Crystal Structure and Conformation of the 3′-*O*-Methyl Derivative of 1-β-D-Arabinofuranosylcytosine[1]

G. I. Birnbaum,*[2a] E. Darżynkiewicz,[2b] and D. Shugar[2c]

Contribution from the Division of Biological Sciences, National Research Council, Ottawa, Ontario, Canada, Department of Biophysics, Institute of Experimental Physics, University of Warsaw, 02-089 Warszawa, Poland, and the Departement de Biochimie, Faculté de Médecine, Université Laval, Québec 10, Québec, Canada. *Received January 2, 1975*

Abstract: The three-dimensional structure of the 3′-*O*-methyl derivative of 1-β-D-arabinofuranosylcytosine, $C_{10}H_{15}N_3O_5$ (araC), was determined by X-ray crystallography. The substance crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules in a unit cell with dimensions $a = 12.721 \pm 0.002$, $b = 12.229 \pm 0.001$, and $c = 7.522 \pm 0.002$ Å. Intensity data were collected with a diffractometer and the structure was solved by direct methods. Anisotropic refinement by least squares converged at R 0.038 for 1140 observed reflections. The conformation about the glycosidic bond is, as usual, anti. The pucker of the sugar ring is C(2′) endo, very similar to that of the unmethylated arabinofuranosylcytosine. However, the conformation about the exocyclic C(4′)–C(5′) bond is, somewhat unexpectedly, gauche-trans, thus precluding the formation of an intramolecular hydrogen bond between O(5′) and O(2′). The orientation of the methyl group attached to O(3′) is + antiperiplanar with respect to C(4′). The results are discussed in relation to reported data on the solution and solid-state conformations of various arabinosyl nucleosides, including those with antiviral and antitumour activities. In particular, the conformations in the solid state of araC (and other nucleosides) are appreciably modified by O′-methylation, whereas the solution conformations are only minimally affected by such methylation.

The known antiviral and antitumour activities of arabinosyl nucleosides such as 1-β-D-arabinofuranosylcytosine (araC)[3,4] and 1-β-D-arabinofuranosyladenine[4,5] have stimulated considerable interest in the structure and conformation of these antimetabolites. Although it is the conformation in aqueous medium which is of major interest in relation to the biological activity of a given analog, a fact frequently overlooked by many observers, structure determinations by crystallographic methods have proven of considerable value in the interpretation of NMR data on the solution conformation of nucleosides and nucleoside analogs.[6] The crystal structures of a number of arabinosyl nucleosides have now been reported[7-15] (see Discussion, below).

We report here on the structure and conformation in the solid state of an araC analog etherified on one of the sugar hydroxyls, 3′-OMe-araC. The solution conformation of this derivative does not appear to differ appreciably from that of the parent araC.[16] Unlike araC, the therapeutic efficiency of which is frequently reduced as a result of intracellular enzymatic deamination (for review see ref 17), the susceptibility of 3′-OMe-araC to cytidine deaminase is too low to be detectable (E. Krajewska, personal communication). Despite this, the in vitro antiviral activity of this analog is essentially *nil*.[18]

Additional interest attaches to crystallographic determinations of the structure and conformation of *O*′-alkyl nucleosides in general because of the widespread occurrence of 2′-*O*-methyl nucleosides in tRNA[19,20] and of 2′-*O*-ethyl nucleosides in the tRNA of L-ethionine induced hepatic carcinoma.[21] Preliminary reports have appeared on the solid-state structures of 2′-*O*-methylcytidine[22] and 2′-*O*-methyladenosine.[23]

Experimental Section

3′-OMe-araC, $C_{10}H_{15}N_3O_5$, was prepared according to the method of Darżynkiewicz et al.[24] It was crystallized from water to give colorless prisms (mp 264–266°) with a diamond-shaped cross section. Precession photographs indicated orthorhombic symmetry with systematic absences of reflections $h00$ for h odd, $0k0$ for k odd, and $00l$ for l odd. The space group was thus uniquely determined to be $P2_12_12_1$. A crystal fragment with dimensions 0.3 × 0.3 × 0.4 mm was mounted along the prism (c) axis on a card-controlled Picker four-circle diffractometer. Cell dimensions were determined from angular settings of 11 high-angle reflections and both Cu $K\alpha_1$ (λ 1.54051 Å) and Cu $K\alpha_2$ (λ 1.54433 Å) radiations were used. The following crystal data were obtained: $a = 12.721 \pm 0.002$, $b = 12.229 \pm 0.001$, $c = 7.522 \pm 0.002$ Å; $V = 1170.2$ Å^3; $d_x = 1.46$ g cm^{-3}; $Z = 4$; $F(000) = 544$; μ (Cu $K\alpha$) = 10.8 cm^{-1}.

