Intramolecular Hydrogen Bonding and Acidities of Nucleoside Sugar Hydroxyls. Crystal Structure and Conformation of O^2,2′-Anhydro-1-α-D-xylofuranosyluracil[1]

George I. Birnbaum,*[2a] Jerzy Giziewicz,[2b] Carol P. Huber,[2a] and David Shugar[2b,c]

Contribution from the Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada, K1A 0R6, Institute of Biochemistry and Biophysics, Academy of Sciences, 02-532 Warszawa, Poland, and Department of Biochemistry, Faculty of Medicine, Université Laval, Quebec, Canada. *Received October 14, 1975*

Abstract: The title compound crystallizes in the orthorhombic space group $P2_12_12_1$ in a cell with dimensions a = 9.468 (1), b = 9.735 (2), and c = 9.909 (1) Å. The structure was solved by direct methods; least-squares refinement, which included hydrogen atoms, converged at R = 0.040. The pyrimidine ring and the adjacent five-membered ring are coplanar within 0.04 Å, and this plane forms an angle of 106.0° with the mean plane of the furanose ring. The sugar ring has a C(4′) exo pucker and the conformation of the exocyclic 5′-CH$_2$OH is gauche–gauche. There is a strong O(3′)–H ··· O(5′) intramolecular hydrogen bond. By analogy with previous findings for ribo- and arabinonucleosides, where enhanced acidities of sugar hydroxyls have been shown to be associated with intramolecular hydrogen bonding to a sugar O$^-$ and resultant stabilization of the anion, the ability of the xylofuranosyl ring to adopt a conformation permitting of such hydrogen bonding between O(5′) and the "up" O(3′) is extended to interpret the known high acidity of the sugar hydroxyl(s) in 9-β-D-xylofuranosyladenine and to identify the most acidic hydroxyl as the 3′-OH.

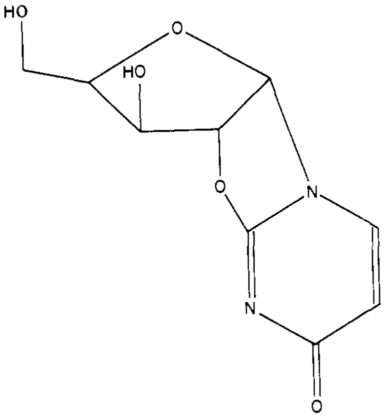
Nucleoside anhydrides are widely employed as intermediates in a variety of synthetic reactions, e.g., the O^2,2′-anhydrides of uridine and cytidine for inversion of the 2′-OH to yield the corresponding araU[3] and araC, respectively, or for the preparation of the 2′-deoxy-2′-halogeno nucleosides,[4] incorporation of cycloU into dinucleoside monophosphates,[5] etc. This subject has been extensively reviewed.[6] In several instances the intrinsic lability of the anhydro linkage has been put to practical use; e.g., the instability of cycloaraC, even at physiological pH and temperature, which is converted to araC, has been exploited to use this anhydronucleoside as a depot form of the therapeutically active araC.[7] A similar application has been described for O^2,2′-anhydro-5-fluorocytidine,[8] currently undergoing clinical trial as an antileukemic agent.[9]

The presence, in an anhydronucleoside, of a polycyclic fused ring system imposes additional conformational rigidity, which might be expected to prevail equally well both in the solid state and in solution. It may therefore be anticipated that anhydronucleosides would be useful model systems for testing the Karplus relationship[10] by measuring the dihedral angles in the crystal structures and comparing these with the corresponding angles calculated from the coupling constants in solution by NMR spectroscopy. The results of several such studies have already been reported,[11] with some interesting conclusions regarding the effect of anomalous bonding electron density on non-Karplus-type behavior relating torsional angles to measured coupling constants.[11a]

Our interest in the O^2,2′-anhydronucleosides prompted us to prepare the readily accessible α-cycloxyloU (**1**), the structure and conformation of which in the solid state are reported here. As will be shown below, the presence of an "up" 3′-OH is of direct relevance to the problem of *intra*molecular hydrogen bonding in furanose rings of nucleosides and the dissociation properties of the sugar hydroxyls. It is also worthy of note that some xylofuranosyl nucleosides exhibit antimetabolic properties and potential therapeutic activity,[12] while there are now several reported instances of antimetabolic activities of α-nucleosides.[8c,13]

