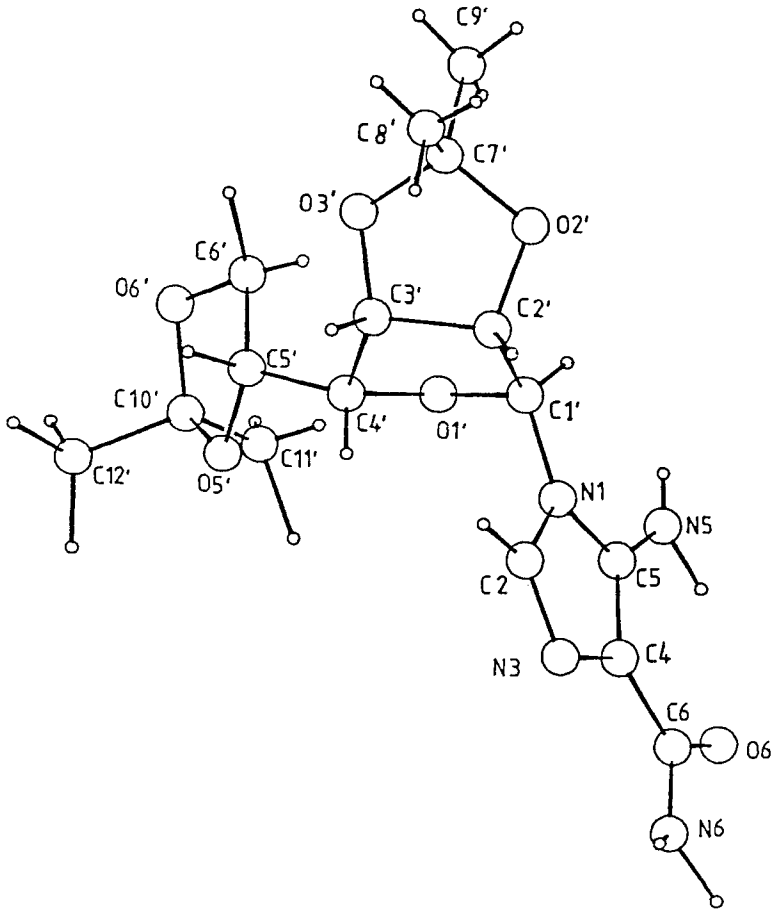

FIG. 1 Solid-state molecular structure and atom numbering of ADIMIC

bond with N5...O6 = 2.93 Å and O6...H = 2.28 Å between 5-amino (donor) and 4-carboxamide substituents (carboxyl oxygen as acceptor), much as apparently in 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR),[13] benzyl 5-amino-1-(2,3isopropylidene-β-D-ribofuranosyl-4-carboxylate (BARIC)[14], 1-diphenylmethyl-5-amino- imidazole-4-carboxamide[15], and 5-amino-imidazole-4 carboxamide (contrast 4-amino in which the NH_2 group from $CO.NH_2$ acts as donor for the intramolecular hydrogen bond[16]). For ethyl 5-amino-1-(2,3-O-isopropylidene-β-ribofuranosyl)-imidazole-4-carboxylate (EARIC)[17], on the other hand, the acceptor oxygen in the intramolecular hydrogen bond from the amino group is the ethoxy O7 rather than O6 but the endocyclic dimensions of the imidazole rings in ADIMIC (Table 2) are almost