The moving-crystal–moving-counter method (ω–2θ scan) was used to collect the intensity data and monochromatization was achieved by the use of a nickel filter and pulse height analyzer. A net count of 50 or 10% of the background, whichever was higher, was determined as threshold intensity below which reflections were considered unobserved. There were 1155 unique reflections accessible to the diffractometer ($2\theta \leq 129°$) of which 1148 had intensities above threshold values. The intensities were corrected for Lorentz and polarization factors; in view of the low value of μ and the regular shape of the crystal, absorption corrections were considered unnecessary.

The structure was determined by direct methods by use of a multisolution procedure similar to that described by Kennard et al.[25] With $\alpha_{min} = 2.45$ and $t_{min} = 0.3$, one of the permutations yielded $R_E = 0.22$ for 260 reflections with $E \geq 1.20$ after a tangent refinement carried out in four steps. The E map revealed the positions of all 18 nonhydrogen atoms. Atomic parameters were refined by block-diagonal least squares. The scattering factors for C, N, and O were those given by Hanson et al.[26] and those of Stewart et al.[27] were used for bonded H. The oxygen curve was corrected for anomalous dispersion.[28] All hydrogen atoms were located on difference Fourier maps; their contributions were included in the calculations of structure factors but their parameters were not refined. Throughout the refinement the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized and a factor of 0.8 was applied to all shifts. The following weighting scheme was used during the final stages: $w = w_1w_2$, where $w_1 = 1$ for $|F_o| \leq 6$, $w_1 = 6/|F_o|$ for $|F_o| > 6$; and $w_2 = \sin^2\theta/0.4$ for $\sin^2\theta < 0.4$, $w_2 = 1$ for $\sin^2\theta \geq 0.4$. Eight strong reflections suffered severely from extinction effects and they were given zero weights. After the final cycle the average parameter shift equalled 0.07 σ and the largest one 0.26 σ. The agreement index $R(\Sigma|\Delta F|/\Sigma|F_o|)$ is 0.038 and the weighted index $R'(\Sigma w\Delta F^2/\Sigma wF_o^2)$ is 0.046 for 1140 observed reflections. A final difference Fourier map was featureless.

Results

The final coordinates and temperature parameters, as well as their estimated standard deviations, are listed in Table I. The precise molecular geometry can be seen in Figure 1 which gives the torsional angles in the arabinose ring as well as all bond lengths and bond angles. The conformation of the molecule can best be seen in the stereographic representation shown in Figure 2. The pyrimidine ring is

Table I. Final Parameters and Their Standard Deviations

(a) Nonhydrogen Atoms[a]

Atom	x	y	z	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{13}$	$2U_{12}$
N(1)	11,851 (14)	23,569 (14)	49,263 (27)	20 (1)	24 (1)	28 (1)	3 (1)	−2 (2)	5 (1)
C(2)	20,041 (17)	16,724 (17)	54,919 (31)	21 (1)	24 (1)	30 (1)	1 (2)	−8 (2)	1 (2)
O(2)	28,840 (12)	17,810 (14)	48,061 (25)	20 (1)	38 (1)	49 (1)	18 (2)	5 (2)	4 (1)
N(3)	18,083 (15)	9,210 (15)	67,756 (26)	27 (1)	26 (1)	31 (1)	9 (2)	−6 (2)	4 (1)
C(4)	8,424 (18)	7,856 (18)	74,012 (28)	30 (1)	25 (1)	22 (1)	−6 (2)	−4 (2)	−1 (2)
N(4)	6,803 (18)	−240 (17)	85,668 (29)	40 (1)	34 (1)	31 (1)	15 (2)	7 (2)	6 (2)
C(5)	−100 (18)	14,432 (19)	68,004 (33)	27 (1)	32 (1)	31 (1)	8 (2)	9 (2)	6 (2)
C(6)	1,907 (17)	22,084 (18)	55,511 (32)	23 (1)	26 (1)	30 (1)	0 (2)	0 (2)	6 (2)
C(1′)	14,265 (17)	31,163 (17)	34,755 (31)	22 (1)	23 (1)	31 (1)	8 (2)	3 (2)	1 (2)
O(1′)	6,813 (13)	39,716 (12)	34,907 (20)	33 (1)	24 (1)	25 (1)	−1 (1)	−3 (1)	15 (1)
C(2′)	13,470 (17)	25,794 (18)	16,378 (32)	26 (1)	24 (1)	31 (1)	0 (2)	8 (2)	8 (2)
O(2′)	4,761 (14)	18,696 (12)	15,349 (24)	38 (1)	22 (1)	39 (1)	−3 (1)	−8 (2)	−4 (1)
C(3′)	11,121 (18)	35,770 (18)	4,862 (30)	30 (1)	23 (1)	26 (1)	2 (2)	9 (2)	−2 (2)
O(3′)	20,435 (14)	41,894 (14)	1,558 (25)	38 (1)	34 (1)	44 (1)	−4 (2)	33 (2)	−14 (1)
CO(3′)	26,572 (30)	37,647 (28)	−12,669 (52)	61 (2)	53 (2)	65 (2)	−19 (3)	73 (4)	−14 (3)
C(4′)	4,091 (17)	42,648 (16)	16,598 (28)	30 (1)	19 (1)	22 (1)	5 (2)	0 (2)	1 (2)
C(5′)	−7,550 (18)	41,118 (17)	13,757 (31)	29 (1)	20 (1)	30 (1)	0 (2)	−3 (2)	2 (2)
O(5′)	−12,970 (12)	49,740 (12)	22,475 (25)	25 (1)	23 (1)	50 (1)	−1 (1)	9 (1)	−6 (1)