Experimental Section

The title compound, $C_9H_{10}N_2O_5$ (mol wt = 226.2), was synthesized, with only minor modifications, by the method of Holý.[14] It melted at 255–260° with evolution of gas; Holý[14] reports no melting to 250°. In aqueous medium at pH 7.4, λ_{max} was 223 nm (ϵ_{max} 8.4 × 10^3) and 249 nm (ϵ_{max} 8.2 × 10^3); λ_{min} 235 nm (ϵ_{min} 6.8 × 10^3). The extinction values given by Holý[14] are about 10–15% lower, but our data are in agreement with those for the analogous cycloU reported by Hampton and Nichol,[15] as was to be anticipated.



1

In aqueous medium at approximately neutral pH, the compound was relatively stable at room temperature. At 100° it underwent very slow hydrolysis to 1-α-D-xylofuranosyluracil. In the presence of 0.15 M phosphate buffer, pH 7.4, the rate of hydrolysis at 100° was appreciably increased, the rate constant being 1.5 × 10^{-2} min^{-1}.

Suitable crystals for an x-ray analysis were obtained from a hot ethanolic solution by addition of about 10% water, followed by slow cooling to room temperature. 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 0.25 × 0.30 × 0.30 mm was mounted along the a axis on a card-controlled Picker four-circle diffractometer. Cell dimensions were determined from angular settings of nine high-angle reflections and both Cu Kα_1 (λ 1.54051 Å) and Cu Kα_2 (λ 1.54433 Å) radiations were used. The following crystal data were obtained: a = 9.468 (1), b = 9.735 (2), c = 9.909 (1) Å; V = 913.3 Å^3; D_x = 1.64, D_m = 1.63 g cm^{-3}; Z = 4; F(000) = 472; μ (Cu Kα) = 11.9 cm^{-1}.

The moving-crystal/moving-counter technique (θ–2θ scan) was used to collect the intensity data and monochromatization was achieved by the use of a nickel filter and a 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 919 unique reflections accessible to

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)	4777 (3)	3538 (3)	5095 (3)	34 (1)	37 (1)	40 (1)	9 (2)	14 (2)	3 (2)
C(2)	4004 (3)	2646 (3)	5816 (3)	40 (1)	39 (1)	35 (1)	12 (3)	5 (3)	8 (3)
O(2)	3599 (3)	3178 (2)	6988 (2)	58 (1)	36 (1)	35 (1)	5 (2)	17 (2)	−3 (2)
N(3)	3653 (3)	1411 (3)	5474 (3)	43 (1)	36 (1)	38 (1)	10 (2)	10 (2)	−2 (2)
C(4)	4138 (4)	949 (3)	4235 (3)	43 (1)	40 (1)	45 (2)	3 (3)	5 (3)	16 (3)
O(4)	3871 (3)	−241 (3)	3898 (3)	80 (2)	41 (1)	54 (1)	−14 (2)	28 (3)	−4 (3)
C(5)	4937 (4)	1882 (4)	3396 (3)	47 (2)	50 (2)	38 (2)	3 (3)	18 (3)	21 (3)
C(6)	5262 (3)	3149 (4)	3837 (3)	37 (1)	46 (2)	42 (2)	26 (3)	17 (3)	19 (3)
C(1′)	4902 (3)	4877 (3)	5759 (4)	39 (1)	38 (1)	47 (2)	6 (3)	1 (3)	−10 (3)
O(1′)	4128 (2)	5898 (2)	5101 (2)	46 (1)	35 (1)	45 (1)	20 (2)	20 (2)	0 (2)
C(2′)	4163 (4)	4574 (3)	7113 (3)	47 (2)	39 (1)	39 (1)	4 (3)	−14 (3)	−4 (3)
C(3′)	2950 (3)	5593 (3)	7156 (3)	43 (1)	39 (2)	35 (1)	−10 (3)	−7 (3)	−2 (3)
O(3′)	3390 (3)	6753 (3)	7905 (3)	60 (1)	50 (1)	47 (1)	−27 (2)	−29 (2)	3 (3)
C(4′)	2721 (3)	5886 (3)	5656 (3)	43 (1)	33 (1)	33 (1)	−2 (2)	−5 (2)	−4 (3)
C(5′)	1960 (4)	7203 (4)	5280 (3)	54 (2)	42 (2)	43 (2)	−9 (3)	−11 (3)	14 (3)
O(5′)	2508 (3)	8372 (2)	5949 (3)	68 (1)	39 (1)	53 (1)	−4 (2)	2 (3)	−5 (2)

