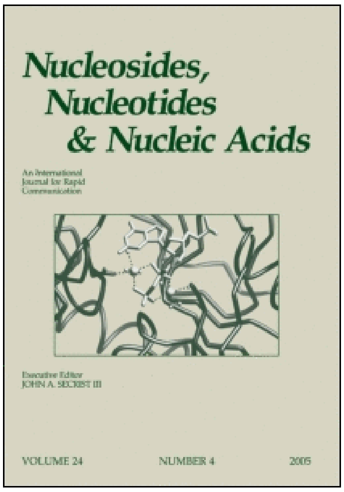

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SOLUTION AND SOLID STATE STRUCTURE OF 2',5'-BIS-(O-TRITYL)-3'-OXIMINOURIDINE

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Abstract: *Comparison of the solution (in $CDCl_3$ at 500 MHz ^1H NMR) and X-ray crystal studies of 3'-oximinouridine 1 shows in general good agreement with the high anti glycosidic angle and in the conformation about C4'-C5'. The sugar pucker (C2'-endo) is qualititatively identical in both cases. This is the first example of a conformationally sugar-rigid nucleoside in which the rigidity arises from the sp^2 character of an endocyclic carbon (i.e. C3'), not from the strain due to the ring fusion (see ref. 7 for conformationally strained nucleosides).*

In connection with the synthesis 2',3'-dideoxy-3'-nitro uridine, we synthesized 2',5'-bis-(O-trityl)-3'-oximinouridine (**1**) as an intermediate. We herein report both the solid (X-ray) and the solution structure (^1H-NMR spectroscopy at 500 MHz) of oximinouridine **1**. Chemical shifts of **1** and the proton-proton coupling constants (*i.e* $^3J_{HH}$ and $^4J_{HH}$) in deuterochloroform at -20 °, 25 ° and 50 °C are shown in Table 1 and Fig. 1. The pentofuranose ring of a ribonucleoside exists in an equilibrium of two rapidly interconverting conformers denoted by North (C3'-*endo*, C2'-*exo*) and South (C2'-*endo*, C3'-*exo*). The geometries of the North (N) and the South (S) conformers are expressed as their phase angles of pseudorotation (P_N, P_S) and their puckering amplitudes (ϕ_N, ϕ_S)[1].

Table 1. ^{1}H-NMR (500 MHz) Spectral data (δ in ppm relative to TMS, J in ±0.1 Hz) and relative poulations (%) of Staggered C4'-C5' Rotamers $\gamma(+)$, γ (trans), and $\gamma(-)$*.

T°C	δ1'	δ2'	δ4'	δ5'	δ5"	$J_{1',2'}$	$J_{2',4'}$	$J_{4',5'}$	$J_{4',5''}$	$J_{5',5''}$	$x(\gamma(+))$*
-20°C	6.09	5.37	5.03	3.74	2.93	6.8	1.1	1.7	1.7	10.3	100%
25°C	6.07	5.30	5.01	3.72	3.05	6.8	1.5	2.2	2.1	10.3	93%
50°C	6.07	5.26	5.0	3.71	3.12	6.7	1.5	2.4	2.1	10.3	91%

* the poupulation of γ (trans), and $\gamma(-)$ rotamers is negligible

The molar fractions of the N and S population, P_N, P_S, ϕ_N and ϕ_S can be calculated from the $^3J_{HH}$ coupling constants ($^3J_{1'2'}$, $^3J_{2'3'}$, $^3J_{3'4'}$) using suitable Karplus -Altona equation[5].

In the case of oximinouridine **1**, it is not possible to perform a full pseudorotational analysis[5] by NMR spectroscopy due to the absence of parameters of 3'-oximino group as substituent in pseudorotational parameters in addition to the absence of $^3J_{2'3'}$ and $^3J_{3'4'}$ coupling constants. Altona *et al.* however has shown that it is possible to use equation (1) to determine the percentage of the North population (%N)[2] from simply $^3J_{1'2'}$ for qualitative determination of pouplation in the two-state North-South equilibrium:

$$\%N = (7.9 - {}^3J_{1'2'})/6.9 \qquad .... \qquad (1)$$

Using the $^3J_{1'2'}$ coupling constants in eqn. (1), it can be seen that the pentofuranose ring in oximinouridine **1** in chloroform solution is predominantly in a South type conformation (~84 % S from -20 ° to 50 °C). This shows that the C2'-*endo* pucker of the pentofuranose ring observed by X-ray crystallography (vide supra) also exists in the chloroform solution. It is not however possible to calculate phase angle P and puckering amplitude ϕ from $^3J_{1'2'}$ alone and therefore we are unable to compare the X-ray derived data with that of the qualitatively determined solution structure. The conformation of the pentofuranose ring does not seem to be appreciably influenced by temperature changes. This temperature independency of chemical shifts and coupling constants suggest the inflexibility of the sugar ring. Clearly, this rigidity of the pentofuranose ring arise from the sp^2 hybridized character of the C3'. Indeed, X-ray studies have shown that all three atoms substituted at C3' is planar explaining the rigid character of the pentofuranose ring (vide infra).

