Solid State and Solution Structures of an Adenine Analogue of the Antiviral Acyclonucleoside 9-(1,3-Dihydroxy-2-propoxymethyl)guanine

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The title compound, 9-(1,3-dihydroxy-2-propoxymethyl)adenine (DHP-Ade), an analogue of the antiviral acyclonucleoside 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG), crystallizes in the monoclinic space group $P2_1$, with unit cell dimensions of a = 10.848(4), b = 8.765(3), c = 11.432(4) Å, β = 102.14(3)°, with two independent molecules in the asymmetric unit.

The crystal structure of DHP-Ade was determined and compared with that for DHPG. The solution conformations of both acyclonucleosides were also determined with the aid of ^{1}H and ^{13}C NMR spectroscopy.

In the solid state the acyclic chain may adopt a "folded" form, *i.e. gauche* about the C(1′)–O(1′) bond (as in DHP-Ade), or an "extended" form (as in DHPG), results which correspond to the rotations about this bond in solution.

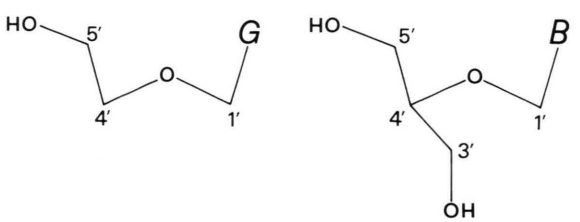
A general discussion is presented of the conformations of the acyclic chains of various acyclonucleosides, from the antiviral 9-(2-hydroxyethoxymethyl)guanine (Acyclovir, ACV) through to 2′,3′-*seco*-nucleosides, both in the solid state and in solution, and the relevance of these to biological activities.

Introduction

Since the advent of Acyclovir (ACV), 9-(2-hydroxyethoxymethyl)guanine (see Scheme 1), an acyclonucleoside analogue of guanosine and a potent antiherpetic agent licensed for clinical use [1], a variety of other acyclonucleosides with differing aglycons and acyclic chains have been synthesized and tested for antiviral activity [2]. These include, amongst others, 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG, see Scheme 1), with *in vitro* antiviral activity superior to that of ACV [3–5]. Simultaneously, several acyclonucleosides have been found to be effective inhibitors in various enzyme systems [6–8].

While the flexibility of the acyclic chains of such compounds would be expected to lead to an equilibrium mixture of different conformers in solution, one of these may mimic a portion of the pentose ring of the parent nucleoside (as is depicted in Scheme 1), a factor which undoubtedly plays some role in its biological activity [9].

Solid state structures and solution conformations have already been reported for several acyclonucleosides [9, 10]. We report here on the crystal structure of DHP-Ade, an adenine ana-



ACV (G = guanine) DHPG (B = guanine) DHP-Ade (B = adenine)

Scheme 1.

Abbreviations: ACV, Acyclovir, 9-(2-hydroxyethoxymethyl)guanine; DHPG, 9-(1,3-dihydroxy-2-propoxymethyl)guanine; DHP-Ade, 9-(1,3-dihydroxy-2-propoxymethyl)adenine. In the text we use primed numbers for the carbon atoms of the acyclic chains (see Scheme 1).

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logue of DHP, as well as its solution conformational equilibria determined by ^1H and ^{13}C NMR spectroscopy. Some ^1H NMR data were also collected for DHPG, permitting a qualitative comparison of its conformation with that of DHP-Ade. Although DHP-Ade itself apparently exhibits no antiviral activity, a number of its phosphorylated derivatives act as substrates in several enzyme systems [11].

Experimental

DHP-Ade was synthesized as described by Ogilvie *et al.* [12]. DHPG was a kind gift of Dr. J. P. Verheyden of Syntex. DHP-Ade ($C_9H_{13}N_5O_3$) was crystallized from aqueous solution in the form of well shaped, monoclinic prisms. The structure has monoclinic space group $P2_1$ and two independent molecules in the asymmetric unit, with unit cell constants a = 10.848(4), b = 8.765(3), c = 11.432(4) Å, β = 102.14(3)°, as determined by least squares refinement of 20 independent reflections measured on a STOE four-circle diffractometer. The data were collected in the $\omega/2\theta$ scan mode with stationary background counts on both sides of each reflection to $2\theta_{max}$ = 120° (CuKα radiation). The crystal structure was solved by direct methods and refined by full matrix least squares calculations using the SHELX program package [14]. In reducing the data, Lorentz and polarization factors were applied and an empirical absorption correction was made [13]. 1560 reflections with intensities greater than $2\sigma(I)$ were considered observed and included in the following analysis. Near the end of the refinement, the hydrogen atoms were located from a difference Fourier syn-

