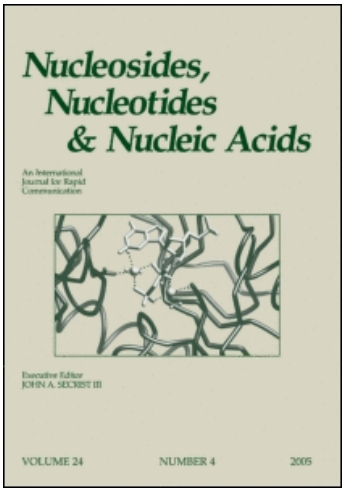

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The Crystal and Molecular Structure of the Complex of 2'3'-Didehydro-2'3'-Dideoxyguanosine with Pyridine

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THE CRYSTAL AND MOLECULAR STRUCTURE OF THE COMPLEX OF 2',3'-DIDEHYDRO-2',3'-DIDEOXYGUANOSINE WITH PYRIDINE

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ABSTRACT: The structure of 2',3'-didehydro-2',3'-dideoxyguanosine was determined by X-ray crystallographic analysis of the complex with pyridine. The two independent nucleoside molecules have similar, commonly observed glycosyl link (χ = -102.3° and -94.2°) and 5'-hydroxyl (γ = 54.0° and 47.6°) conformations. The five-membered rings are very planar with r.m.s. deviations from planarity of less than 0.015 Å. 2',3'-Didehydro-2',3'-dideoxyadenosine has a similar glycosyl link conformation but a different 5'-hydroxyl group orientation and a slightly less planar 5-membered ring.

INTRODUCTION

Since the emergence of 3'-azido-3'-deoxythymidine (AZT) as the first drug for the treatment of AIDS, much effort has been devoted to the synthesis and evaluation of other nucleosides analogues as potential new anti-HIV agents[1]. Modification of the sugar moiety of standard nucleosides has produced many compounds with highly varied activity and toxicity.

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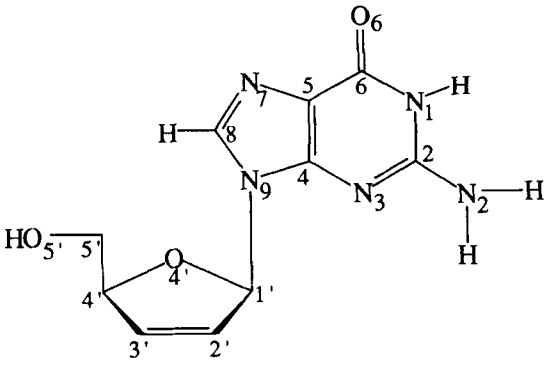

Figure 1: Schematic diagram of D4G showing the numbering scheme.

In previous studies[2-4] we have hypothesized that there may be a correlation between the conformation of the nucleoside and the activity. Active compounds, particularly 2',3'-dideoxynucleosides and their 3'-azido derivatives, showed to have a preference for an unusual sugar ring conformation with an extreme C3'-*exo*/C4'-*endo* puckering geometry[2-3] and an increased stabilization of the *ap*-conformation for the 5'-hydroxyl group[4].

The 2',3'-didehydro-2',3'-dideoxynucleosides are one class of compounds that has demonstrated interesting activities[5-8]. Some of the compounds of the group, most specifically the thymidine (D4T)[5-7], cytidine (D4C)[8] and adenosine (D4A)[8] analogues have proven to be quite active and D4T is undergoing phase II clinical trials. As a part of our drug discovery program, the guanosine analogue (D4G), shown in Figure 1, was synthesized and tested but proved to have very low activity (EC_{50} > 100. μM in PBM cells)[8]. The crystal structure of D4G was determined and is compared with that of D4A with the purpose of determining if any conformational differences between the two compounds can be correlated with activity levels. This was of particular interest because D4A and D2A have similar structures[9] as well as activities, EC_{50} ~ 0.76 and 0.91 μM in PBM cells respectively.