(b) Hydrogen Atoms[b]

	x	y	z		x	y	z		x	y	z
H1N(4)	3	−3	935	H(2′)	204	224	120	H2(5′)	−86	406	−9
H2N(4)	128	−38	917	HO(2′)	79	114	204	HO(5′)	−189	463	253
H(5)	−68	131	762	H(3′)	71	324	−62	H1CO(3′)	220	384	−222
H(6)	−39	275	496	H(4′)	63	512	128	H2CO(3′)	267	297	−128
H(1′)	212	333	354	H1(5′)	−102	341	195	H3CO(3′)	335	423	−133

[a] The coordinates were multiplied by 10^5 and the thermal parameters by 10^3. The thermal parameters are expressed as $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{13}hla^*c^* + 2U_{12}hka^*b^*)]$. [b] The coordinates were multiplied by 10^3; they were obtained from a difference Fourier map.

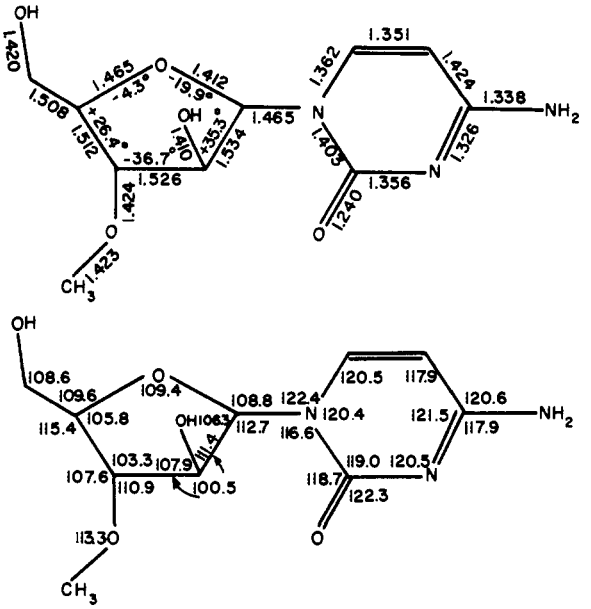

Figure 1. Molecular geometry. Top: torsional angles in the sugar ring in degrees (their esd's are 0.2°) and bond lengths in ångströms (esd's are 0.002–0.004 Å). Bottom: bond angles in degrees (esd's are 0.2°).