Table I. Final parameters and their standard deviations. $U_{eq} = 1/3\,\Sigma_i\Sigma_j\,U_{ij}\,a_i^*\,a_j^*\,a_i\,a_j$ (Å^2).
U_{iso}: $T = \exp[-8\pi^2U_{iso}(\sin\theta/\lambda)^2]$. * = U_{iso}. (+) = fixed by symmetry. During the refinement following coordinates were fixed: H 3, H 4, H 9, H 3 B, H 4 B, H 9 B, H 13 B.

	Molecule A					Molecule B			
Atom	*x/a*	*y/b*	*z/c*	U_{eq}	Atom	*x/a*	*y/b*	*z/c*	U_{eq}
N 1	0.0908(5)	−0.1426(6)	0.6145(5)	0.062	N 1 B	0.9097(5)	0.1841(5)	0.8828(5)	0.048
C 2	0.1602(6)	−0.1796(6)	0.7267(5)	0.056	C 2 B	0.8406(6)	0.2190(6)	0.7799(6)	0.064
H 1	0.1713(8)	−0.2868(8)	0.7422(8)	0.045*	H 1 B	0.8228(8)	0.3255(8)	0.7676(8)	0.045*
N 3	0.2104(5)	−0.0923(5)	0.8151(5)	0.060	N 3 B	0.7877(5)	0.1294(6)	0.6874(5)	0.057
C 4	0.1832(5)	0.0578(+)	0.7867(5)	0.052	C 4 B	0.8153(5)	−0.0149(5)	0.7146(6)	0.050
C 5	0.1143(6)	0.1151(6)	0.6802(5)	0.052	C 5 B	0.8817(5)	−0.0707(6)	0.8169(5)	0.047
C 6	0.0685(6)	0.0056(6)	0.5896(5)	0.055	C 6 B	0.9336(5)	0.0358(6)	0.9054(5)	0.048
N 7	0.1075(5)	0.2736(5)	0.6876(5)	0.056	N 7 B	0.8905(5)	−0.2294(6)	0.8143(5)	0.054
C 8	0.1702(6)	0.3044(6)	0.7939(5)	0.052	C 8 B	0.8282(6)	−0.2617(6)	0.7057(5)	0.059
H 2	0.1825(8)	0.4068(8)	0.8236(8)	0.045*	H 2 B	0.8185(8)	−0.3637(8)	0.6756(8)	0.045*
N 9	0.2171(5)	0.1816(6)	0.8604(5)	0.053	N 9 B	0.7781(5)	−0.1383(6)	0.6393(4)	0.052
N 10	−0.0011(5)	0.0491(5)	0.4838(4)	0.050	N 10 B	1.0046(6)	0.0031(6)	1.0180(6)	0.080
H 3	−0.0195(0)	0.0003(0)	0.4378(0)	0.068*	H 3 B	0.9749(0)	0.0894(0)	1.0662(0)	0.068*
H 4	−0.0339(0)	0.1501(0)	0.4626(0)	0.068*	H 4 B	0.9925(0)	−0.0234(0)	0.9413(0)	0.068*
C 1′	0.2949(6)	0.1789(6)	0.9821(5)	0.054	C 1 B′	0.7063(6)	−0.1364(6)	0.5207(6)	0.063
H 5	0.2976(8)	0.0759(8)	1.0113(8)	0.066*	H 5 B	0.7480(8)	−0.1986(8)	0.4717(8)	0.066*
H 6	0.2552(8)	0.2431(8)	1.0317(8)	0.066*	H 6 B	0.7019(8)	−0.0332(8)	0.4921(8)	0.066*
O 1′	0.4172(5)	0.2297(5)	0.9908(4)	0.054	O 1 B′	0.5819(4)	−0.1907(5)	0.5100(4)	0.052
C 3′	0.5060(6)	0.1972(6)	0.8135(6)	0.080	C 3 B′	0.4867(5)	−0.1543(6)	0.6804(5)	0.048
H 7	0.4228(8)	0.2002(8)	0.7632(8)	0.066*	H 7 B	0.4267(8)	−0.0937(8)	0.7111(8)	0.066*
H 8	0.5589(8)	0.1312(8)	0.7782(8)	0.066*	H 8 B	0.5666(8)	−0.1519(8)	0.7362(8)	0.066*
O 3′	0.5591(5)	0.3522(6)	0.8257(5)	0.080	O 3 B′	0.4453(5)	−0.3009(5)	0.6697(4)	0.063
H 9	0.5052(0)	0.4305(0)	0.8582(0)	0.193*	H 9 B	0.5441(0)	−0.2665(0)	0.7429(0)	0.193*
C 4′	0.4979(5)	0.1373(5)	0.9374(5)	0.042	C 4 B′	0.5028(6)	−0.0873(6)	0.5624(6)	0.064
H 10	0.4649(8)	0.0359(8)	0.9223(8)	0.045*	H 10 B	0.5391(8)	0.0129(8)	0.5748(8)	0.045*
C 5′	0.6235(6)	0.1258(6)	1.0243(5)	0.058	C 5 B′	0.3774(5)	−0.0814(6)	0.4772(6)	0.058
H 11	0.6567(8)	0.2270(8)	1.0399(8)	0.066*	H 11 B	0.3206(8)	−0.0184(8)	0.5102(8)	0.066*
H 12	0.6789(8)	0.0665(8)	0.9872(8)	0.066*	H 12 B	0.3444(8)	−0.1833(8)	0.4660(8)	0.066*
O 5′	0.6196(4)	0.0571(5)	1.1354(4)	0.048	O 5 B′	0.3888(5)	−0.0215(6)	0.3634(5)	0.070
H 13	not found				H 13 B	0.4475(0)	0.0809(0)	0.3967(0)	0.193*