EXPERIMENTAL

D4G was recrystallized by slow evaporation of a pyridine solution. The compound crystallizes as a 1:1 complex with the crystallization solvent. The crystals belong to the monoclinic space group $P2_1$ with cell dimensions a = 16.429(2) Å, b = 9.179(1)Å. c = 10.864(2) Å, β = 101.49(2)°, V = 1605.5(3)Å^3, Z=4. The crystal used for data collection was needle shaped with approximate dimensions of 0.08 x 0.12 x 0.80 mm. The data were measured at room temperature on a Siemens P3V diffractometer using Nb-filtered MoKα radiation (λ = 0.71069 Å). The data were processed using Blessing's data reduction package[10]. Lorentz and polarization corrections were applied but no absorption correction. In total 4008 data were measured in the range of 2.<2θ<50.°. Of the 3032 unique data , 2568 had F > 3σ(F) and were used in the refinement. The structures were determined by direct methods, program MULTAN[11], and refined by full-matrix least-squares. The locations of all hydrogen atoms, except for that bonded to O5' for molecule B, were determined from difference maps and were included in the refinement. In total 556 parameters were refined. The y-coordinate of atom N1 of molecule A was held fixed to define the origin. Final R-values are R= 0.044 and R_w= 0.031 for the data used in the refinement and R= 0.057 for all data. The standard deviation of an observation of unit weight is 1.770. Minimum and maximum values of final the difference map are -0.477 and 0.268 e.Å^{-3}. The atomic coordinates are listed in Table 1. Tables of anisotropic thermal parameters and observed and calculated structure factors are available from PVR upon request.

RESULTS and DISCUSSION

Figure 2 shows the molecular conformations of the two independent nucleoside molecules in the structure. Bonds lengths and angles are listed in Table 2. The most important conformational parameters of D4G are compared with those of D4A in Table 3.

Both molecules have very similar conformations. This is in contrast to what has been observed for most nucleosides that crystallize with two molecules in the

TABLE 1: Atomic coordinates ($x10^4$ for the non-hydrogen atoms and $x10^3$ for the hydrogen atoms) and isotropic thermal parameters ($x10^2$) for D4G. The e.s.d.'s are given in parentheses. Equivalent isotropic thermal parameters for the non-hydrogen atoms was calculated from the anisotropic thermal parameters using the equation: $B_{eq} = (1/3)\Sigma_i\Sigma_j B_{ij} a_i^* a_j^* a_i.a_j$.