(b) Hydrogen Atoms[b]

Atom	x	y	z	B	Atom	x	y	z	B
H(5)	529 (4)	157 (4)	255 (4)	3.0 (0.7)	HO(3′)	327 (6)	757 (6)	736 (6)	6.1 (1.3)
H(6)	581 (4)	389 (4)	342 (4)	3.0 (0.7)	H(4′)	228 (4)	509 (4)	521 (4)	3.3 (0.8)
H(1′)	589 (5)	517 (5)	581 (5)	4.4 (0.9)	H1(5′)	209 (5)	729 (5)	432 (5)	4.6 (0.9)
H(2′)	479 (3)	460 (3)	793 (3)	2.1 (0.6)	H2(5′)	103 (4)	708 (4)	569 (4)	4.0 (0.8)
H(3′)	206 (4)	513 (4)	761 (4)	3.1 (0.8)	HO(5′)	302 (6)	879 (6)	537 (6)	6.4 (1.3)

[a] The coordinates were multiplied by 10^4 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.

Table II. Comparison of Some Bond Lengths (in Å) and Bond Angles (in Deg) in Cyclouridines and in Uridine

	CycloU[a,b]	α-CycloU	α-CycloxyloU	U[a]
N(1)-C(2)	1.350	1.366	1.342	1.371
C(2)-O(2)	1.335	1.325	1.328	1.222
O(2)-C(2′)	1.461	1.461	1.466	1.418
C(2)-N(3)	1.293	1.287	1.293	1.370
C(1′)-N(1)-C(2)	112.1	111.6	112.4	117.2
C(1′)-N(1)-C(6)	128.3	128.6	128.5	122.2
N(1)-C(2)-O(2)	111.4	111.6	111.8	122.2
N(1)-C(2)-N(3)	127.0	125.8	127.1	115.4
C(2)-N(3)-C(4)	116.5	117.3	116.7	126.8
N(1)-C(1′)-C(2′)	100.6	100.6	100.6	112.7

[a] Averages from two independent molecules in the asymmetric unit. [b] From ref 19.

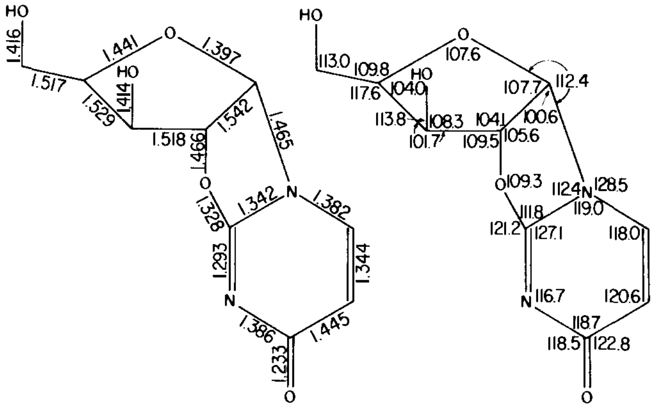


Figure 1. Molecular geometry: left, bond lengths in ångströms (all esd's are 0.004–0.005 Å); right, bond angles in degrees (all esd's are 0.2–0.3°).

the diffractometer ($2\theta \leq 130°$) of which 894 (97%) had intensities above threshold values. The intensities were corrected for Lorentz and polarization factors; absorption corrections were considered unnecessary in view of the low value of μ and the regular shape of the crystal.