Table II. Least-Squares Planes and Deviations of Atoms from Them[a]

Plane 1[b]		Plane 2[b]		Plane 3[b]	
Atom	Δ, Å[c]	Atom	Δ, Å[c]	Atom	Δ, Å[c]
N(1)	−0.017	C(1′)	0.176	C(1′)	0.019
C(2)	0.027	C(2′)	−0.233	C(3′)	−0.018
N(3)	−0.011	C(3′)	0.204	C(4′)	0.025
C(4)	0.000	C(4′)	−0.104	O(1′)	−0.015
C(5)	0.003	O(1′)	−0.043	C(2′)*	0.582
C(6)	0.010			N(1)*	0.852
C(1′)*	0.093				
O(2)*	0.092				
N(4)*	0.064				

Dihedral angles (deg) between planes: 1,2 59.4; 1,3 51.8

[a] Atoms marked with an asterisk were not included in the calculation of the plane. [b] Plane 1: $0.1954X + 0.6639Y + 0.7218Z - 4.8652 = 0$. Plane 2: $0.8365X + 0.5474Y - 0.0240Z - 3.3645 = 0$. Plane 3: $0.7243X + 0.6890Y + 0.0270Z - 4.0298 = 0$. [c] Esd's are 0.002 Å.

significantly nonplanar, the largest deviation from the least-squares plane being 0.027 (2) Å (Table II). The bond lengths and angles agree very well with those found in araC. The conformation of the arabinose ring is given by the endocyclic torsional angles (Figure 1) from which the phase angle of pseudorotation (P) can be calculated. The value of P (167.8°) corresponds to a C(2′) endo pucker ($^2T_3$) and the displacement of C(2′) from the least-squares plane through the other four atoms in the ring amounts to 0.582 (2) Å. The dihedral angle between this best plane and the plane of the pyrimidine ring is 51.8°. The conformation about the glycosidic bond is, as usual, anti, the torsional angle (χ) O(1′)-C(1′)-N(1)-C(6) being 28.7°. This is approximately within the expected range, if allowance is made for steric hindrance to rotation about this bond by the "up" 2′-OH. A Newman projection along this bond is shown in Figure 3a. The position of O(5′) with respect to the sugar ring is described by the two torsional angles, O(5′)-C(5′)-C(4′)-O(1′) and O(5′)-C(5′)-C(4′)-C(3′). These angles are 74.1 and −166.6°, respectively, corresponding to a gauche-trans conformation (Figure 3b). The orientation of the methyl group attached to O(3′), also shown in a Newman projection, is + antiperiplanar relative to C(4′).[29] As can be seen in Figure 3c, the O(3′)-CO(3′) bond is not exactly staggered. In this connection it should be noted that the distance between one of the hydrogen atoms of this methyl group and H(2′) is 2.2 Å, corresponding to van der Waals contact. Some additional torsional angles are given in Table III.

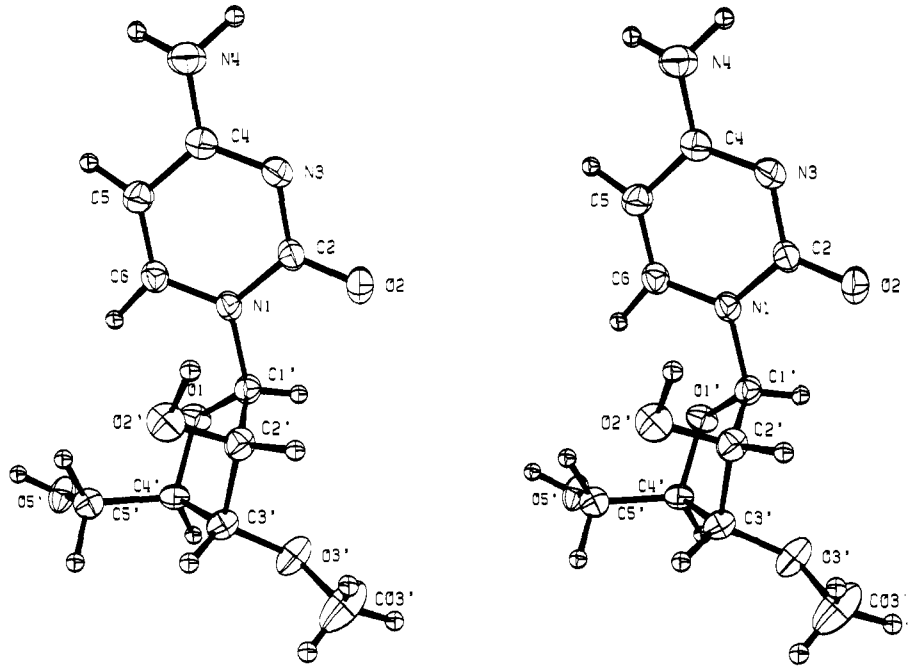

Figure 2. Stereoscopic view of the molecule; the thermal ellipsoids correspond to 50% probability. Hydrogen atoms are represented by spheres with an arbitrary radius.