	x	y	z	B_{iso}		x	y	z	B_{iso}
C(2A)	1661(2)	8250(5)	2351(4)	28(1)	C(2B)	3610(2)	11500(6)	-2028(4)	30(1)
C(4A)	1263(2)	8311(5)	4197(3)	25(1)	C(4B)	4049(2)	11422(6)	28(4)	31(1)
C(5A)	1880(2)	9247(5)	4732(3)	25(1)	C(5B)	3452(2)	10448(6)	235(3)	31(1)
C(6A)	2446(2)	9797(6)	4019(3)	26(1)	C(6B)	2869(2)	9919(6)	-789(4)	30(1)
C(8A)	1166(2)	8858(6)	6130(4)	32(1)	C(8B)	4185(3)	10937(7)	2039(4)	42(1)
C(1'A)	34(3)	7210(6)	4999(4)	33(1)	C(1'B)	5262(3)	12646(6)	1444(4)	39(1)
C(2'A)	27(3)	6338(6)	6147(4)	36(1)	C(2'B)	5377(3)	13420(6)	2657(4)	38(1)
C(3'A)	-586(3)	6748(6)	6658(4)	38(1)	C(3'B)	6075(2)	13049(6)	3373(4)	36(1)
C(4'A)	-1083(3)	7875(6)	5899(5)	39(1)	C(4'B)	6512(3)	11936(6)	2739(5)	41(1)
C(5'A)	-1210(3)	9270(7)	6578(6)	49(2)	C(5'B)	6664(4)	10520(8)	3400(7)	59(2)
N(1A)	2281(2)	9215	2810(3)	28(1)	N(1B)	3000(2)	10518(5)	-1918(3)	29(1)
N(2A)	1609(3)	7776(6)	1181(3)	41(1)	N(2B)	3629(3)	11959(6)	-3186(4)	40(1)
N(3A)	1123(2)	7756(5)	3020(3)	29(1)	N(3B)	4166(2)	11988(5)	-1063(3)	34(1)
N(7A)	1817(2)	9582(5)	5958(3)	30(1)	N(7B)	3541(2)	10168(5)	1516(3)	38(1)
N(9A)	806(2)	8049(5)	5103(3)	31(1)	N(9B)	4525(2)	11724(5)	1195(3)	37(1)
O(6A)	3012(2)	10669(5)	4333(2)	37(1)	O(6B)	2298(2)	9038(5)	-810(2)	39(1)
O(4'A)	-651(1)	8155(5)	4888(3)	38(1)	O(4'B)	5978(2)	11784(5)	1518(3)	47(1)
O(5'A)	-452(2)	9866(5)	7183(3)	42(1)	O(5'B)	5954(2)	9959(5)	3797(3)	54(1)
H(N1A)	264(2)	949(4)	234(3)	37(9)	H(N1B)	261(2)	1029(4)	-260(3)	25(8)
H(N2AA)	185(3)	821(6)	73(5)	73(17)	H(N2BA)	344(2)	1150(4)	-379(3)	22(9)
H(N2AB)	115(3)	704(6)	73(5)	78(14)	H(N2BB)	406(3)	1263(6)	-330(5)	64(14)
H(8A)	92(2)	887(4)	690(3)	34(8)	H(8B)	446(2)	1102(4)	299(4)	42(9)
H(1'A)	0(2)	660(4)	421(3)	26(8)	H(1'B)	519(2)	1333(4)	82(3)	28(9)
H(2'A)	36(2)	563(4)	642(3)	36(10)	H(2'B)	504(2)	1407(5)	289(4)	47(11)
H(3'A)	-66(2)	640(4)	740(4)	36(10)	H(3'B)	626(3)	1328(6)	438(4)	70(12)
H(4'A)	-158(2)	742(4)	556(3)	31(9)	H(4'B)	698(3)	1223(5)	257(4)	56(12)
H(5'AA)	-149(2)	898(5)	722(4)	45(11)	H(5'BA)	714(3)	1063(6)	411(5)	73(15)
H(5'AB)	-148(3)	979(6)	586(5)	69(16)	H(5'BB)	687(3)	992(6)	293(4)	57(14)
H(O5'A)	-43(3)	1068(6)	741(5)	60(16)					
C(2C)	9408(4)	8789(8)	2(5)	61(2)	C(2D)	6060(4)	1523(9)	6997(9)	79(3)
C(3C)	9291(4)	7478(8)	530(6)	65(2)	C(3D)	6193(5)	1454(10)	8303(9)	80(3)
C(4C)	8794(4)	7465(10)	1413(8)	76(3)	C(4D)	6587(5)	300(13)	8921(8)	82(3)
C(5C)	8439(4)	8706(11)	1680(6)	70(2)	C(5D)	6847(4)	-793(11)	8274(8)	74(3)
C(6C)	8572(4)	9933(10)	1063(6)	62(2)	C(6D)	6697(4)	-690(11)	6983(8)	70(3)
N(1C)	9056(3)	10020(6)	236(4)	58(1)	N(1D)	6306(3)	426(8)	6332(5)	71(2)
H(2C)	978(3)	893(6)	-61(5)	78(14)	H(2D)	560(3)	233(7)	606(6)	96(16)
H(3C)	967(3)	656(6)	40(5)	73(14)	H(3D)	582(4)	221(7)	847(6)	99(20)
H(4C)	878(3)	665(5)	170(4)	49(13)	H(4D)	664(4)	28(9)	983(7)	117(24)
H(5C)	814(4)	875(8)	223(6)	93(21)	H(5D)	702(4)	-169(8)	853(7)	106(27)
H(6C)	841(3)	1071(5)	118(5)	44(14)	H(6D)	667(3)	-133(7)	643(6)	80(20)