The structure was determined by direct methods with a multisolution procedure similar to that described by Kennard et al.[16] With $\alpha_{\min} = 2.37$ and $t_{\min} = 0.3$ one of the 16 permutations yielded $R_E = 0.19$ for 250 reflections with $E \geq 1.12$ after a tangent refinement carried out in four steps. The E map revealed the positions of all 16 nonhydrogen atoms. Atomic parameters were refined by block-diagonal least squares. All scattering factors were taken from the "International Tables for X-Ray Crystallography"[17] and the oxygen curve was corrected for anomalous dispersion. All hydrogen atoms were located on difference Fourier maps and their parameters were refined isotropically. 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: $w = w_1 w_2$, where $w_1 = 1$ for $|F_o| \leq 11$, $w_1 = 11/|F_o|$ for $|F_o| > 11$; and $w_2 = \sin^2\theta/0.5$ for $\sin^2\theta < 0.5$, $w_2 = 1$ for $\sin^2\theta \geq 0.5$. After the final cycle the average parameter shift equalled 0.13σ and the largest one 0.47σ. The agreement index R ($\Sigma|\Delta F|/\Sigma|F_o|$) is 0.040 and the weighted index R' ($\Sigma w \Delta F^2/\Sigma w F_o^2$) is 0.050 for 897 reflections, including three unobserved ones for which $|F_o| < |F_c|$. 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 bond lengths and bond angles. As expected, some of these values are greatly distorted as a result of the cyclization. In addition to this structure, we are aware of only two other cyclouridine compounds whose structures have been determined by x-ray analysis, viz. cycloU[18,19] and α-cycloU.[20] In Table II selected bond lengths and angles in these three cyclouridine structures are compared with the equivalent values in uridine.[21] It can be seen that the geometry is very similar in all three cyclouridines, that it is independent of the configuration at C(1′), and that it differs considerably from that in uridine.

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

Plane 1[b]		Plane 2[b]		Plane 3[b]		Plane 4[b]	
Atom	Δ, Å[c]	Atom	Δ, Å[c]	Atom	Δ, Å[c]	Atom	Δ, Å[c]
N(1)	−0.006	N(1)	−0.019	N(1)	−0.021	O(1′)	0.006
C(2)	0.004	C(2)	0.005	C(2)	0.003	C(1′)	−0.019
N(3)	0.006	O(2)	0.010	N(3)	0.024	C(2′)	0.017
C(4)	−0.018	C(2′)	−0.035	C(4)	0.006	C(3′)	−0.010
C(5)	0.013	C(1′)	0.040	C(5)	0.023	C(4′)*	0.557
C(6)	0.001	N(3)*	0.025	C(6)	−0.007	C(5′)*	0.258
C(1′)*	0.071	C(4)*	0.006	C(1′)	0.036		
C(2′)*	−0.009	C(5)*	0.024	C(2′)	−0.040		
O(2)*	0.016	C(6)*	−0.005	O(2)	0.007		
O(4)*	−0.069			O(4)	−0.026		

[a] Atoms marked with an asterisk were not included in the calculation of the plane. [b] Plane 1: $0.8378X - 0.3481Y + 0.4206Z - 4.7074 = 0$. Plane 2: $0.8422X - 0.3350Y + 0.4224Z - 4.7693 = 0$. Plane 3: $0.8424X - 0.3342Y + 0.4228Z - 4.7719 = 0$. Plane 4: $0.5856X + 0.6877Y + 0.4291Z - 8.4121 = 0$. [c] Esd's are 0.002-0.003 Å.

Table IV. Torsion Angles (Deg)

C(1′)-C(2′)-C(3′)-C(4′)	+24.2
C(2′)-C(3′)-C(4′)-O(1′)	−37.5
C(3′)-C(4′)-O(1′)-C(1′)	+37.5
C(4′)-O(1′)-C(1′)-C(2′)	−21.6
O(1′)-C(1′)-C(2′)-C(3′)	−3.0
O(1′)-C(1′)-C(2′)-O(2)	+112.3
O(1′)-C(1′)-N(1)-C(2)	−108.9
O(1′)-C(1′)-N(1)-C(6)	+66.5
C(2)-O(2)-C(2′)-C(3′)	+115.8
O(2)-C(2′)-C(3′)-C(4′)	−88.3
O(2)-C(2′)-C(3′)-O(3′)	+151.6
C(1′)-C(2′)-C(3′)-O(3′)	−95.9
O(1′)-C(4′)-C(3′)-O(3′)	+78.6
C(5′)-C(4′)-C(3′)-O(3′)	−43.0
C(5′)-C(4′)-O(1′)-C(1′)	+164.2
O(1′)-C(4′)-C(5′)-O(5′)	−69.8
C(3′)-C(4′)-C(5′)-O(5′)	+48.8
O(1′)-C(4′)-C(5′)-H1(5′)	+45
C(3′)-C(4′)-C(5′)-H2(5′)	−62
H1(5′)-C(4′)-C(5′)-H(4′)	−64
H2(5′)-C(4′)-C(5′)-H(4′)	+66