Table III. Some Torsional Angles (deg)

N(1)–C(1′)–C(2′)–C(3′)	+154.4
N(1)–C(1′)–C(2′)–O(2′)	+40.3
N(1)–C(1′)–O(1′)–C(4′)	−141.5
C(1′)–C(2′)–C(3′)–O(3′)	+78.2
O(2′)–C(2′)–C(3′)–O(3′)	−165.1
O(2′)–C(2′)–C(3′)–C(4′)	+80.0
C(2′)–C(3′)–C(4′)–C(5′)	−94.9
O(3′)–C(3′)–C(4′)–C(5′)	+147.8
O(3′)–C(3′)–C(4′)–O(1′)	−90.9
C(1′)–O(1′)–C(4′)–C(5′)	+120.8

Several bond angles in the vicinity of C(3′) differ from values usually observed in arabinonucleosides in which the sugar ring is in the C(2′) endo conformation. The angle C(2′)-C(3′)-O(3′) is larger than average while O(2′)-C(2′)-C(3′) and O(3′)-C(3′)-C(4′) are smaller than average. Except for the C(4′)-O(1′) bond, which is longer than average, all bond lengths in the arabinose moiety are normal. All distances and angles involving hydrogen atoms are normal and they are not tabulated. The following nonbonded distances in the vicinity of the glycosidic bond are shorter than normal van der Waals contacts: N(1)···O(2′), 2.771; O(1′)···C(6), 2.728; O(1′)···HC(6), 2.30; and O(2)···H(1′), 2.33 Å.

The crystal structure can be seen in Figure 4, which gives a stereoscopic view of the packing. There is an extensive network of intermolecular hydrogen bonds, some of which are indicated by dashed lines. With the exception of O(3′) all available oxygen and nitrogen atoms participate in hydrogen bonds. The geometrical details are given in Table IV. Apart from these hydrogen bonds there are no intermolecular distances which are significantly shorter than the sums of van der Waals radii.

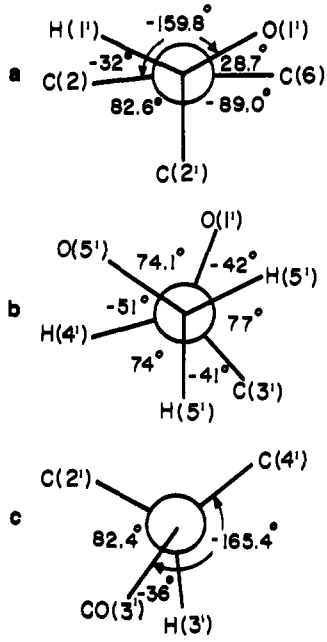

Figure 3. Newman projections showing the conformations about (a) the C(1′)-N(1) bond, (b) the C(5′)-C(4′) bond, and (c) the O(3′)-C(3′) bond.

Discussion

The orientation of the 3′-*O*-methyl, trans to C(4′), is such that it would hardly be expected to *directly* affect the conformation of the exocyclic CH_2OH, the more so in that theoretical calculations point to only minor modifications of the electron density distribution in the pentose ring when an -OH is replaced by an -OMe.[16] The departure of the CH_2OH conformation from gauche-gauche to gauche-trans in the solid state as a result of 3′-O-methylation is therefore of interest inasmuch as the arabinose ring pucker is precisely that required for formation of an *intra*molecular hydrogen bond of the form O(2′)-H···O(5′), expected to be energetically more favored, and actually observed for the neutral form of araC in the solid state[8,9] (see Table V).

In the ribonucleoside series, where some preliminary data are available, O′-methylation may affect not only the exocyclic CH_2OH conformation but also the sugar puckering, relative to the parent derivative. Adenosine in the crystalline state is C(3′) endo and gauche-trans,[30] but 2′-*O*-meth-

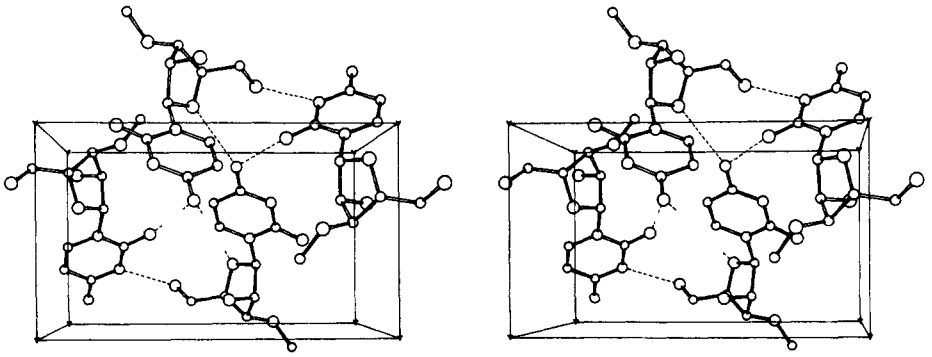

Figure 4. Stereoscopic view, along the *y* direction, of the contents of a unit cell. Dashed lines indicate hydrogen bonds; interrupted lines are bonds between molecules displaced by *b*.

