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Pyridazine Nucleosides. The Structure and Conformational Analysis of 5-Hydroxy-2-(1-β-D-ribofuranosyl)-3(2*H*)-pyridazinone

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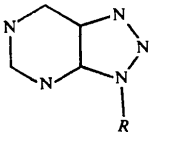
Abstract

The crystal structure of the doubly modified nucleoside 5-hydroxy-2-(1-β-D-ribofuranosyl)-3(2*H*)-pyridazinone or 3-deaza-6-azauridine ($C_9H_{12}N_2O_6$, $M_r = 244{\cdot}206$) has been determined using three-dimensional X-ray counter data. The uridine analog crystallizes in the monoclinic space group $P2_1$ with two molecules in a unit cell of dimensions $a = 7{\cdot}136$ (7), $b = 7{\cdot}636$ (7), $c = 10{\cdot}119$ (8) Å, and $\beta = 101{\cdot}54$ (6)°. D_o (by flotation in tetrahydrofuran–tribromomethane) = 1·50, $D_c = 1{\cdot}504$ Mg m^{-3}, μ(Cu $K\alpha$) = 1·06 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least squares using 848 independent data with $I > 3\sigma(I)$. The structure was refined to a final R factor of 0·046. In the crystal, the nucleoside adopts the 'high-*anti*' conformation around the glycosyl bond with a torsional angle, χ, of 98·6 (4)°. The conformation about the extracyclic bond, C(4′)—C(5′), is *gauche-trans* (*gt*) and the sugar pucker is C(3′)-*endo*—C(2′)-*exo* or $^3T_2$. Conformational analysis as a function of rotation around the glycosyl bond, N(1)—C(1′), has been performed through extensive use of CNDO/2 molecular-orbital calculations. These calculations show that the observed conformation is 5·4 kJ mol^{-1} above the calculated global minimum. The two energy barriers between the *syn* and *anti* regions are 12·1 and 30·5 kJ mol^{-1}.

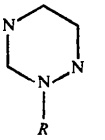
Introduction

Certain modifications of the bases and corresponding nucleosides and nucleotides of ribonucleic acids (RNA) and deoxyribonucleic acids (DNA) have proven to possess very interesting biological and chemotherapeutic properties (Skoda, 1963; Roblin, Lampen, English, Cole & Vaughan, 1945; Kidder, Dewey, Parks & Woodside, 1949; Montgomery, Elliot & Thomas, 1975). The differences in activity between the naturally occurring bases and the modified bases are due in part to the structural changes and in part to the electronic effects brought about by the various modifications. One general class of modified bases is characterized by the substitution of an N atom for a C—H group or *vice versa*. This class includes the 8-azapurines, 6-azapyrimidines, and 3-deazapyrimidines.

Nucleosides of 8-azapurines (I) and 6-azapyrimidines (II), which are known collectively as *ortho*-azanucleosides, have the interesting feature that without the H atom at the *ortho* position, the steric barrier to rotation of the base around the glycosyl bond is greatly reduced (Donohue & Trueblood, 1960). In addition, the *ortho* substitution provides the nucleoside with another potentially basic site which may alter the basicity of other N atoms and/or interact (hydrogen bond) with certain groups within the ribose moiety. Changes of this variety are presumably responsible for the cytostatic activity of 6-azauridine (Skoda, 1963); the inhibitory (to DNA synthesis) effect of 6-azathymidine (Prusoff, Lajth & Welch, 1956); the antiviral (Kahre, Sidwell, Huffman, Tollman & Robins, 1972; Schannon, Arnett & Schabel, 1972), antileukemic (Robins, Currie, Robins & Bloch, 1969; Bloch, Dutschman, Currie, Robins & Robins, 1973), and inhibitory (to RNA polymerase from *E. coli*) (Wang & Bloch, 1972) activities of 3-deazauridine and 3-deazacytidine; and the antineoplastic (Kidder & Dewey, 1949) and antitumor (Law, 1950) activity of 8-azaguanine.



(I)



(II)

R = Ribose

In view of the biological activity of these analogs, a pyrimidine nucleoside which incorporates both the 6-aza and 3-deaza modifications might prove to possess equally or even more interesting properties. The synthesis of one such analog has been achieved to yield the title complex, 3-deaza-6-azauridine (Katz, Wise & Townsend, 1975). The activity of this analog has not yet been fully tested. We have, therefore, undertaken a crystal structure determination of this molecule in order to attempt to predict the likelihood of biological activity

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similar to that of the other analogs. A preliminary report on the crystal structure of this nucleoside has appeared (Graves, Hodgson, Katz, Wise & Townsend, 1978). We present here a final, more precise determination of the crystal and molecular structure of 3-deaza-6-azauridine. In order to elucidate the electronic effects of this double modification of uridine, we also report molecular-orbital calculations of the atomic charge densities for this molecule. Finally, a conformational energy map as a function of rotation around the glycosidic bond has been calculated.

Experimental

X-ray data collection

Colorless crystals of 3-deaza-6-azauridine (3-deaza-6-azaUrd) were generously donated to us by Professor Leroy B. Townsend of the University of Utah. The crystal selected for data collection was flat and nearly triangular with approximate dimensions 0·29 × 0·27 × 0·07 mm in the [100], [010], and [001] directions, respectively. Preliminary Weissenberg and precession photographs show that the crystal is in the monoclinic system. The only systematic absences occur in the $0k0$ zone for odd values of k. This leads to a choice of either $P2_1$ or $P2_1/m$ for the space group, but since the molecular unit can neither lie on a mirror plane nor possess a center of inversion, the space group must be $P2_1$. Least-squares refinement of the diffractometer settings for 12 independent reflections yielded the cell constants a = 7·136 (7), b = 7·636 (7), c = 10·119 (8) Å, and β = 101·54 (6)°.