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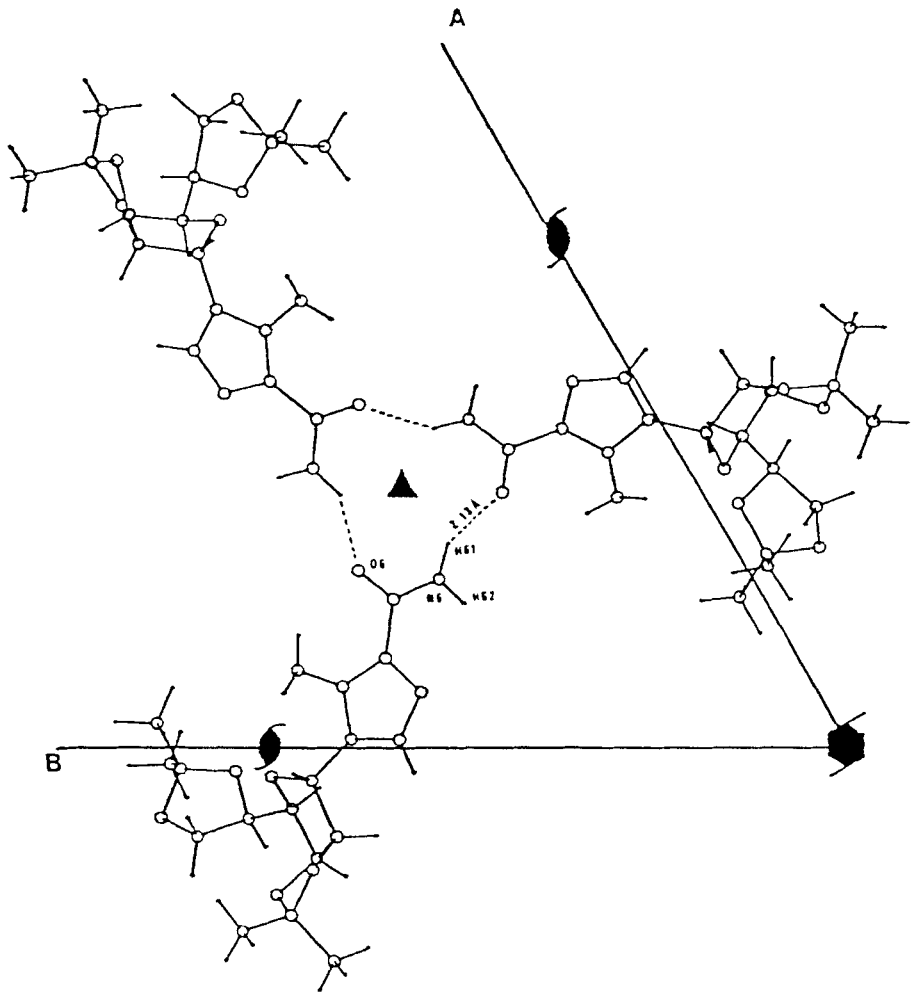

FIG. 2 Crystal packing of ADIMIC, viewed down c axis, showing hydrogen bonding round 3-fold crystallographic axis.

identical[14] with those in EARIC. The carbonyl bond, C6-O6 = 1.233(4) Å, in ADIMIC is rather longer than the carbonyl in EARIC which is not a hydrogen bond acceptor and, at 1.211(3) Å, is normal for that in a system of conjugated bonds.

Table 3 shows the conformational characteristics of the nucleoside. At the junction of the bicyclic furandioxolane group, torsion angles are C7'-O2'-C2'-C1' = 125°, C7'-O3'-C3'-C4' = -140°, and O1'C1'-C2'-O2' = -98°, O3'-C3'-C4'-O1' = 80°. As a consequence of the five-membered dioxolane ring (C2'-O2'-C7'-O3'-C3'), the furanose

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TABLE 2 Molecular dimensions of ADIMIC (with e.s.d.s in parentheses)

(a) Bond lengths (Å)

N1-C2	1.379(5)	N1-C5	1.372(4)
N1-C1'	1.451(4)	N3-C2	1.302(5)
N3-C4	1.390(5)	N5-C5	1.361(5)
N6-C6	1.332(5)	O1'-Cl'	1.415(4)
O1'-C4'	1.439(5)	O2'-C2'	1.413(4)
O2'-C7'	1.434(4)	O3'-C3'	1.420(5)
O3'-C7'	1.422(5)	O5'-C5'	1.430(5)
O5'-C10'	1.437(5)	O6'-C6'	1.424(5)
O6'-C10'	1.408(5)	O6-O6	1.233(4)
C4-C5	1.369(4)	C4-C6	1.456(4)
C1'-C2'	1.533(5)	C3'-C4'	1.522(5)
C4'-C5'	1.513(6)	C5'-C6'	1.507(6)
C7'-C8'	1.510(6)	C7'-C9'	1.501(6)
C10'-C11'	1.486(7)	C10'-C12'	1.510(8)
		C2'-C3'	1.527(6)

(b) Bond angles (°)