Table IV. Distances and Angles for the Hydrogen Bonds

	Distances, Å		Angles, deg	
D–H · · · *A*	*D* · · · *A*	H · · · *A*	*D*–H · · · *A*	H–*D* · · · *A*
N(4)–H1(N4) · · · O(1′) ($\bar{x}$, $-½ + y$, $3/2 - z$)	3.067	2.22	139	28
N(4)–H2(N4) · · · O(2) ($½ - x$, $\bar{y}$, $½ + z$)	2.970	2.07	150	20
O(2′)–H(O2′) · · · O(5′) ($\bar{x}$, $½ + y$, $½ - z$)	2.702	1.65	178	1
O(5′)–H(O5′) · · · N(3) ($-½ + x$, $½ - y$, $1 - z$)	2.747	1.86	173	5

Table V. Comparison of Conformational Parameters in Arabinonucleosides

Molecule	O(5′)–C(5′)–C(4′)–O(1′), deg		O(5′)–C(5′)–C(4′)–C(3′), deg	O(1′)–C(1′)–N(1)–C(6), deg	*P*,[a] deg	Ref
AraC[b]	−68.4	g-g	51.7	28.8	162.7 [C(2′) endo]	8, 9
AraC·HCl	68.7	g-t	−171.5	26.7	176.9 [C(2′) endo]	12
3′-OMe-araC	74.1	g-t	−166.6	28.7	167.8 [C(2′) endo]	This study
AraU[b]	−63.3	g-g	55.8	34.0	153.9 [C(2′) endo]	10
Ara-br^{5}U	−60	g-g	61	30	108 [O(1′) endo–C(1′) exo]	13
Ara-s^{4}U	−55.5	g-g	62.2	36.0	13.8 [C(3′) endo]	7
AraT	−59.5	g-g	60.2	24.1	104.8 [O(1′) endo]	11
AraA	62.1	g-t	178.8	57.8	25.2 [C(3′) endo]	14
AraA·HCl	−62.3	g-g	55.1	29.7	9.3 [C(3′) endo]	15

[a] Phase angle of pseudorotation of the furanose ring [cf. C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, 94, 8205 (1972)]. The values, when not given by the original authors, were calculated from published torsional angles. [b] There is an intramolecular hydrogen bond between O(2′) and O(5′).

yladenosine contains two independent molecules in the unit cell, one with the conformation C(3′) endo, gauche-gauche, the other the hitherto unobserved C(2′) exo, gauche-trans.[23] Crystalline cytidine exhibits the conformation C(3′) endo, gauche-gauche,[31] whereas 2′-*O*-methylcytidine is C(2′) endo–C(3′) exo, gauche-gauche.[22]

The difficulties involved in the interpretation of the foregoing differences in conformation of related analogs are even more strikingly underlined by the solid-state conformations of araU and araT (Table V), the latter of which differs from the former only by the presence of a 5-methyl substituent in the pyrimidine ring. AraU is C(2′) endo, gauche-gauche, with an intramolecular O(2′)–H···O(5′) hydrogen bond;[10] but no such bond exists in araT, due to the unfavorable pentose conformation, C(1′) exo–O(1′) endo. By contrast, no difference is observed between uridine[32] and 5-methyluridine,[33] both of which are C(3′) endo, gauche-gauche, and with closely similar glycoside torsion angles, 16.8 and 29.4°, respectively. Furthermore, ara-brU, in which the 5-methyl substituent is replaced by 5-bromo with a virtually identical van der Waals radius, but with an electronegativity which profoundly affects the p*K* for dissociation of the pyrimidine N(3) hydrogen,[34] exhibits a conformation similar to that for araT.[13]

It is clear that so-called "packing forces" are responsible for the foregoing effects in the solid state and are necessarily related to the *inter*molecular hydrogen bonds in the crystal structure. It is therefore conceivable that some correlation may exist between the different conformations of a related series of analogs and that this might be placed in evidence by an analysis of the intermolecular hydrogen bonds for a series of such analogs. The relative role of such intermolecular hydrogen bonds might, however, be more readily assessed by spectroscopic methods for those derivatives for which sufficiently high-solution concentrations are attainable.[35]

From Table V, which lists the major conformational parameters of the nine arabinonucleosides hitherto examined in the solid state, it will be seen that, relative to the corresponding β-ribonucleosides,[6] there is a considerably wider diversity of sugar puckers in the β-arabinonucleosides, viz. four are C(2′) endo, three are C(3′) endo, and two are O(1′) endo–C(1′) exo.