Diffraction data were collected on a Picker four-circle, automatic diffractometer equipped with copper radiation, a nickel filter, and a scintillation counter. The wavelength of the radiation was assumed to be λ(Cu $K\alpha$) = 1·5418 Å. The data were collected at a take-off angle of 1·2° by the θ–2θ scan technique in the range $2\theta \leq 125°$ at a scan rate of 2° (2θ) min^{-1}. To allow for the presence of both $K\alpha_1$ and $K\alpha_2$ radiations, the reflections were scanned from 0·90° (2θ) below the calculated $K\alpha_1$ peak position to 0·90° (2θ) above the calculated $K\alpha_2$ position. Stationary-counter, stationary-crystal background counts of 10 s were measured at both ends of every scan. Throughout data collection the intensities of three standard reflections were monitored after every 100 reflections. The intensities did not deviate from the mean by more than would be predicted by counting statistics.

Data reduction was carried out according to the method of Corfield, Doedens & Ibers (1967). After correction for background radiation, the intensities, I, were assigned standard deviations using the formula $\sigma(I) = [C + 0{\cdot}25(t_s/t_b)^2(\mathrm{BH} + \mathrm{BL}) + (pI)^2]^{1/2}$ where the quantities have their usual definitions and a value of 0·04 was assigned to the correction factor, p. The intensities and their standard deviations were then corrected for Lorentz–polarization effects. No attempt was made to correct the data for absorption. A total of 876 independent reflections were processed and of these 855 had $I > 3\sigma(I)$. Only these latter data were considered to be observed and used in subsequent calculations. Seven reflections of the observed set were rejected because it was apparent that they had flooded the scintillation counter.

Solution and refinement of the structure

The structure was solved (with a great deal of difficulty due to the hypercentrosymmetry of the structure) by direct methods (Karle & Karle, 1966) using the multiple-solution program *MULTAN* (Germain, Main & Woolfson, 1971). Program *NORMAL* (Main, 1970) was used with the pyridazine unit as an atomic group to calculate a set of 74 normalized structure factors, E, with values greater than 1·65. This set of E values was used as input to *MULTAN* which then generated 16 possible solutions. Sixteen of seventeen non-hydrogen atoms were eventually picked out of the solution with the third lowest value of R_{Karle} (21·5%) and the third highest figure of merit, ABS FOM (0·9595).

The atomic parameters were refined by full-matrix, least-squares techniques. The refinement was carried out on F, the function minimized being $\sum w(|F_o| - |F_c|)^2$ where the weights, w, were taken as $w = 4F_o^2/\sigma^2(F_o^2)$. The atomic scattering factors for all atoms were taken from *International Tables for X-ray Crystallography* (1974). The last non-hydrogen atom was found in a subsequent difference Fourier map. Isotropic refinement of these 17 atoms gave values of the usual residuals, $R_1 = \sum ||F_o| - |F_c||/\sum |F_o|$ and R_2 (weighted R factor) = $[\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$, of 0·123 and 0·178, respectively. Anisotropic refinement of these atoms lowered the two R factors to 0·081 and 0·119. At this stage all H atoms were found in a difference Fourier map and their isotropic thermal parameters, B, were successfully varied. It was apparent at this point that the data were suffering from secondary extinction, since for strong low-order data $|F_o|$ was consistently smaller than $|F_c|$, so a correction of the type suggested by Zachariasen (1963, 1968) was applied. The value of the extinction coefficient, c, was found to refine to 6·5 (2) × 10^{-8}. Thus, in the final cycle of least squares there were 848 observations and 166 variables; no parameter shifted by more than 0·1σ, which is taken as evidence of convergence. The final derived values of R_1 and R_2 are 0·046 and 0·063, respectively. The difference Fourier map following the last cycle of least squares revealed no significant residual electron density; the highest peak was 0·34 e Å^{-3}.

Table 1. *Atomic positional parameters for 3-deaza-6-azauridine*

	x	y	z	U_{eq}‡ or U (Å^2)
N(1)*	0·3425 (4)	0·2863	0·1329 (3)	0·033 (1)
C(2)	0·2822 (5)	0·3071 (7)	−0·0035 (3)	0·038 (2)
O(2)	0·1069 (3)	0·2959 (8)	−0·0537 (2)	0·059 (1)
C(3)	0·4267 (5)	0·3360 (8)	−0·0795 (3)	0·046 (2)
C(4)	0·6119 (5)	0·3463 (7)	−0·0151 (4)	0·038 (2)
O(4)	0·7479 (4)	0·3766 (7)	−0·0871 (3)	0·055 (1)
C(5)	0·6557 (5)	0·3298 (8)	0·1268 (4)	0·047 (2)
N(6)	0·5279 (4)	0·3016 (7)	0·1996 (3)	0·043 (2)
C(1′)	0·1980 (5)	0·2617 (7)	0·2177 (3)	0·035 (2)
C(2′)	0·2743 (5)	0·1897 (7)	0·3575 (4)	0·039 (2)
O(2′)	0·1214 (5)	0·1081 (6)	0·4043 (3)	0·052 (2)
C(3′)	0·3184 (5)	0·3569 (7)	0·4407 (3)	0·035 (2)
O(3′)	0·3284 (3)	0·3359 (6)	0·5809 (2)	0·046 (2)
C(4′)	0·1518 (5)	0·4742 (7)	0·3746 (3)	0·034 (2)
O(4′)	0·1105 (3)	0·4254 (5)	0·2340 (2)	0·036 (1)
C(5′)	0·1950 (6)	0·6671 (7)	0·3847 (4)	0·041 (2)
O(5′)	0·0292 (3)	0·7715 (6)	0·3284 (2)	0·040 (2)
H(3)†	0·388	0·345	−0·177	0·04 (1)
HO(4)	0·875	0·346	−0·029	0·11 (2)
H(5)	0·787	0·336	0·175	0·07 (1)
H(1′)	0·099	0·177	0·174	0·05 (1)
H(2′)	0·388	0·122	0·358	0·05 (1)
HO(2′)	0·098	0·004	0·364	0·10 (2)
H(3′)	0·437	0·405	0·432	0·01 (1)
HO(3′)	0·235	0·259	0·600	0·11 (2)
H(4′)	0·042	0·453	0·415	0·03 (1)
H(15′)	0·292	0·690	0·339	0·04 (1)
H(25′)	0·229	0·695	0·478	0·07 (1)
HO(5′)	−0·013	0·758	0·230	0·04 (1)

* The y coordinate defines the origin.