C5-N1-C2	106.0(3)	C1-N1-C2	129.2(3)
C1-N1-C5	124.2(3)	C4-N3-C2	104.8(3)
C4'-O1'-Cl'	106.3(2)	C7'-O2'-C2'	108.1(3)
C7-O3'-C3'	106.9(3)	C10'-O5'-C5'	108.4(3)
C10'-O6'-C6'	106.5(3)	N3-C2-N1	112.8(3)
C6-C4-C5	125.7(3)	N3-C4-C5	110.2(3)
N3-C4-C6	124.1(3)	N5-C5-N1	122.4(3)
C4-C5-N1	106.2(3)	C4-C5-N5	131.4(3)
O6-C6-N6	122.6(3)	C4-C6-N6	117.1(3)
C4-C6-O6	120.3(3)	N1-C1'-C2'	114.1(3)
O1'-C1'-C2'	106.0(3)	O1'-C1'-N1	110.4(3)
O2'-C2'-C3'	105.1(2)	C1'-C2'-C3'	104.5(3)
O1'-C2'-O2'	109.4(3)	O3'-C3'-O4'	111.1(3)
C2'-C3'-O4'	103.6(3)	C2'-C3'-O3'	103.4(3)
O1'-C4'-C5'	112.0(3)	C3'-C4'-C5'	116.0(3)
C3'-C4'-O1'	103.8(3)	O5'-C5'-C6'	103.6(3)
C4'-C5'-O6'	117.2(4)	C4'-C5'-O5'	110.2(4)
C5'-C6'-O6'	102.5(4)	C9'-C7'-C8'	113.9(4)
O2'-C7'-C8'	110.2(3)	O2'-C7'-C9	108.0(3)
O3'-C7'-C8'	111.3(3)	O3'-C7'-C9'	109.7(4)
O3'-C7'-O2'	103.2(3)	C12'-C10'-C11'	112.8(5)
O5'-C10'-C11'	109.1(4)	O5'-C10'-C12'	108.7(4)
O6'-C10'-C11'	111.7(4)	O6'-C10'-C12'	108.1(4)
O6'-C10'-O5'	106.1(3)		

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TABLE 3. Conformational features in crystal structure of ADIMIC

Torsion angles(°)			Phase angle(P)	Maximum puckering amplitude	Mode of ring pucker
Sugar ring					
C4'-O1'-C1'-C2'	τ_0	-34.6			
O1'-C1'-C2'-C2'	τ_1	13.8			
C1'-C2'-C3'-C4'	τ_2	10.5	75.0	$\theta_m = 40.6$	$^{O_1'}T_{C4'}$
C2'-C3'-C4'-O1'	τ_3	-30.9			
C3'-C4'-O1'-C1'	τ_4	41.4			
2,3 dioxolane ring					
O3'-C7'-O2'-C2'	λ_o	-30.7			
C7'-O2'-C2'-C3'	λ_1	13.0			
O2'-C2'-C3'-O3'	λ_2	9.6	75.0	$\lambda_m = 37.1$	$^{C7'}T_{O3'}$
C2'-C3'-O3'-C7'	λ_3	-29.0			
C3'-O8'-C7'-O2'	λ_4	37.3			
5,6 dioxolane ring					
O6'-C10'-O5'-C5'	δ_0	-7.3			
O5'-C5'-C6'-O6'	δ_1	-14.7			
C5'-C6'-O6'-C10'	δ_2	30.9	31.0	$\delta_m = 36.0$	$^{C6'}T_{O6'}$
C6'-O6'-C10'-O5'	δ_3	-36.5			
O6'-C10'-O5'-C5'	δ_4	28.0			
Glycosyl torsion angle χ_{cn} (C2-N1-C1'-O1')				-89.7 (anti)	

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ring adopts the unusual O1' endo-C4' exo ($^oT_4$) conformation[18], while the pucker forms of the dioxolane rings are C7' endo-O3' exo ($^{C7'}T_{O3'}$) for the 2,3 ring and C6' endo-O6' exo ($^{C6'}T_{O6'}$) for the 5,6 ring. As often with nucleoside derivatives, the ring oxygen bonds C1'-O1' = 1.415(4) and C4'-O1' = 1.4339(5) Å differ slightly (though less than in EARIC).

SUPPLEMENTARY MATERIAL

Tables of observed and calculated structure factors, anisotropic thermal parameters and torsion angles are available from CEB or DWJ.

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