thesis except for one of the two O(5′) hydrogens. The refinement of the positional and anisotropic temperature parameters of the non-hydrogen atoms and isotropic temperature parameters for the hydrogen atoms converged at $R = 5.3\%$.

NMR spectroscopy, at frequencies of 270.13 MHz for ^1H and 67.93 MHz for ^{13}C, were recorded on a Bruker 270 AM instrument at a concentration of 0.05 M in $(CH_3)_2SO$ at a temperature of 30 °C. Chemical shifts, *vs.* internal Me_4Si, are accurate to ±0.005 ppm; and coupling constants to an accuracy of ±0.1 Hz for $^1H-^1H$ and ±0.3 Hz for $^1H-^{13}C$.

Results and Discussion

Solid-state structure of DHP-Ade

In Table I are listed the atomic parameters of DHP-Ade from which the atomic distances and bond angles were calculated (Table II). Corresponding bond lengths and bond angles in the two molecules deviate in some cases (s. Table II) by 0.05 Å and 4° which we associate with different conformations and crystal environment of the two molecules.

The conformation of the two molecules in the asymmetric units is described by the torsion angles

Table II. Bond distances (Å) and angles (°) and their standard deviations (in parentheses).

Molecule A		Molecule B	
C2–N1	1.383(7)	C2B–N1B	1.292(7)
C6–N1	1.341(7)	C6B–N1B	1.340(7)
C6–N1–C2	117.6(5)	C6B–N1B–C2B	117.2(5)
N3–C2	1.293(8)	N3B–C2B	1.345(8)
N3–C2–N1	130.1(5)	N3B–C2B–N1B	130.4(5)
C4–N3	1.372(5)	C4B–N3B	1.322(7)
C4–N3–C2	110.4(5)	C4B–N3B–C2B	109.6(5)
C5–C4	1.382(7)	C5B–C4B	1.331(8)
C5–C4–N3	127.3(4)	C5B–C4B–N3B	127.8(5)
N9–C4	1.375(6)	N9B–C4B	1.389(7)
N9–C4–N3	126.5(5)	N9B–C4B–N3B	125.3(5)
N9–C4–C5	106.1(3)	N9B–C4B–C5B	106.9(4)
C6–C5	1.423(7)	C6B–C5B	1.404(7)
C6–C5–C4	115.9(4)	C6B–C5B–C4B	116.7(5)
N7–C5	1.395(7)	N7B–C5B	1.395(7)
N7–C5–C4	109.5(5)	N7B–C5B–C4B	112.0(5)
N7–C5–C6	134.5(5)	N7B–C5B–C6B	131.3(5)
C5–C6–N1	118.6(5)	C5B–C6B–N1B	118.3(5)
N10–C6	1.339(7)	N10B–C6B	1.383(8)
N10–C6–N1	120.7(5)	N10B–C6B–N1B	115.3(5)
N10–C6–C5	120.6(5)	N10B–C6B–C5B	126.3(5)
C8–N7	1.291(8)	C8B–N7B	1.313(7)
C8–N7–C5	104.0(5)	C8B–N7B–C5B	102.2(5)
N9–C8	1.354(7)	N9B–C8B	1.366(7)
N9–C8–N7	115.0(5)	N9B–C8B–N7B	114.8(5)
C1′–N9	1.469(7)	C1B′–N9B	1.415(8)