The conformation of the molecule is shown in the stereographic representation in Figure 2. The pyrimidine ring is almost planar, as is the adjacent five-membered ring. The two rings together are coplanar within 0.04 Å and their plane forms an angle of 106.0° with the mean plane through the furanose ring. Details of several least-squares planes are given in Table III. The conformation of the sugar ring can be assessed on the basis of endocyclic torsion angles (Table IV). The value of the phase angle of pseudorotation[22] ($P = 51.5°$) corresponds to a C(4′) exo pucker ($_4E$) and the displacement of C(4′) from the least-squares plane through the other four atoms in the ring amounts to 0.557 Å. This conformation is not normally observed in nucleosides. It is remarkable, however, that in all O^2,2′-anhydronucleosides investigated thus far an x-ray analysis showed the sugar ring to have a conformation close to a C(4′) envelope. It is C(4′) endo ($P = 227°$) and C(4′) endo-C(3′) exo ($P = 213°$) in the two independent molecules in cycloU,[18,19] C(4′) endo ($P = 233°$) in cycloC·HCl,[23] C(4′) exo ($P = 48°$) in α-cycloU,[20] and C(4′) exo in our structure. It appears, therefore, that *the preferred conformation is C(4′) endo in β-anhydronucleosides and C(4′) exo in α-anhydronucleosides*. The glycosidic torsion angle O(1′)-C(1′)-C(1)-C(6) is in the anti range, being constrained to this form in an O^2,2′-α-anhydronucleoside. The conformation of the C(5′)-O(5′) side chain is gauche-gauche.

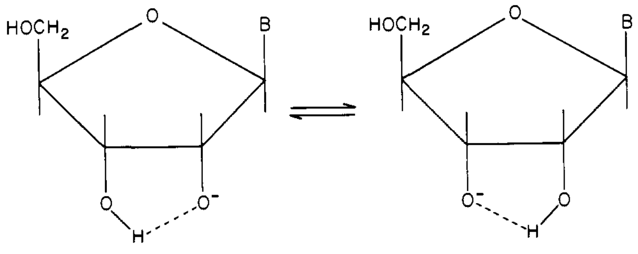
Table V. Distances and Angles for Hydrogen Bonds

	Distances, Å		Angles, deg	
	D···*A*	H···*A*	*D*-H···*A*	H-*D*···*A*
O(3′)-H···O(5′)	2.634	1.76	149	20
O(5′)-H···O(4) (*x*,1 + *y*,*z*)	2.760	1.92	170	7

This conformation facilitates the formation of a strong O(3′)-H···O(5′) intramolecular hydrogen bond. It should be pointed out, however, that the possible formation of an intramolecular hydrogen bond does not necessarily impose a gauche-gauche conformation on the side chain.[24] There is also an intermolecular hydrogen bond in the crystal structure, with O(5′) donating its proton to O(4) in the molecule translated by *b*. Geometrical details of the two hydrogen bonds are given in Table V. There is one very short (2.907 Å) intermolecular contact between C(2) and O(3′) in a molecule related by a screw axis parallel to *b*. A packing diagram is shown in Figure 3.