It is also of importance to note that, in those instances where solution data are available, the sugar puckers are quite different from those in the crystals, e.g., araC in aqueous medium exhibits a preference for C(2′) exo[16] and araU for C(3′) endo.[36] Furthermore, in the case of araC in aqueous medium, O′-methylation (or ethylation) only minimally affects the sugar puckering, that of 3′-OMe-araC being similar to araC itself.[16]

A rather remarkable exception to the foregoing are ara-

binonucleosides of uracil and cytosine with free 2′ and 5′ hydroxyls in strongly alkaline medium where the 2′-OH is ionized. Under these conditions araC, 3′-OMe-araC, and 3′-OMe-araU assume the conformation C(2′) endo–C(1′) exo, and almost 90% gauche-gauche for the exocyclic 5′-CH_2OH group, with concomitant formation of an intramolecular hydrogen bond of the form $O(5')-H\cdots O(2')^-$,[37] similar to that observed for the neutral forms of araC and araU in the solid state (see Table V). Studies on the conformation of araA in strongly alkaline medium are in progress.

The solution conformation of the pentose ring in cytidine and uridine is also unaltered when one or more of the sugar hydroxyls are etherified,[16,38] in contrast to the results for the solid state (see above). If these solution data may be extrapolated to the polynucleotide level, it would appear that the properties of the 2′-*O*-methyl nucleosides in tRNA should be considered in terms of factors other than modifications of the ribose conformation.

It is of interest that the conformation of araA in the solid state is C(3′) endo, gauche-trans,[14] hence, similar to that for adenosine.[31] The glycosidic bond in both molecules is also anti, although it is 57.8° for adenosine and only 9.9° for araA. The conformational similarities between the two have been taken to indicate that araA may be a participant in the metabolic pathways that normally utilize adenosine, as is, in fact, true for several enzymatic reactions. But, in the light of the results obtained herein for 3′-OMe-araC, and those discussed in the text (above), it appears to us that, in the absence of appropriate conformational data for solutions, such a conclusion may be somewhat premature and in any event cannot be generalized.

Finally, it will be of interest to determine whether the absence of antiviral activity of 3′-OMe-araC, notwithstanding its resistance to cytidine deaminase (see above), is due to its failure to undergo phosphorylation by the appropriate cellular kinase to the 5′-triphosphate, or, if it does undergo such phosphorylation, whether the 5′-triphosphate is an inhibitor of DNA polymerase. Such trials are now in progress, as well as attempts to determine the solid-state conformation of 2′-OMe-araC.

Acknowledgments. Figures 2 and 4 were drawn with the help of the ORTEP program of C. K. Johnson. All computations were carried out with programs written by Ahmed, Hall, Pippy, and Huber. One of us (D.S.) is indebted to the Medical Research Council of Canada for a Visiting Scientist grant.

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 Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-75-5904.