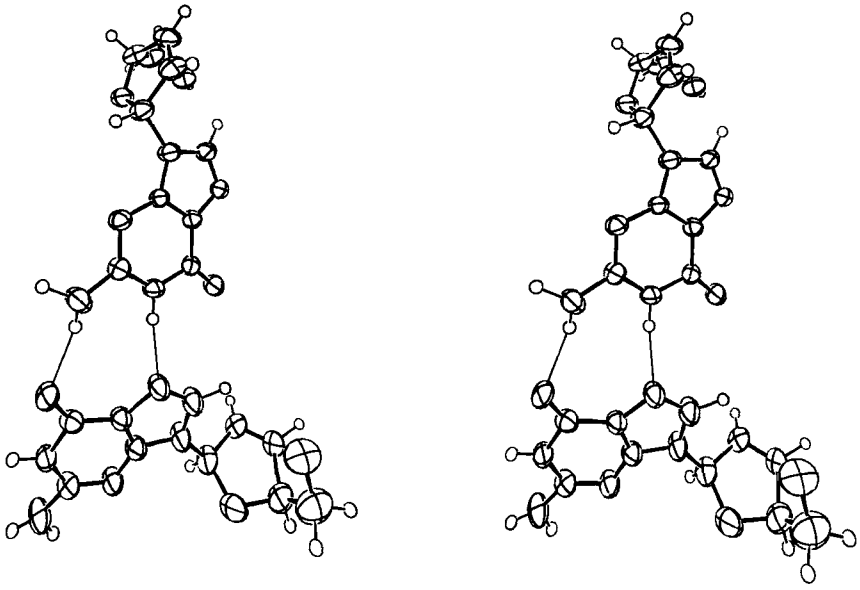

Figure 2: Stereo diagram (ORTEP[12]) showing the molecular conformations of the two independent molecules of D4G in the asymmetric unit and the hydrogen bonds between them.

asymmetric unit where the two molecules have clearly distinct conformations. Least-squares fitting of all atoms in both molecules shows average deviations of 0.099 Å between equivalent atoms and a maximum deviation of 0.149 Å for C8. The glycosyl links are in the *anti* conformation with $\chi \sim -100°$. This conformation, although commonly observed conformation for various nucleosides, is not as common for 2'-deoxyguanosine analogues, which have a greater tendency towards *syn*-conformations[13]. The O5'-hydroxyl groups are in +*sc* conformations. This conformation is stabilized by weak intramolecular contacts between C8 and O5'. The C8•••O5'and H8•••O5' distances are 3.233 and 2.52 Å in molecule A, and 3.269 and 2.63 Å in molecule B, respectively.

The 5-membered rings are very planar. The r.m.s and maximum deviations of planarity listed in Table 3 show that the 5-membered rings are as planar as the bases and that the largest deviations form planarity are observed for C3'A (*endo*) and C4'B (*endo*),

respectively. Because O4' is the only atom that could conceivably deviate significantly form the plane through the 5-atom ring, the magnitude of the deviations of C3'A and C4'B probably indicates the level of precision of the structure. O4' is less than 0.03 Å from the plane of the other four atoms. The pseudorotation torsion angles (P) and maximum torsion angles (ν_m), although not meaningful in view of the absence of ring puckering, are listed in Table 3. The pyridine rings are also very planar with r.m.s. deviations of planarity of 0.011Å and 0.005Å for molecules C and D, respectively.

The main conformational parameters for D4A are compared with those of D4G in Table 3. The three conformations are very similar with the only major difference

TABLE 2: Bond lengths (Å) and Angles (°) for D4G-pyridine.

C(2A)-N(1A)	1.366(5)	C(5B)-C(6B)	1.403(5)
C(2A)-N(2A)	1.331(6)	C(5B)-N(7B)	1.394(5)
C(2A)-N(3A)	1.331(5)	C(6B)-N(1B)	1.399(6)
C(4A)-C(5A)	1.367(6)	C(6B)-O(6B)	1.235(6)
C(4A)-N(3A)	1.353(5)	C(8B)-N(7B)	1.305(6)
C(4A)-N(9A)	1.372(5)	C(8B)-N(9B)	1.372(7)
C(5A)-C(6A)	1.417(6)	C(1'B)-C(2'B)	1.475(7)
C(5A)-N(7A)	1.391(5)	C(1'B)-N(9B)	1.458(6)
C(6A)-N(1A)	1.394(5)	C(1'B)-O(4'B)	1.408(6)
C(6A)-O(6A)	1.223(5)	C(2'B)-C(3'B)	1.296(6)
C(8A)-N(7A)	1.303(6)	C(3'B)-C(4'B)	1.494(8)
C(8A)-N(9A)	1.372(6)	C(4'B)-C(5'B)	1.481(9)
C(1'A)-C(2'A)	1.484(7)	C(4'B)-O(4'B)	1.444(5)
C(1'A)-N(9A)	1.469(6)	C(5'B)-O(5'B)	1.418(8)
C(1'A)-O(4'A)	1.407(6)	C(2C)-C(3C)	1.363(10)
C(2'A)-C(3'A)	1.299(7)	C(2C)-N(1C)	1.317(9)
C(3'A)-C(4'A)	1.465(7)	C(3C)-C(4C)	1.378(11)
C(4'A)-C(5'A)	1.513(9)	C(4C)-C(5C)	1.338(13)
C(4'A)-O(4'A)	1.444(6)	C(5C)-C(6C)	1.351(12)
C(5'A)-O(5'A)	1.398(6)	C(6C)-N(1C)	1.315(9)
C(2B)-N(1B)	1.372(6)	C(2D)-C(3D)	1.393(14)
C(2B)-N(2B)	1.334(6)	C(2D)-N(1D)	1.347(11)
C(2B)-N(3B)	1.323(5)	C(3D)-C(4D)	1.349(14)
C(4B)-C(5B)	1.378(6)	C(4D)-C(5D)	1.343(14)
C(4B)-N(3B)	1.343(6)	C(5D)-C(6D)	1.378(12)
C(4B)-N(9B)	1.378(5)	C(6D)-N(1D)	1.335(11)