Discussion

The ability of α-cycloxyloU to form an intramolecular O(3′)-H···O(5′) hydrogen bond is of direct relevance to the experimentally observed acidities of the pentose hydroxyls of nucleosides. In the case of ribonucleosides, the relatively high acidity of the sugar hydroxyl(s) has been ascribed[25] to the cis 2′-OH and 3′-OH and the ability of these to hydrogen bond in the anion, as shown below. This is, in turn, dependent on the O(2′)···O(3′) distance and the conformations of the hydroxyl groups about the C-O bonds. The O···O distances in the commonly encountered conformations C(2′) endo and C(3′) endo are 2.75 and 2.78 Å, respectively.[26] Although these distances are well within normal hydrogen bond range, the O-H···O⁻ angle would have to be considerably smaller than usual, possibly as small as 130-135°. Nevertheless, we feel that such



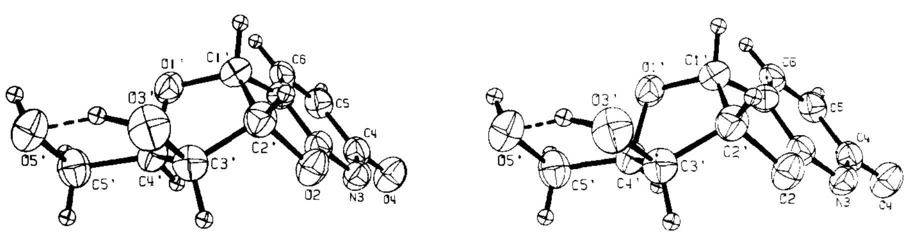


Figure 2. Stereoscopic view of the molecule; the thermal ellipsoids correspond to 50% probability.

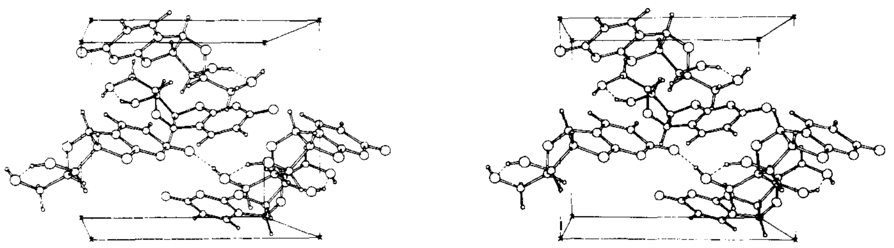


Figure 3. Stereoscopic view along *z* of the contents of a unit cell. The directions of the axes are *x* ↑ (0.0–1.0), *y* ← (−0.5–0.5), and *z* ⊙.

hydrogen bonds may occur in all ribonucleoside anions in solution. The O-H···O^- angle increases as the O···O^- distance decreases, and this decrease could be brought about by a change of the pentose ring conformation and by a small decrease of the C-O-H bond angle. It has been emphasized that the requirement of linearity is *not* important,[27] while the oxygen anion is clearly a very good proton acceptor. These arguments are corroborated by the recent observation of an O(3′)-H···O(2′) hydrogen bond in the crystal structure of the picrate salt of isodeazatubercidin,[28] where the O···O and H···O distances are 2.68 and 1.97 Å, respectively. If such a bond is possible in the solid state with a neutral -OH group as a proton acceptor, then clearly it could also exist in solution with $-O^-$ as an acceptor.

Additional, and more direct, support for this concept is provided by the D-arabinonucleosides. Although the hydroxyls in the arabinose ring are apparently isolated from each other, the pK_a for the arabinose hydroxyl(s) is almost equal to that for the ribose nucleosides.[29] This apparent anomaly was resolved when it was found (by ^{1}H NMR spectroscopy) that the conformations of various arabinonucleosides, which differ in neutral medium, all adopt a common new conformation in highly alkaline medium, C(2′) endo and about 90% gauche-gauche.[30] This is the conformation exhibited by the neutral forms of araU[31] and araC[32] in the solid state, with an intramolecular O(2′)-H···O(5′) hydrogen bond. One can therefore conclude that, in strongly alkaline medium, the geometrical requirements are fulfilled for formation of a hydrogen bond between the 5′-OH and the ionized 2′-hydroxyl, O(5′)-H···$O(2')^-$.

This concept was extended by Schwarz and Totty,[33] who proposed that a major factor responsible for the enhanced acidities of some sugars and glycosides is the stabilization of the anionic forms via intramolecular hydrogen bonding to a sugar O^- as acceptor. A good illustration is provided by the pyranose rings in methyl 3,6-anhydro-α-D-glucopyranose and 1,6-anhydro-β-D-glucopyranose. Both of these are so distorted as a result of the strain due to the cis-fused five-membered ring that the distance between the axial oxygens O(2) and O(4) should be shorter in the former, and longer in the latter, relative to the corresponding unstrained system. This was confirmed by x-ray analyses, which showed that the O(2)···O(4) distance was 3.30 Å in the 1,6-anhydro derivative[34] and 2.76 Å in the 3,6-anhydro derivative,[35] so that hydrogen bonding of the two oxygens is feasible in the latter. In striking agreement with this is the finding of Totty and Schwarz[33] that the 3,6-anhydro derivative is a much stronger acid (pK = 12.2) than the 1,6-anhydro derivative (pK = 13.5).