C1′–N9–C4	126.5(4)	C1B′–N9B–C4B	127.9(5)
C1′–N9–C8	128.1(5)	C1B′–N9B–C8B	128.1(5)
O1′–C1′	1.383(7)	O1B′–C1B′	1.412(8)
O1′–C1′–N9	114.5(5)	O1B′–C1B′–N9B	113.7(6)
C4′–O1′	1.421(7)	C4B′–O1B′	1.460(8)
C4′–O1′–C1′	117.0(4)	C4B′–O1B′–C1B′	112.9(4)
O5′–C5′	1.414(7)	O5B′–C5B′	1.433(8)
C4′–C5′–O5′	115.2(5)	C4B′–C5B′–O5B′	111.2(5)
C5′–C4′	1.512(8)	C5B′–C4B′	1.498(8)
C5′–C4′–O1′	107.9(4)	C5B′–C4B′–O1B′	106.7(5)
C3′–C4′	1.530(8)	C3B′–C4B′	1.516(8)
C3′–C4′–O1′	111.3(4)	C3B′–C4B′–O1B′	108.2(4)
C3′–C4′–C5′	114.3(5)	C3B′–C4B′–C5B′	109.4(5)
C3′–O3′	1.471(8)	C3B′–O3B′	1.359(7)

in Table III and by Fig. 1. In both molecules, the torsion angles C(4)–N(9)–C(1′)–O(1′) (corresponding to the glycosidic torsion angle χ in nucleosides) are comparable but differ in sign, *viz.* 104.3° for molecule A and −107.5° for molecule B. Since this behaviour is seen for all the torsion angles given in Table III, the absolute magnitude being about the same, whereas the signs differ, molecules A and B are related structurally by a mirror plane. This indicates that the observed conformation in the crystal is preferred over others that this flexible molecule can in principle adopt, as we know from solution studies (see below).

The packing of the molecules in the crystal is such that the adenine heterocycles are stacked in a hydrophobic region along the $a-b$ plane and the hydrophilic substituents form a hydrophilic layer. There is extensive hydrogen bonding between the hydroxyl groups and the amino groups of the adenines, as indicated in Table IV.

Table III. Torsion angles (°) (a), molecule A (b), molecule B.

Angles	(a)	(b)
C4–N9–C1′–O1′	104.3	−107.5
N9–C1′–O1′–C4′	−68.0	70.0
C1′–O1′–C4′–C5′	−135.5	137.8
O1′–C4′–C5′–O5′	61.5	−61.9
O1′–C4–C3′–O3′	61.4	−52.6
O3′–C3′–C4′–C5′	−61.1	62.3
C3′–C4′–C5′–O5′	−174.2	−178.8

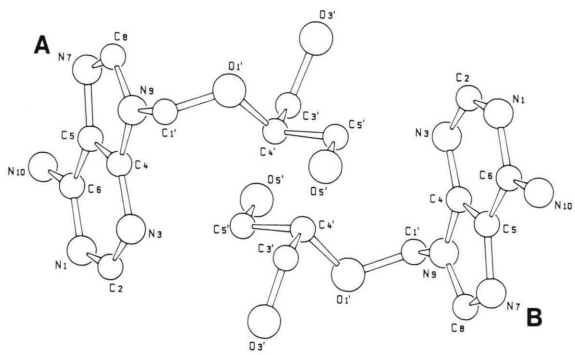

Fig. 1.

Comparison of DHP and DHP-Ade

Comparison of the solid state structures of DHP-Ade and DHPG*, which have a common acyclic chain that mimics the upper portion of the pentose ring but with different aglycons, demonstrates differences in conformation about the C–O bonds, which define the overall shapes of the molecules.