(continued)

TABLE 2 Cont.

N(1A)-C(2A)-N(2A)	117.5(3)	C(4B)-C(5B)-C(6B)	119.4(3)
N(1A)-C(2A)-N(3A)	123.4(3)	C(4B)-C(5B)-N(7B)	110.2(3)
N(2A)-C(2A)-N(3A)	119.1(3)	C(6B)-C(5B)-N(7B)	130.3(3)
C(5A)-C(4A)-N(3A)	127.6(3)	C(5B)-C(6B)-N(1B)	111.0(3)
C(5A)-C(4A)-N(9A)	105.7(3)	C(5B)-C(6B)-O(6B)	129.6(3)
N(3A)-C(4A)-N(9A)	126.7(3)	N(1B)-C(6B)-O(6B)	119.4(3)
C(4A)-C(5A)-C(6A)	120.3(3)	N(7B)-C(8B)-N(9B)	113.4(3)
C(4A)-C(5A)-N(7A)	110.8(3)	C(2'B)-C(1'B)-N(9B)	113.6(3)
C(6A)-C(5A)-N(7A)	128.8(3)	C(2'B)-C(1'B)-O(4'B)	105.2(3)
C(5A)-C(6A)-N(1A)	110.7(3)	N(9B)-C(1'B)-O(4'B)	109.8(3)
C(5A)-C(6A)-O(6A)	128.8(3)	C(1'B)-C(2'B)-C(3'B)	110.6(4)
N(1A)-C(6A)-O(6A)	120.5(3)	C(2'B)-C(3'B)-C(4'B)	110.6(4)
N(7A)-C(8A)-N(9A)	113.1(3)	C(3'B)-C(4'B)-C(5'B)	115.2(4)
C(2'A)-C(1'A)-N(9A)	111.6(3)	C(3'B)-C(4'B)-O(4'B)	103.3(3)
C(2'A)-C(1'A)-O(4'A)	105.3(3)	C(5'B)-C(4'B)-O(4'B)	111.9(4)
N(9A)-C(1'A)-O(4'A	110.3(3)	C(4'B)-C(5'B)-O(5'B)	113.4(4)
C(1'A)-C(2'A)-C(3'A)	109.8(4)	C(2B)-N(1B)-C(6B)	125.3(3)
C(2'A)-C(3'A)-C(4'A)	110.9(4)	C(2B)-N(3B)-C(4B)	111.8(3)
C(3'A)-C(4'A)-C(5'A)	116.0(4)	C(5B)-N(7B)-C(8B)	104.5(3)
C(3'A)-C(4'A)-O(4'A)	104.5(3)	C(4B)-N(9B)-C(8B)	106.1(3)
C(5'A)-C(4'A)-O(4'A)	110.9(4)	C(4B)-N(9B)-C(1'B)	125.8(3)
C(4'A)-C(5'A)-O(5'A)	111.3(4)	C(8B)-N(9B)-C(1'B)	128.0(3)
C(2A)-N(1A)-C(6A)	125.6(3)	C(1'B)-O(4'B)-C(4'B)	110.3(3)
C(2A)-N(3A)-C(4A)	112.4(3)	C(3C)-C(2C)-N(1C)	124.9(5)
C(5A)-N(7A)-C(8A)	104.1(3)	C(2C)-C(3C)-C(4C)	117.0(5)
C(4A)-N(9A)-C(8A)	106.2(3)	C(3C)-C(4C)-C(5C)	119.2(6)
C(4A)-N(9A)-C(1'A)	128.6(3)	C(4C)-C(5C)-C(6C)	118.8(6)
C(8A)-N(9A)-C(1'A)	124.9(3)	C(5C)-C(6C)-N(1C)	124.7(6)
C(1'A)-O(4'A)-C(4'A)	109.4(3)	C(2C)-N(1C)-C(6C)	115.4(4)
N(1B)-C(2B)-N(2B)	116.4(3)	C(3D)-C(2D)-N(1D)	120.6(6)
N(1B)-C(2B)-N(3B)	123.7(3)	C(2D)-C(3D)-C(4D)	120.3(7)
N(2B)-C(2B)-N(3B)	119.9(3)	C(3D)-C(4D)-C(5D)	119.8(6)
C(5B)-C(4B)-N(3B)	128.8(3)	C(4D)-C(5D)-C(6D)	118.1(6)
C(5B)-C(4B)-N(9B)	105.8(3)	C(5D)-C(6D)-N(1D)	124.2(6)
N(3B)-C(4B)-N(9B)	125.4(3)	C(2D)-N(1D)-C(6D)	117.0(5)