† H atom positional parameters were not refined.

‡ For anisotropic atoms, U_{eq} was calculated from the expression $U_{eq} = (1/6\pi^2)\sum_i\sum_{j\geq i}\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

The atomic positional parameters obtained from the last cycle of least squares, along with their standard deviations as estimated from the inverse matrix, are presented in Table 1.*

Molecular-oribital calculations

Conformational analysis of rotation around the glycosidic bond was performed using MO calculations with the CNDO/2 approximation (Pople & Beveridge, 1970). The geometry of the starting molecule was the crystallographically observed conformation except that the C—H and O—H distances were extended along the bond direction to 1·08 and 0·97 Å, respectively. Atomic coordinates for alternate conformations were obtained by rotating the ribose moiety as a rigid unit at 15° intervals around the N(1)—C(1′) bond while maintaining the base at a fixed position. Smaller rotation intervals were used in the neighborhood of maxima and minima.

Electronic charge densities were calculated for the nucleoside in its crystallographic conformation using the CNDO/2 method. The net atomic charge is defined as the number of valence electrons minus the nuclear charge, which is calculated as the sum of the diagonal elements in the density matrix for the particular atom.

* Lists of observed and calculated structure amplitudes and of anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36035 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion

The base

A view of 3-deaza-6-azaUrd is shown in Fig. 1. Lists of all bond lengths and angles within the nucleoside are compiled in Tables 2 and 3, respectively. A comparison of bond lengths within the pyrimidine portion of uridine (Green, Rosenstein, Shiono, Abraham, Trus & Marsh, 1975), cytidine (Furberg, Petersen & Rømming, 1965), thymidine (Young, Tollin & Wilson, 1969), and their 3-deaza (Schwalbe & Saenger, 1973*a*; Hutcheon & James, 1977) and 6-aza derivatives (Schwalbe & Saenger, 1973*b*; Singh & Hodgson, 1974*b*; Banerjee & Saenger, 1978) reveals that a primary feature of the 6-aza structures is the expected shortening of the C(5)—N(6) bond and concomitant lengthening of the C(4)—C(5) bond relative to the corresponding bonds in the natural nucleosides. Another interesting characteristic is that the N(6)—N(1) bond length is very similar to the C(6)—N(1) distance in the natural analogs, indicating a loss of some double-bond character in the aza analogs. The common features of the two 3-deaza structures are the lengthening of the C(2)—C(3) bond and of the extracyclic C(4)—O(4) [C(4)—N(4) in cytidine] bond

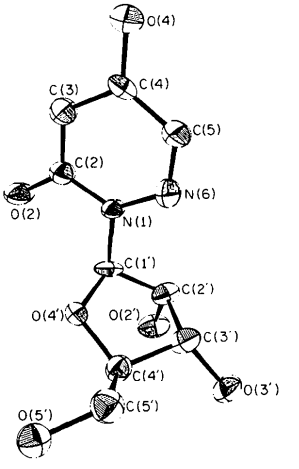

Fig. 1. An *ORTEP* drawing (Johnson, 1965) of 3-deaza-6-azauridine with H atoms removed for clarity. Thermal ellipsoids are shown at 50% probability.

relative to the parent nucleosides. The expected lengthening of the C(3)–C(4) bond is exhibited in 3-deazacytidine (3-deazaCyd) but this bond is actually somewhat shorter (3σ) in 3-deazauridine (3-deazaUrd) compared to uridine (Urd). This is due to the fact that Urd is in the diketo form while 3-deazaUrd is necessarily in the keto–enol form [as confirmed by a much longer C(4)–O(4) bond in 3-deazaUrd] which forces C(3)–C(4) to be a formal double bond. This same effect is observed in the structure of 3-deaza-4-deoxyuridine (Egert, Lindner, Hillen & Gassen, 1977) in which the C(3)–C(4) bond distance (1·334 Å) is clearly indicative of a full double bond.

Table 2. *Bond lengths* (Å) *in* 3-*deaza*-6-*azauridine*

No e.s.d. is provided for distances involving H atoms since H-atom coordinates were not refined.

N(1)–C(2)	1·371 (4)	C(1′)–O(4′)	1·422 (5)
C(2)–O(2)	1·255 (4)	C(1′)–C(2′)	1·514 (5)
C(2)–C(3)	1·421 (5)	C(2′)–O(2′)	1·418 (5)
C(3)–C(4)	1·354 (5)	C(2′)–C(3′)	1·527 (5)
C(4)–O(4)	1·345 (4)	C(3′)–O(3′)	1·415 (4)
C(4)–C(5)	1·413 (5)	C(3′)–C(4′)	1·532 (6)
C(5)–N(6)	1·300 (5)	C(4′)–O(4′)	1·443 (4)
N(6)–N(1)	1·365 (4)	C(4′)–C(5′)	1·504 (6)
N(1)–C(1′)	1·479 (4)	C(5′)–O(5′)	1·446 (5)
C(3)–H(3)	0·97	C(3′)–H(3′)	0·94
O(4)–HO(4)	1·00	O(3′)–HO(3′)	0·94
C(5)–H(5)	0·97	C(4′)–H(4′)	0·96
C(1′)–H(1′)	1·00	C(5′)–H(15′)	0·92
C(2′)–H(2′)	0·96	C(5′)–H(25′)	0·95
O(2′)–HO(2′)	0·90	O(5′)–HO(5′)	0·99

Table 3. *Bond angles* (°) *in* 3-*deaza*-6-*azauridine*

No e.s.d. is provided for angles involving H atoms since H-atom coordinates were not refined.