In DHP-Ade the atoms N(9) and C(4′) are located in a typical *gauche* orientation relative to each other about the C(1′)–O(1′) bond (Table III); whereas in DHPG the orientation is close to *trans*, and the torsion angle N(9)–C(1′)–O(1′)–C(4′) is −152.1°. DHP-Ade exhibits a non-typical conformation about the O(1′)–C(4′) bond with a torsion angle for C(1′)–O(1′)–C(4′)–C(5′) of −135.5°, hence deviating from the classical *trans* form by 44°. The analogous conformer of DHPG shows a considerably smaller deviation (23°) from the classical *trans* form. The acyclic chain of DHP-Ade is consequently more folded relative to the extended form of the chain in DHPG, so that its

* We are indebted to Dr. R. L. Tolman for diffraction data for DHPG.

Table IV. Hydrogen-bond distances (Å) and angles (°).

Donor atom	Acceptor atom	Position of acceptor atom	Distance D···A	Distance H···A	Angle	
N10	N7	$-x,y-0.5,1-z$	3.170	2.52	N10–H3–N7	164
N10	N1	$-x,y+0.5,1-z$	3.009	2.06	N10–H4–N1	168
O3′	O5′	$1-x,y+0.5,2-z$	2.747	1.76	O3′–H9–O5′	160
N10B	N7B	$2-x,y+0.5,2-z$	3.090	2.38	N10B–H3B–N7B	125
N10B	N7B	x,y,z	3.146	2.43	N10B–H4B–N7B	137
O5B′	O3B′	$1-x,y+0.5,1-z$	2.722	1.84	O5B′–H13B–O3B′	133
O5B′	O1B′	$1-x,y+0.5,1-z$	3.226	1.84	O5B′–H13B–O1B′	136

$C(3')H_2OH$ strongly interacts with the adenine base. The vicinal oxygens exhibit a *gauche* orientation about the C–C bonds, except for the C(4′)–C(5′) bond in DHPG, where O(1′) and O(5′) are *trans*. One of the independent molecules of DHP-Ade in the unit cell exhibits a conformation about the glycosidic bond similar to that in DHPG (corresponding to the *syn* form in normal nucleosides), but with a glycosidic torsion angle differing by 34° (the angle C(4)–N(9)–C(1′)–O(1′) in DHPG is 69.7°).

Acyclonucleosides may adopt a large number of conformations with only minimal differences in energy. Quantum mechanical calculations have shown the existence, in DHPG, of 10 energy minima located less than 1 kcal mol^{-1} above the global minimum [15].

The minimum corresponding to the solid-state structure is 3.7 kcal mol^{-1} above the global minimum. The preferred theoretically derived "folded" conformations, which assure stronger interactions between the aglycon and the acyclic chain, are in better correspondence with the solid-state structure of DHP-Ade.

Solution conformation

Determination of solution conformations was based on analyses of ^1H and ^{13}C NMR spectra in the case of DHP-Ade and the ^1H NMR spectrum in the case of DHPG. The measured NMR parameters, chemical shifts and coupling constants, are listed in Table V. The methods used are those previously applied to a variety of acyclonucleosides and acyclonucleotides [11].

Analysis of the vicinal proton-proton coupling constants $J[^1H(3'),^1H(4')]$ and $J[^1H(3''),^1H(4')]$ leads to the conformation about the C(3′)–C(4′) bond; and of $J[^1H(4'),^1H(5')]$ and $J[^1H(4'),^1H(5'')]$ to the conformation about the C(4′)–C(5′) bond. Application of the modified Karplus relationship of Haasnot *et al.* [16] to foregoing, as elsewhere described [11], reveals rotation about these bonds, involving a dynamic equilibrium of three classical conformers with *gauche* and *trans* orientation of vicinal oxygens. Because of the symmetry of the system, $\delta H(5') = \delta H(3')$ and $\delta H(5'') = \delta H(3'')$, only mean values of conformer populations can be determined; and these are similar for all three allowable conformers, 30–40%.