occuring in the C5'-O5' orientation of D4A which is *ap*. Also, the 5-membered ring is somewhat less planar in D4A than it is in D4G, with r.m.s. deviations of planarity of 0.030 Å and a maximum of 0.040 Å for C4' and O4'. It should be noted that the unsaturated five-membered ring in D4C[14] and D4T[15] are also significantly less planar.

Figure 3 shows the overlap of the two molecules of D4G with that of D4A produced by least-squares fitting the central atoms in the molecules (N9, C1', C2' and

TABLE 3: Most Important Conformational Parameters of D4G and Comparison with those of D4A.

PARAMETER	D4G Mol. A	D4G Mol. B	D4A
N9-C1′ (Å)	1.469(6)	1.458(6)	1.464(3)
χ (C4-N9-C1′-O4′) (°)	-102.3(5)	-94.2(5)	-100.2(3)
γ (C3′-C4′-C5′-O5′) (°)	54.0(6)	47.6(7)	179.8(3)
P (pseudorotation) (°)	38.	244.	243.
ν_m (°)	3.4	3.4	12.1
Deviation of L.S. plane (Å)			
Base r.m.s.	0.018	0.012	0.006
5-membered ring			
r.m.s.	0.013	0.014	0.0
maximum	0.018 (C3′)	0.019 (C4′)	0.040 (C4′)
O4′ distance from plane			
C1′,C2′,C3′,C4′	0.029	0.012	0.094

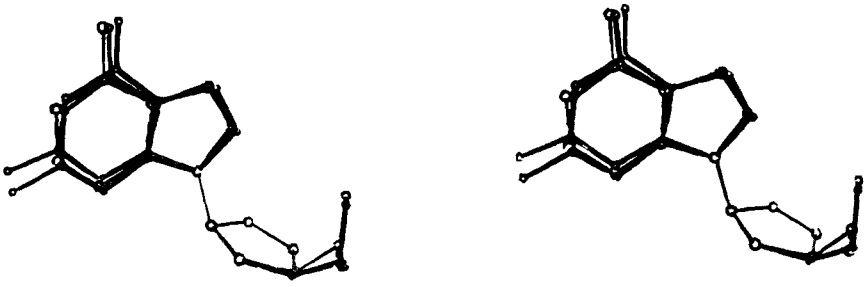

Figure 3: Stereodiagram showing the least-squares overlap of both molecules of D4G and the molecule of D4A. Note that the only difference is in the orientation of the O5′-hydroxyl group of D4A.