N(6)–N(1)–C(1′)	116·3 (3)	C(2)–C(3)–H(3)	118
N(6)–N(1)–C(2)	124·5 (3)	C(4)–C(3)–H(3)	122
C(1′)–N(1)–C(2)	118·9 (3)	C(4)–O(4)–HO(4)	108
N(1)–C(2)–O(2)	119·1 (3)	C(4)–C(5)–H(5)	120
N(1)–C(2)–C(3)	116·6 (3)	N(6)–C(5)–H(5)	116
O(2)–C(2)–C(3)	124·3 (3)	N(1)–C(1′)–H(1′)	110
C(2)–C(3)–C(4)	119·5 (3)	C(2′)–C(1′)–H(1′)	106
C(3)–C(4)–O(4)	119·4 (3)	C(1′)–C(2′)–H(2′)	110
C(3)–C(4)–C(5)	118·7 (3)	O(2′)–C(2′)–H(2′)	118
O(4)–C(4)–C(5)	121·9 (3)	C(3′)–C(2′)–H(2′)	112
C(4)–C(5)–N(6)	123·6 (3)	C(2′)–O(2′)–HO(2′)	109
C(5)–N(6)–N(1)	117·1 (3)	C(2′)–C(3′)–H(3′)	112
N(1)–C(1′)–O(4′)	109·2 (3)	O(3′)–C(3′)–H(3′)	106
N(1)–C(1′)–C(2′)	115·2 (3)	C(4′)–C(3′)–H(3′)	111
O(4′)–C(1′)–C(2′)	107·1 (3)	C(3′)–O(3′)–HO(3′)	113
C(1′)–C(2′)–O(2′)	108·3 (3)	C(3′)–C(4′)–H(4′)	110
C(1′)–C(2′)–C(3′)	102·0 (3)	O(4′)–C(4′)–H(4′)	110
O(2′)–C(2′)–C(3′)	105·7 (3)	C(5′)–C(4′)–H(4′)	108
C(2′)–C(3′)–O(3′)	114·9 (3)	C(4′)–C(5′)–H(15′)	109
C(2′)–C(3′)–C(4′)	101·1 (3)	C(4′)–C(5′)–H(25′)	107
O(3′)–C(3′)–C(4′)	112·6 (3)	O(5′)–C(5′)–H(15′)	110
C(3′)–C(4′)–C(5′)	114·3 (3)	O(5′)–C(5′)–H(25′)	107
C(3′)–C(4′)–O(4′)	105·5 (3)	H(15′)–C(5′)–H(25′)	112
C(5′)–C(4′)–O(4′)	108·6 (4)	C(5′)–O(5′)–HO(5′)	114
C(4′)–O(4′)–C(1′)	109·5 (3)	O(4′)–C(1′)–H(1′)	110
C(4′)–C(5′)–O(5′)	111·9 (3)		

Dihedral angles

N(6)–N(1)–C(1′)–O(4′)	98·6 (4)
O(4′)–C(4′)–C(5′)–O(5′)	66·2 (4)
C(3′)–C(4′)–C(5′)–O(5′)	−176·2 (3)

Within the base portion, the structure of 3-deaza-6-azauridine exhibits most of the structural changes that are observed in the 3-deaza structures: there is a lengthening of the C(2)–O(2) and C(2)–C(3) bonds (8 and 10σ, respectively, relative to Urd). A shortening (5σ) of the C(3)–C(4) bond, similar to that observed in 3-deazaUrd and 3-deaza-4-deoxyuridine, is also observed here. As in 3-deazaUrd, 3-deaza-6-azaUrd is in the keto–enol form and consequently a large elongation of C(4)–O(4) is observed. Again, despite the 6-aza substitution, there is very little change in the N(6)–N(1) bond length over the C(6)–N(1) distance in Urd, but the expected diminution of the C(5)–N(6) bond is seen (7σ). It is interesting to note, though, that this change is not more than is expected since an N atom has a smaller covalent radius (Pauling, 1960) (by about 0·04 Å) than a C atom. One feature that appears in the doubly modified nucleoside that is not observed in either of the singly modified nucleosides of uridine is a slight shortening of the C(4)–C(5) bond which indicates an increase of aromatic character in the ring. This effect is even more pronounced in the structure of 3-deaza-4-deoxyUrd in which this bond is ~0·04 Å shorter than it is in Urd. In all the derivatives mentioned so far, the N(1)–C(1′) glycosidic bond is shorter than it is in the parent nucleoside. The change ranges from 1σ for 6-azathymidine (6-azaThd) to 8σ for 3-deazaCyd. In 3-deaza-6-azaUrd the N(1)–C(1′) bond is $2{\cdot}8\sigma$ (0·011 Å) shorter than it is in Urd.

The primary effects of the N substitution in the 6-aza structures are a smaller internal angle at N(6) and corresponding larger internal angles at both C(5) and N(1). The two 3-deaza structures exhibit only a few common, significant changes relative to their parent structures. The problem, again, is due to the tautomeric alteration which must accompany the C(3) substitution in uridine. Thus, while we expect to observe internal-angle expansion at the 3 position (as is the case for 3-deazaCyd), this angle is almost 6° smaller in 3-deazaUrd than it is in Urd. The internal angles at the adjacent atoms also show changes which are in the opposite direction as expected. Thus, while the angles at C(2) and C(4) expand in 3-deazaUrd, they contract in 3-deazaCyd. The other significant angle changes involve the two external angles at C(4) and in this case they are in the same direction: C(3)–C(4)–O(4)-[N(4)] is expanded and C(5)–C(4)–O(4)[N(4)] is contracted.