In the light of the foregoing, as well as the demonstration in the present study of the existence of the intramolecular hydrogen bond O(3′)-H···O(5′) in the crystal structure of α-cycloxyloU, we are now in a position to interpret what Christensen et al.[36] regarded as the anomalously high acidity of the sugar hydroxyl(s) of 9-β-D-xylofuranosyladenine (pK = 12.34), almost identical with that for adenosine (pK = 12.35).[25] Christensen et al.[36] suggested that the high acidity of the former might be due to enhanced hydration. A more reasonable explanation is the formation in the anion of the intramolecular hydrogen bond O(5′)-H···$O(3')^-$, with the accompanying change in conformation of the pentose ring to that observed herein in the solid state, and resultant stabilization of the anion. It also follows that the most acidic hydroxyl in xylofuranosyl nucleosides is the "up" 3′-OH, whereas in arabinofuranosyl nucleosides it is the 2′-OH.[30] If the foregoing interpretation is correct, then one would expect the pK for anion formation in a xylofuranosyl nucleoside to be modified only slightly, if at all, by etherification of the 2′-OH. Attempts to prepare the various *O*′-methyl derivatives of xylofuranosyladenine are therefore being undertaken.

Acknowledgments. 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 (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Issued as NRCC No. 15419.
(2) (a) National Research Council; (b) Academy of Sciences; (c) Université Laval.
(3) Abbreviations used in this paper: araU, 1-β-D-arabinofuranosyluracil, or arabinosyluracil; araC, arabinosylcytosine; cycloU, O^2,2′-anhydro-1-β-D-arabinofuranosyluracil; cycloC, O^2,2′-anhydro-1-β-D-arabinofuranosylcytosine; α-cycloU, O^2,2′-anhydro-1-α-D-ribofuranosyluracil; α-cycloxyloU, O^2,2′-anhydro-1-α-D-xylofuranosyluracil.
(4) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); T. Sowa and K. Tsunoda, *Bull. Chem. Soc. Jpn.*, **48**, 505 (1975); K. Kikugawa and M. Ichino, *J. Org. Chem.*, **37**, 284 (1972); T. Kanai, T. Kojima, O. Maruyama, and M. Ichino, *Chem. Pharm. Bull.*, **18**, 2569 (1970); R. A. Sanchez and L. E. Orgel, *J. Mol. Biol.*, **47**, 531 (1970).
(5) K. K. Ogilvie and D. J. Iwacha, *Can. J. Chem.*, **52**, 1787 (1972).
(6) J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1969).
(7) A. Hoshi, F. Kanzawa, and K. Kuretani, *Gann*, **63**, 353 (1972); T. L. Loo, D. H. W. Ho, G. P. Bodey, and E. J. Freireich, *Ann. N.Y. Acad. Sci.*, **255**, 252 (1975).
(8) (a) J. J. Fox, E. A. Falco, I. Wempen, D. Pomeroy, M. D. Dowling, and J. H.

Burchenal, *Cancer Res.*, **32**, 2269 (1972); (b) J. J. Fox and B. A. Otter, *Ann. N.Y. Acad. Sci.*, **255**, 59 (1975); (c) D. Shugar, *FEBS Lett.*, **40**, S48 (1974).

(9) J. H. Burchenal, V. E. Currie, M. D. Dowling, J. J. Fox, and I. H. Krakoff, *Ann. N.Y. Acad. Sci.*, **255**, 202 (1975).

(10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(11) (a) L. T. J. Delbaere, M. N. G. James, and R. U. Lemieux, *J. Am. Chem. Soc.*, **95**, 7866 (1973); (b) L. T. J. Delbaere and M. N. G. James, *Acta Crystallogr., Sect. B*, **30**, 1241 (1974); (c) W. Guschlbauer, S. Tran-Dinh, M. Blandin, and J. C. Catlin, *Nucleic Acids Res.*, **1**, 855 (1974), and references cited therein.