References and Notes

(1) Issued as N.R.C.C. No. 14882.
(2) (a) National Research Council; (b) University of Warsaw; (c) Université Laval.
(3) Abbreviations employed: araC, 1-β-D-arabinofuranosylcytosine or arabinosylcytosine; araA, arabinosyladenine; araU, arabinosyluracil; araT, arabinosylthymine; ara-s^4U, arabinosyl-4-thiouracil; ara-brU, arabinosyl-5-bromouracil; 3′-OMe-araC, 3′-*O*-methyl-araC, with similar connotations for other *O*′-methyl derivatives of araC or other nucleosides.
(4) S. S. Cohen, *Prog. Nucl. Acid Res. Mol. Biol.*, **5**, 1 (1966); P. Roy-Burman, *Recent Results Cancer Res.*, **25**, 1 (1970); R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970.
(5) L. T. Chi'en, F. M. Schabel, Jr., and C. A. Alford, Jr., in "Selective Inhibitors of Viral Functions", W. Carter, Ed., CRC Press, Cleveland, Ohio, 1973.
(6) C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **94**, 8205 (1972); **95**, 2333 (1973).
(7) W. Saenger, *J. Am. Chem. Soc.*, **94**, 621 (1972).
(8) A. K. Chwang and M. Sundaralingam, *Nature (London), New Biol.*, **243**, 78 (1973).
(9) P. Tougard and O. Lefebvre-Soubeyran, *Acta Crystallogr., Sect. B*, **30**, 86 (1974).
(10) P. Tollin, H. R. Wilson, and D. W. Young, *Acta Crystallogr., Sect. B*, **29**, 1641 (1973).
(11) P. Tougard, *Acta Crystallogr., Sect. B*, **29**, 2227 (1973).
(12) J. Sherfinski and R. Marsh, *Acta Crystallogr., Sect. B*, **29**, 192 (1973).
(13) P. Tougard, *Biochim. Biophys. Acta*, **319**, 116 (1973).
(14) G. Bunick and D. Voet, *Acta Crystallogr., Sect. B*, **30**, 1651 (1974).
(15) A. K. Chwang, M. Sundaralingam, and S. Hanessian, *Acta Crystallogr., Sect. B*, **30**, 2273 (1974).
(16) M. Remin and D. Shugar, *J. Am. Chem. Soc.*, **95**, 8146 (1973).
(17) D. Shugar, *FEBS Lett., Suppl.*, **40**, S48 (1974).
(18) E. De Clercq, E. Darżynkiewicz, and D. Shugar, *Biochem. Pharmacol.*, **24**, 523 (1975).
(19) R. Y. Lau and B. G. Lane, *Can. J. Biochem.*, **49**, 431 (1971).
(20) R. H. Hall, "The Modified Nucleoside in Nucleic Acids", Columbia University Press, New York, N.Y., 1971.
(21) B. J. Ortwerth and G. D. Novelli, *Cancer Res.*, **29**, 380 (1969).
(22) B. Hingerty, P. J. Bond, R. Langridge, and F. Rottman, *Biochem. Biophys. Res. Commun.*, **61**, 875 (1974).
(23) M. Sundaralingam and P. Prusiner, Abstracts, American Crystallographic Association Meeting, Storrs, Conn., June 1973.
(24) E. Darżynkiewicz, J. T. Kuśmierek, and D. Shugar, *Biochem. Biophys. Res. Commun.*, **46**, 1734 (1972); E. Darżynkiewicz and D. Shugar, *Acta Biochim. Pol.*, **21**, 305 (1974).
(25) O. Kennard, N. W. Isaacs, W. D. S. Motherwell, J. C. Coppola, D. L. Wampler, A. C. Larson, and D. G. Watson, *Proc. Roy. Soc., Ser. A*, **325**, 401 (1971).
(26) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
(27) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(28) D. T. Cromer and D. Liberman, *J. Chem. Phys.*, **53**, 1891 (1970).
(29) W. Klyne and W. Prelog, *Experientia*, **16**, 521 (1960).
(30) T. F. Lai and R. E. Marsh, *Acta Crystallogr., Sect. B*, **28**, 1982 (1972).
(31) S. Furberg, C. S. Peterson, and C. Romming, *Acta Crystallogr.*, **18**, 313 (1965).
(32) E. A. Green, R. Shiono, R. D. Rosenstein, and D. J. Abraham, *Chem. Commun.*, 53 (1971).
(33) D. J. Hunt and E. Subramanian, *Acta Crystallogr., Sect. B*, **25**, 2144 (1969).
(34) K. Berens and D. Shugar, *Acta Biochim. Pol.*, **10**, 25 (1963).
(35) This has now been done for adenosine 5′-phosphate by NMR spectroscopy over the concentration range 10^{-3}–2 *M*. At the lower concentration the sugar ring is largely C(2′) endo; at the highest concentration it is predominantly C(3′) endo, as in the solid state [F. E. Evans and R. H. Sarma, *J. Biol. Chem.*, **249**, 4754 (1974)].
(36) F. E. Hruska, *Conform. Biol. Mol. Polym., Proc. Jerusalem Symp. Quantum Chem. Biochem.*, **5**, 345 (1973).
(37) E. Darżynkiewicz, M. Remin, A. Dworak, and D. Shugar, *Cancer Biochem. Biophys.*, in press.
(38) F. E. Hruska, A. Mak, H. Singh, and D. Shugar, *Can. J. Chem.*, **51**, 1039 (1973).