A common feature of all the modified nucleosides is the significant contraction of the C(1′)–N(1)–C(6)-[N(6)] angle. This is probably related to the con-

Table 4. *Least-squares planes in 3-deaza-6-azauridine and atom deviations* (Å)

Plane 1: Least-squares plane through the six base-ring atoms.
Plane 2: Best four-atom least-squares plane in the ribose moiety.
Plane 3: Three-atom plane defining the ribose conformation.

Plane 1		Plane 2		Plane 3	
*N(1)	0·020 (1)	*C(1′)	0·046 (4)	*C(1′)	0·000 (4)
*C(2)	−0·015 (5)	*C(2′)	−0·027 (4)	*O(4′)	0·000 (3)
*C(3)	−0·000 (6)	*C(4′)	0·029 (4)	*C(4′)	0·000 (4)
*C(4)	0·011 (5)	*O(4′)	−0·048 (3)	C(2′)	−0·219 (4)
*C(5)	−0·007 (6)	C(3′)	0·579 (4)	C(3′)	0·404 (4)
*N(6)	−0·008 (5)	C(5′)	0·891 (4)	C(5′)	0·937 (4)
O(2)	−0·029 (6)				
O(4)	0·003 (5)				
C(1′)	−0·038 (5)				

* Denotes atoms included in the plane calculation.

formation of the ribose and of the base relative to the ribose and will be discussed later. 3-Deaza-6-azaUrd exhibits this same effect; a contraction of almost 6° is observed.

As a rule, the angle changes in 3-deaza-6-azaUrd, compared to Urd, conform to the changes observed in the singly modified nucleosides. That is, the values of Δ (analog-parent) for angles involving C(2), C(3), or C(4) follow those for 3-deazaUrd and for N(1), N(6), or C(5) they follow those for 6-azaUrd. The lone exception to this rule is with the C(3)–C(4)–O(4) angle. In 6-azaUrd and 3-deazaUrd this angle is 3·5 and 3·9° larger, respectively, than it is in Urd while it is 0·1° smaller in 3-deaza-6-azaUrd.

The pyridazine ring is planar. The results of a least-squares plane calculation including the six atoms of the base ring are shown in Table 4. The maximum deviation for a ring atom is 0·020 Å and for an exocyclic atom it is 0·038 Å. The planarity of the pyridazine ring reflects the overall aromatic character of the ring, and the bond distances are further support: no distance approaches that of a single bond and only C(3)–C(4) and C(5)–N(6) are close to values for a full double bond.

The ribose

It has been noted by Singh & Hodgson (1977) and by Sundaralingam (1973) that the bond angles and, to a much lesser extent, distances within the ribose unit are related to the conformational pucker of the ring. Compared to other nucleosides referenced in this paper {Urd [C(3′)-*endo*], Cyd [C(3′)-*endo*], Thd [C(3′)-*exo*], 3-deazaUrd [C(2′)-*endo*], 3-deazaCyd [C(2′)-*endo*], 6-azaUrd [C(3′)-*endo*], 6-azaCyd [C(3′)-*endo*], and 6-azaThd [C(2′)-*exo*–C(3′)-*endo*]}, the distances within the sugars vary minimally: most are within 3σ and all but four are within 4σ of the ribose distances in 3-deaza-6-azaUrd. From the ribose least-squares planes tabulated in Table 4 it can be seen that 3-deaza-6-azaUrd adopts a C(3′)-*endo*–C(2′)-*exo** or ${}^3T_2$ conformation (Sundaralingam, 1972) in the crystal. Thus, it is expected to conform most closely to the C(3′)-*endo* sugars. This is, in fact, clearly demonstrated for the ribose bond angles. The average angular differences between the 3-deaza-6-azaUrd ribose and those of 3-deazaCyd, 3-deazaUrd and Thd are 2·3, 2·1, and 1·9°/angle, respectively. But for sugars with at least some component of C(3′)-*endo* pucker, the differences range from 1·2 to 1·6°/angle. The angles which deviate the most, on average, are the ones involving extracyclic atoms. This is due, in part, to the diminished constraint (relative to ring atoms) on these atoms and, in part, to the fact that these atoms are involved in various hydrogen-bonding schemes. Thus, while the difference per angle for the five endocyclic angles is between 0·7 and 1·3°, the worst extracyclic deviations range from 1·9 to 5·0°/angle.

Statistics show (Sundaralingam, 1973) that nucleosides in general and pyrimidine nucleosides in particular have a great deal of conformational flexibility relative to the corresponding nucleotides. This is evident not only in the sugar pucker but also in the conformation of C(5′)–O(5′) about the extracyclic C(4′)–C(5′) bond (Sundaralingam, 1965). While there is a slight preference for the *gg* conformer in pyrimidine nucleosides, *gt* and *tg* conformations do occur. Thus, 3-deaza-6-azaUrd is in the *gt* conformation, as are 3-deazaCyd, 6-azaUrd, and Thd, but 3-deazaUrd, 6-azaCyd, 6-azaThd, Urd, and Cyd are all *gg*. The dihedral angles which define this conformation are given for 3-deaza-6-azaUrd in Table 3.