(12) P. Roy-Burman, *Recent Results Cancer Res.*, **25**, 1 (1970); G. A. LePage and S. Naik, *Ann. N.Y. Acad. Sci.*, **255**, 481 (1975).

(13) L. L. Bennett, Jr., W. M. Shannon, P. W. Allan, and G. Arnett, *Ann. N.Y. Acad. Sci.*, **255**, 342 (1975).

(14) A. Holy, *Collect. Czech. Chem. Commun.*, **38**, 428 (1973).

(15) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).

(16) O. Kennard, N. W. Isaacs, W. D. S. Motherwell, J. C. Coppola, D. L. Wampler, A. C. Larson, and D. G. Watson, *Proc. R. Soc., London, Ser. A*, **325**, 401 (1971). All computations were carried out with programs written by Ahmed, Hall, Pippy, and Huber. Figure 2 was drawn with the help of the ORTEP II program of C. K. Johnson.

(17) J. A. Ibers and W. C. Hamilton, Ed., "International Tables for X-Ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974.

(18) D. Suck and W. Saenger, *Acta Crystallogr., Sect. B*, **29**, 1323 (1973).

(19) L. T. J. Delbaere and M. N. G. James, *Acta Crystallogr., Sect. B*, **29**, 2905 (1973).

(20) G. Kartha, unpublished results. We thank Dr. Kartha for communicating his results prior to publication.

(21) E. A. Green, R. D. Rosenstein, R. Shiono, D. J. Abraham, B. L. Trus, and R. E. Marsh, *Acta Crystallogr., Sect. B*, **31**, 102 (1975).

(22) C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **94**, 8205 (1972).

(23) T. Brennan and M. Sundaralingam, *Biochem. Biophys. Res. Commun.*, **52**, 1348 (1973).

(24) G. I. Birnbaum, E. Darzynkiewicz, and D. Shugar, *J. Am. Chem. Soc.*, **97**, 5904 (1975).

(25) R. M. Izatt, L. D. Hansen, J. H. Rytting, and J. J. Christensen, *J. Am. Chem. Soc.*, **87**, 2760 (1965).

(26) These distances were calculated from the coordinates of standard furanose rings given by S. Arnott and D. W. L. Hukins, *Biochem. J.*, **130**, 453 (1972).

(27) W. H. Baur, *Acta Crystallogr., Sect. B*, **28**, 1456 (1972).

(28) E. Bisagni, J. Defaye, C. Ducrocq, A. Ducruix, J. Lhoste, and C. Pascard, *Bull. Soc. Chim. Fr.*, in press.

(29) E. Darzynkiewicz, H. Sierakowski, and D. Shugar, *Z. Naturforsch., C*, **30**, 565 (1975).

(30) E. Darzynkiewicz, M. Remin, A. Dworak, and D. Shugar, *Cancer Biochem. Biophys.*, **1**, 85 (1975); M. Remin, E. Darzynkiewicz, A. Dworak, and D. Shugar, *J. Am. Chem. Soc.*, **98**, 367 (1976).

(31) P. Tollin, H. R. Wilson, and D. W. Young, *Acta Crystallogr., Sect. B*, **29**, 1641 (1973).

(32) A. K. Chwang and M. Sundaralingam, *Nature (London), New Biol.*, **243**, 78 (1973); P. Tougard and O. Lefebvre-Soubeyran, *Acta Crystallogr., Sect. B*, **30**, 86 (1974).

(33) R. N. Totty, Ph.D. Thesis, Department of Chemistry, University of Edinburgh, 1966. We are very much indebted to Professor J. C. P. Schwarz for the loan of a copy of this thesis.

(34) Y. J. Park, H. S. Kim, and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, **27**, 220 (1971).

(35) B. Lindberg, B. Lindberg, and S. Svensson, *Acta Chem. Scand.*, **27**, 373 (1973).

(36) J. J. Christensen, J. H. Rytting, and R. M. Izatt, *J. Am. Chem. Soc.*, **88**, 5105 (1966).