The conformation about the glycosidic bond C(1′)–N(9) may be evaluated from the values of proton-carbon coupling constants, as described by Davies *et al.* [17]. For DHP-Ade, comparison of $J[^1H(1'),^{13}C(4)]$ and $J[^1H(1'),^{13}C(8)]$ (Table V) with those for "normal" nucleosides, where conformations about glycosidic bonds have been accurately determined [17], leads to a two-state dynamic equilibrium, with a slightly higher population (~60%) of the conformer which formally corresponds to the *syn* conformation in normal nucleosides. A similar conformation may be expected for DHPG, based on the similarity of its ^1H spectrum with that for DHP-Ade (Table V).

The conformation of the acyclic chain about the C–O bonds, particularly important for establishment of the overall shape of the molecule, is rather difficult since there is no adequate Karplus relationship between $^1H-^{13}C$ vicinal coupling constants and the torsion angles in the appropriate

Table V. Values of ^1H chemical shifts (in ppm *vs.* internal Me_4Si) and some $^1H-^1H$ and $^1H-^{13}C$ coupling constants for DHP-Ade and DHP in $(C^2H_3)_2SO$ at a temperature of 30 °C.

	H(2)	H(8)	H(1′)	H(1″)	H(3′)	H(3″)	H(4′)	H(5′)	H(5″)	
DHP-Adenine	8.16	8.24	5.65	5.65	3.43	3.31	3.61	3.43	3.31	
DHPG	–	7.79	5.44	5.44	3.43	3.30	3.54	3.43	3.30	
			$J(^1H,^1H)$[a]						$J(^1H,^{13}C)$[b]	
	3′,3″	3′,4′	3″,4′	4′,5′	4′,5″	5′,5″	1′,4	1′,8	4′,1′	1′,4′
DHP-Adenine	11.4	4.8	5.8	4.8	5.8	11.4	3.2	4.2	5.3	4.5
DHPG	11.3	4.8	5.6	4.8	5.6	11.3	–	–	–	–

[a] Because of the magnetic equivalence of $C(3')H_2OH$ and $C(5')H_2OH$, it is possible to determine only the mean values of the coupling constants between these protons and H(4′).

[b] Because of magnetic equivalence of H(1′) and H(1″), only mean values can be measured for coupling constants in which they are involved.

fragment of the molecule; and because it is possible to measure only the one coupling constant $J[^1H(1'),^{13}C(1')]$, and only the *mean* of the two coupling constants $J[^1H(1'),^{13}C(4')]$ (see Table V). However, it is feasible to distinguish between two cases, *viz.* one rigid conformation, or a dynamic equilibrium of several allowable conformers [11]. For C(4′)−O(1′) in DHP-Ade, one (extended) form predominates, with C(5′) and C(1′) *trans* to each other, the torsion angle deviating ~20° from the classical 180°. On the other hand, rotation about C(1′)−O(1′) is observed, with comparable populations of conformers with *gauche* and *trans* orientations of N(9) and C(4′). The conformation of DHPG about C−O bonds may be inferred to be similar from the resemblance of its ^1H spectrum to that of DHP-Ade (Table V).

Hence the overall conformation of DHP-Ade and DHPG, determined from orientations about C−O bonds, are similar both in solution and in the solid. There is, however, a marked preference for *gauche* orientations of oxygens on neighbouring carbons in the crystal relative to that in solution.

Concluding Remarks

The conformation of acyclonucleosides in which the pentose ring is replaced by the 1,3-dihydroxy-2-propoxymethyl (DHP) chain resembles that of ACV. This is so in the solid state, where there are 3 independent molecules in the asymmetric unit, 2 in the "folded" form, *gauche* about the C(1′)−O(1′) bond, and 1 in the extended form, *trans* about the same bond [18]; and also in solution, with observed rotation about C(1′)−O(1′) [11]. In each case the form *trans* about C(4′)−O(1′) is predominant. By contrast, the conformation of the 2′,3′-*seco* chain, which is a DHP chain with an additional C(2′)H_2OH group, is more rigid, with a preference for the extended form from C(2′) to C(5′) in the crystal [10] and in solution [11].

The foregoing differences in conformation undoubtedly play some role in the biological activities of conformationally flexible acyclonucleosides like ACV and DHPG, which are specific substrates for viral kinases and potent antiherpes agents [19], as compared to the inactive 2′,3′-*seco*-nucleosides [11, 19]. This is undoubtedly related to the ability of the "flexible" chains to mimic the conformation of the pentose residue of the parent nucleoside, and is deserving further investigation.

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