The glycosyl conformation

The glycosyl torsion angle, χ [N(6)–N(1)–C(1′)–O(4) as defined by Sundaralingam (1969)], describes the orientation of the base relative to the sugar. The value of χ for 3-deaza-6-azaUrd in the crystal is 98·6° (Table 3). This value is outside the standard *anti* region ($-15° \leq \chi \leq 75°$) suggested by Haschemeyer & Rich (1967) but it is not near the *syn* region ($165° \leq \chi \leq 255°$). Consequently, this region of χ space just above 75° is known as the 'high-*anti*' range (Prusiner, Brennan & Sundaralingam, 1973). This conformation appears to be a common feature of most *ortho*-azanucleosides including 6-azaUrd (81·3 and 76·3°), 6-azaCyd (99·1°), 6-azaThd (88·0°), 8-azaadenosine (103·7°) (Singh & Hodgson, 1977), formycin A (109·5°) (Prusiner *et al.*, 1973) and 8-azatubercidin (102·4°) (Sprang, Scheller, Rohrer & Sundaralingam, 1978). *ortho*-Aza substitution results in the loss of an H atom from and the absence of a positive charge on the atom at that position (see below). This combination of

* Regrettably, in the preliminary report on this structure the ribose conformation was incorrectly reported as C(2′)-*endo*–C(3′)-*exo*.

steric and electronic effects permits the base to rotate to higher values of χ, brings the *ortho* N atom into a close contact with C(2′) and H(2′) (2·78 and 2·48 Å, respectively), and allows the base to tilt more toward the ribose.

A conformational energy diagram as a function of rotation about the glycosidic bond in 3-deaza-6-azaUrd is depicted in Fig. 2. An analogous profile for 6-azaUrd is also included in that figure. A theoretical calculation for 6-azaUrd using an assumed ribose conformation and average bond distances has been carried out by Pullman & Berthod (1972) with the PCILO method. More recent PCILO calculations have been performed by Mitra & Saran (1978) using crystallographic coordinates. The calculations employed here use the crystallographic coordinates and the CNDO/2 approximation. The results of the three different 6-azaUrd calculations are quite similar. Qualitatively they agree very well except that there is an extra energy maximum in the Pullman curve. Quantitatively the agreement is poor. The two PCILO calculations result in a global maximum that is 4–5 times larger than the same maximum in the CNDO/2 calculation. The two curves in Fig. 2 are both qualitatively and quantitatively very similar. This is not surprising due to the similarity of their ribose puckers, of the conformations around the C(4′)–C(5′) bond, and of the extent to which the base is tilted toward the sugar [as measured by the N(6)–N(1)–C(1′) bond angle].

Fig. 3 is a diagram of selected, non-bonded interatomic distances within 3-deaza-6-azaUrd. Most of the features of the energy map in Fig. 2 can be explained on the basis of these contacts. For example, the maximum at $\chi = 310°$ is probably due to the severe steric contacts between O(2) and both C(2′) and H(2′). Similarly, the maximum at $\chi = 170°$ is a result of the close contact of O(2) and O(4′), two atoms with net negative charges. The position of the calculated global minimum appears to be unusual in view of the close contact between N(6) and O(4′) but this contact is neither severe (only ~0·2 Å below the sum of their contact radii) nor electronically unfavorable [since the net residual charge on N(6) is almost zero]. The other low-energy minimum near $\chi = 230°$ is the result of no severe steric or electronic contacts at that point. However, the energy rise at $\chi = 255°$ and fall at $\chi = 280°$ cannot be explained by this diagram.

In the crystal, 3-deaza-6-azauridine is not found to be at the calculated global minimum. However, its conformation is at a local minimum which is only 5·4 kJ mol^{-1} above the global minimum, and hydrogen bonding and crystal-packing forces could easily account for this small shift. The energy barrier for the *syn* ⇌ *anti* conversion is about 12·1 kJ mol^{-1} in one direction and 30·5 kJ mol^{-1} in the other. In solution these barriers are undoubtedly even smaller. The calculated global minimum occurs near $\chi = 0°$ but a region near $\chi = 220°$ is only slightly above this minimum. Thus, for the isolated molecule a high-*anti* conformation may not be preferred. Similarly, our curve for 6-azaUrd does not have its global minimum in the high-*anti* range as the curves of Pullman & Berthod (1972) and Mitra & Saran (1978) do. However, the differences between the curves in terms of the global and low-lying minima are probably not meaningful since an energy shift of 2 kJ mol^{-1} or less will convert one curve into another. In the absence of the intramolecular steric and electronic effects that accompany the 6-aza substitution a high-*anti* nucleoside would be a high-energy conformer. With them, the high-*anti* region is at least accessible if not the lowest energy conformation. Conformations with χ less than

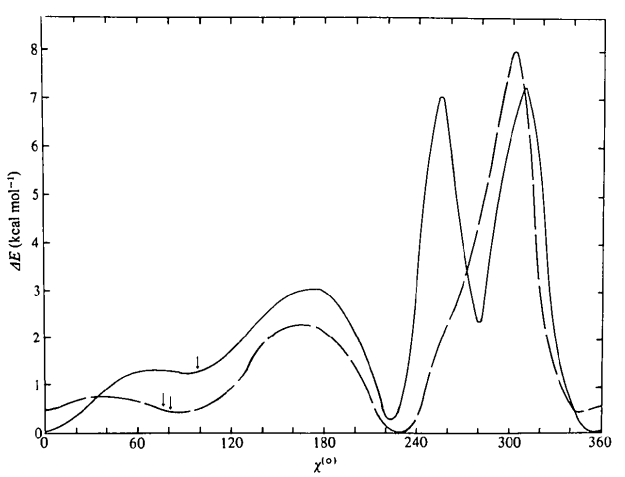

Fig. 2. A conformational energy map for rotation around the glycosyl bond (1 kcal ≡ 4·18 kJ). The solid curve is for 3-deaza-6-azauridine and the broken curve is for 6-azauridine. The arrows indicate the experimentally observed conformations for the two nucleosides.