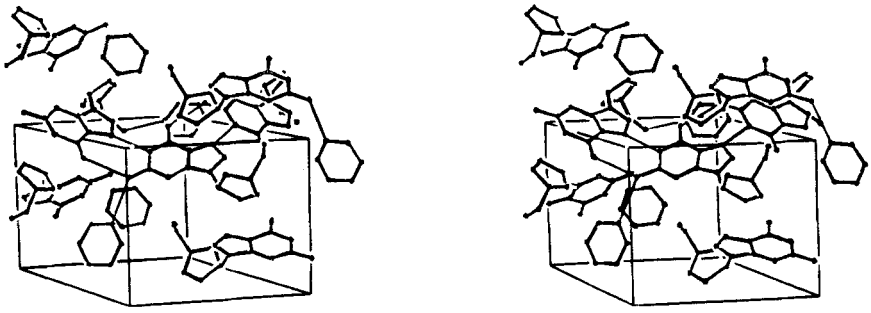

Figure 4: Stereo packing diagram of D4G showing the intermolecular hydrogen bonding between the D4G and the pyridine molecules.

TABLE 4: Geometries of the intermolecular hydrogen bonds in the structure of D4G-pyridine. H•••Y distances for normalized hydrogen atom positions are shown in parenthesis.

X-H•••Y	X•••Y, Å	X-H, Å	H•••Y, Å	X-H•••Y, °	Eq. Position of Y
N1A-HN1A•••N7B	2.860(5)	0.89(4)	1.98(4) (1.79)	172(3)	x,y,z
N2A-HN2AA•••O6B	2.877(5)	0.79(6)	2.10(6) (1.82)	176(4)	x,y,z
N2A-HN2AB•••N1C	3.049(7)	1.06(5)	2.13(6) (2.11)	144(4)	1-x,-.5+y,-z
O5'A-HO5'A•••N3A	2.864(6)	0.78(5)	2.22(5) (2.00)	140(4)	1-x,-.5+y,-z
N1B-HN1B•••N7A	2.838(4)	0.90(3)	1.94(3) (1.76)	174(2)	x,y,-1+z
N2B-HN2BA•••O6A	2.933(5)	0.79(4)	2.16(4) (1.88)	167(3)	x,y,-1+z
N2B-HN2BB•••O5'B	2.945(7)	0.96(5)	2.21(5) (2.13)	133(3)	1-x,.5+y,-z
O5'B-HO5'B•••N1D	2.733(6)				x,1+y,z

O4'). The average distance between equivalent atoms is 0.264 Å in the fit of D4A on D4G A, and 0.280 Å in the fit of D4A on D4G B. This compares to a distance of 0.190 Å in the same fit for molecules A and B of D4G. Excluding O5', the maximum distances from the related atoms in D4A are: in the bases, 0.396 Å for C6 of molecule A and 0.388 Å for C2 of molecule B; and, in the sugar moiety 0.417 Å for C5' in molecule A and 0.219 Å for C5'in molecule B.

Figure 4 shows the crystal packing with the interactions between the nucleoside and pyridine molecules. The intermolecular hydrogen bonds are shown in Table 4. The independent nucleoside molecules have intermolecular base pairing hydrogen bonding that links them into continuous chains in c-direction (A•••B•••A(x,y,z+1)•••B(x,y,z+1)). This base pairing involves N1 and N2 as hydrogen donors for one molecule and N7 and O6 as acceptors for the other. The O5' hydroxyl group of molecule A donates its hydrogen to an N3 of a symmetry related molecule. O5' of molecule B donates its hydrogen to N1 of one of the pyridine molecules and receives one from N2 of a symmetry related molecule. The second pyridine molecule accepts a hydrogen from N2A.

The evaluation of the molecular conformations of two molecules of D4G and one molecule of D4A suggests that the combination of the purine base with a 2',3'-unsaturated sugar moiety would favor one single conformation for the glycosyl link. This is in contrast to most other nucleosides, including 2',3'-unsaturated purine analogues, that are usually observed in two or more conformations often in the same structure. No obvious indication of a correlation between the structures and activity of 2',3'-didehydro-2',3'-dideoxypurines can be drawn from the comparison of the structures of D4A and D4G. The only major difference is in the conformation of the O5' hydroxyl group. Although the more active compound, D4A, has the same *ap* conformation that has been shown to be stabilized in the extreme conformation of the very active saturated nucleosides[4], this is the conformational parameter that is most easily affected by intermolecular interactions in the structure.

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