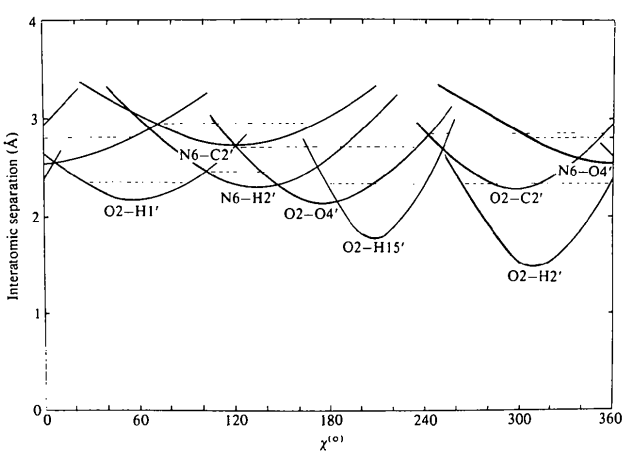

Fig. 3. A diagram of close, intramolecular, nonbonded contacts within 3-deaza-6-azauridine. The dashed horizontal lines represent the sum of the contact radii for the two interacting atoms.

~340° are still prohibited by a large barrier in that region and intermolecular crystal packing and hydrogen bonding seem consistently to stabilize a high-*anti* arrangement. One hydrogen-bonding interaction that is frequently seen in *ortho*-azanucleosides and which is not possible in the parent nucleosides involves O(4′). Of the *ortho*-azanucleosides cited in this paper only 6-azaThd has no interaction involving O(4′) and that may be partially due to the presence of a deoxyribose instead of a ribose ring.

In order to obtain a better understanding of the electronic changes and effects within 3-deaza-6-azaUrd, the CNDO/2 method has been used to calculate the net atomic charge densities. These values, along with the charges for Urd, 3-deazaUrd, and 6-azaUrd, are included in Table 5. As was true for the base bond lengths, 3-deaza-6-azaUrd is most similar to 3-deazaUrd at the 2, 3, and 4 positions and to 6-azaUrd at the 5 and 6 positions. N(1) has approximately the same net charge in all the nucleosides. In 3-deazaUrd, C(3) has the same charge as N(3) in Urd and 6-azaUrd, but in 3-deaza-6-azaUrd C(3) is less negative than 6-azaUrd by 0·025 e. One of the more striking features of the charge density calculation is that N(6) in both 3-deaza-6-azaUrd and 6-azaUrd has almost no net residual negative charge. The same is true for 6-azaCyd (Singh & Hodgson, 1974*b*) and for the bases 6-azauracil (Singh & Hodgson, 1974*a*; Hodgson & Singh, 1976) and 6-azathymine (Singh & Hodgson, 1975) as reflected by the charge densities and bond lengths involving N(6). Thus, 6-aza substitution does not provide a base or nucleoside with an additional basic site. Atomic charges within the ribose moiety are similar for all four nucleosides.

Table 5. *Net residual atomic charges* (e)

The estimated standard deviation for these values is 0·05 e.

	Uridine*	3-Deaza-uridine	6-Aza-uridine†	3-Deaza-6-azaUrd
N(1)	−0·19	−0·14	−0·14	−0·09
C(2)	0·44	0·35	0·44	0·34
O(2)	−0·39	−0·42	−0·37	−0·40
N(3)‡	−0·24	−0·22	−0·23	−0·14
H(3)	0·14	0·05	0·14	0·04
C(4)	0·37	0·27	0·35	0·23
O(4)	−0·36	−0·27	−0·32	−0·23
HO(4)	–	0·17	–	0·15
C(5)	−0·16	−0·15	−0·03	0·00
H(5)	0·04	0·04	0·03	0·01
C(6)§	0·17	0·16	−0·01	−0·03
H(6)	0·01	0·01	–	–
C(1′)	0·22	0·24	0·22	0·22
H(1′)	0·02	0·03	0·01	0·00
C(2′)	0·12	0·10	0·11	0·11
H(2′)	0·00	0·00	−0·01	−0·01
O(2′)	−0·24	−0·28	−0·25	−0·25
HO(2′)	0·15	0·16	0·14	0·14
C(3′)	0·14	0·12	0·13	0·14
H(3′)	−0·02	−0·01	−0·01	−0·01
O(3′)	−0·25	−0·28	−0·26	−0·26
HO(3′)	0·14	0·17	0·15	0·15
C(4′)	0·12	0·13	0·13	0·12
H(4′)	0·00	0·01	0·00	0·00
O(4′)	−0·25	−0·25	−0·24	−0·24
C(5′)	0·14	0·13	0·14	0·13
H(15′)	−0·01	−0·01	−0·02	−0·01
H(25′)	−0·01	0·00	−0·01	−0·01
O(5′)	−0·26	−0·26	−0·25	−0·26
HO(5′)	0·15	0·15	0·14	0·15

* Molecule *A* was used for this calculation.
† Molecule *B* was used for this calculation.
‡ C(3) in 3-deazauridine and 3-deaza-6-azauridine.
§ N(6) in 6-azauridine and 3-deaza-6-azauridine.

Hydrogen bonding and crystal packing

Table 6 contains a list of probable hydrogen-bonding interactions. In the hydrogen-bonding network both O(2) and O(5′) participate as double acceptors. This is relatively uncommon but not without precedence. For example, hydrogen-bonding schemes similar to this have been observed in the inorganic complexes pentaammine(1-methylcytosinato)ruthenium(III) (Graves & Hodgson, 1979), tetraaquabis(8-azahypoxanthinato)-cadmium(II) (Purnell, Estes & Hodgson, 1976) and diaqua(2,2′-bipyridyl)(inosine 5′-monophosphato)-copper(II) nitrate (Aoki, 1977) as well as in the structures of uracil (Stewart & Jensen, 1967) and 6-azacytidine. Atom O(4′) is apparently involved in a weak interaction with H(5), the C···O distance and C—H···O angle being 3·29 Å and 160°, respectively. It is possible that O(2′) is involved in a weak interaction with O(3′) and HO(3′), but the O(3′)—HO(3′)···O(2′) angle of 106·3° suggests that any such interaction must be very weak. It is interesting to note that the one available N atom, N(6), is not part of any hydrogen bond. The same is true for other 6-aza-nucleosides and 6-azapyrimidines, which is further evidence that N(6) is not a basic site.

Fig. 4 is a packing diagram viewed normal to the crystallographic *ab* plane. The columns of hydrophobic and hydrophilic regions are evident. The bases are planar and roughly parallel to the *ac* plane. The ribose moiety is nearly perpendicular to the base plane; the angle between normals to the six-atom base and five-atom ribose least-squares planes is 105·5°. From the figure it is clear that the bases do stack but adjacent

Table 6. *Probable A—H···B hydrogen bonds in 3-deaza-6-azauridine*

A	H	*B*	*A···B* (Å)	H···*B* (Å)*	*A*—H···*B* (°)*
O(4)—HO(4)···O(2)^{i}			2·587 (5)	1·76	137·3
O(2′)—HO(2′)···O(5′)^{ii}			2·725 (5)	1·86	163·2
O(3′)—HO(3′)···O(5′)^{iii}			2·926 (4)	2·15	138·6
O(5′)—HO(5′)···O(2)^{iv}			2·768 (5)	1·80	164·1

Symmetry code: (i) $1+x, y, z$; (ii) $x, y-1, z$; (iii) $-x, y-\frac{1}{2}, 1-z$; (iv) $-x, \frac{1}{2}+y, -z$.

* No estimated standard deviation is given for these data since H atom parameters were not varied.

bases are not parallel; the angle formed is 19·2°. Adjacent bases going up a column are related by a screw axis and a unit-cell translation along **a**. Alternating bases are related by a unit-cell translation along **b**. Hence, the mean stacking distance is $b/2$ or 3·82 Å. Because of the sizable tilt between bases the stacking contacts vary from 3·21 to 4·56 Å. As seen in Fig. 5, the extent of base overlap is quite large. The view in Fig. 5 is along the crystallographic b axis. The highly polar O(2) atoms (−0·40 e) do not overlap the rings of adjacent bases at all. The C(3)—C(4) bond lies directly on top of N(1). The bond-over-ring type of overlap seen here is not as common as having a single polar group or atom sit over the adjacent ring but it is known (Bugg, Thomas, Sundaralingam & Rao, 1971) and the overlap here is similar to what is seen in the crystal structure of 9-methyladenine (Stewart & Jensen, 1964).

The results of this investigation show that 3-deaza-6-azauridine exhibits the structural and electronic alterations that occur in 3-deazauridine and 6-azauridine individually. On this basis, we expect 3-deaza-6-azauridine to possess biological properties similar to those of the singly modified uridine nucleosides.

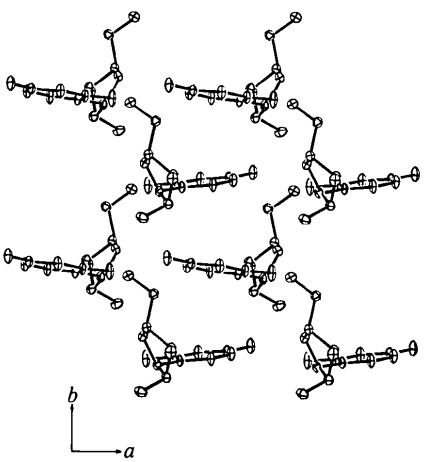

Fig. 4. A packing diagram of 3-deaza-6-azauridine in the crystal showing the tilted bases in the stacking interaction. The view is along the normal of the crystallographic *ab* plane.

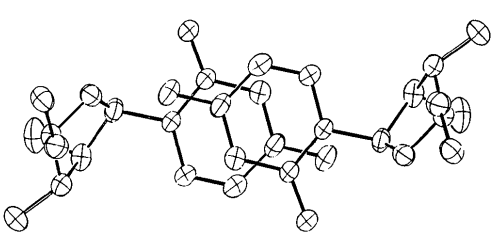

Fig. 5. A view of 3-deaza-6-azauridine along the crystallographic *b* axis showing the extent of base overlap between adjacent nucleosides.

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The Charge Density and Hydrogen Bonding in 9-Methyladenine at 126 K

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Abstract

The charge density distribution in the crystal structure of 9-methyladenine at 126 K has been determined from X-ray diffraction data (Mo $K\alpha$) for 4002 reflections with $F > 3\sigma(F)$ and $\sin\theta/\lambda < 1{\cdot}0$ Å^{-1}. The nuclear positional parameters for all atoms, and anisotropic thermal parameters for the H atoms were assumed to have values determined from a previous neutron structure determination. The electronic charge density was analyzed in terms of Stewart's rigid pseudoatom model, using restricted Slater radial functions and complete angular multipole terms extending to octapoles for C and N and quadrupoles for H pseudoatoms. The least-squares refinement converged with $R_w = 0{\cdot}030$. The net charges on atoms N(1), N(7) and N(3) are consistent with this order of decreasing preference as sites for hydrogen bonding and protonation of adenine derivatives. In the purine C—N bonds there is a correlation between decreasing peak deformation density and increasing bond length. The charge distribution in the two NH···N interactions is consistent with the importance of Coulombic interactions for hydrogen bonding. There are dipole deformations at the C—H and N—H hydrogen atoms which enhance the charge density in the bonding region. Unexpectedly,

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