The conformation across the C4'-C5' bond (γ) could be characterised following standard methods, *i.e.* a relative distribution ("x") of various staggered rotamers population [$\gamma^+ \rightleftarrows$

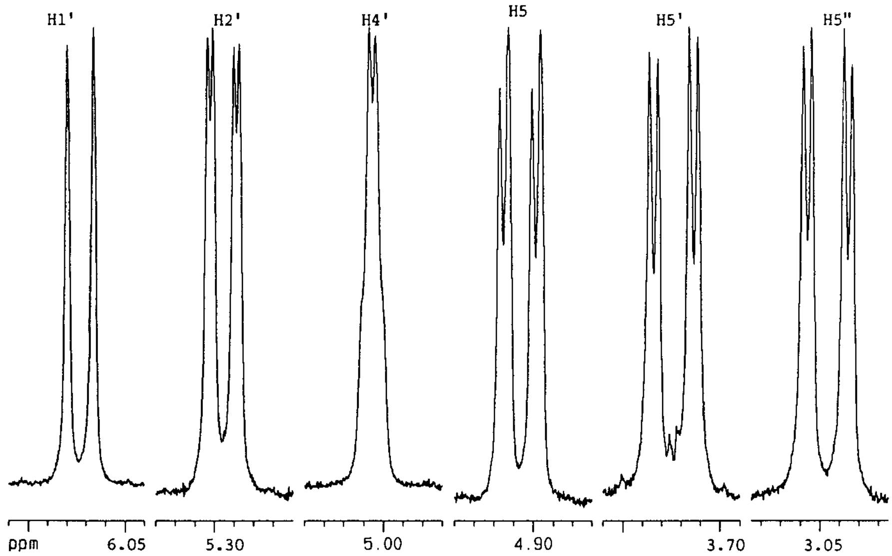

Figure 1. 1D spectrum (500 MHz ^1H) of Oximinouridine **1** showing the expansion of the region containing sugar and H5 absorptions. For J-couplings see Table 1.

$\gamma^- \rightleftarrows \gamma^t$] in an equilibrium can be calculated from the experimental $^3J_{4'5'}$ and $^3J_{4'5''}$ coupling constants using equations (2) and (3)[3].

$$^3J_{4'5'} = x(\gamma^+)2.4 + x(\gamma^-)10.6 + x(\gamma^t)2.6 \qquad .... \quad (2)$$

$$^3J_{4'5''} = x(\gamma^+)1.3 + x(\gamma^-)3.8 + x(\gamma^t)0.5 \qquad .... \quad (3)$$

The use of $^3J_{4'5'}$ and $^3J_{4'5''}$ coupling constants in equations (2) and (3) show that the staggered conformation across 4',5' is always γ^+ (100 % at -20 °C, 93 % at 25 °C and 92 % at 50 °C) and the temperature changes has only a marginal influence on γ^+.

For the determination of the conformation around C1'-N1 bond (χ), it was not possible to employ reliable nOe difference spectroscopy between H1', H2' or H3' and H6 of uracil moiety because overlapping chemical shift of the H6 proton and the protons of 2'-O- and 5'-O-triphenyl groups. This made it impossible to irradiate the H6 selectively and observe relative nOe enhancements in H1', H2' or H3' in order to determine the conformation across the glycosidic bond in a straightforward manner. We therefore assessed the solution conformation around C1'-N1 bond (χ) from the vicinal ^1H, ^{13}C couplings ($^3J_{H1'-C2}$ and $^3J_{H1'-C6}$) using the equation of Lemieux[4].

$$^3J_{H1'C6} = 6.2\cos^2(\phi) - 2.4\cos(\phi) + 0.1 \quad .... \quad (4)$$
$$^3J_{H1'C2} = 5.0\cos^2(\phi + 180) - 2.1\cos(\phi + 180) + 0.1 \quad .... \quad (5)$$

The use of experimental $^3J_{H1'C6}$ = 3.8 Hz and $^3J_{H1'C2}$ = 1.6 Hz in Karplus eqn. (4) and (5) allowed us to conclude that the uracil base is in the *anti* domain [χ = -128° or -112° (*anti*), or χ = -157° (*anti*) or -83° (high *anti*) basing on eqns (4) or (5), respectively]. The average of χ based on $^3J_{H1'C6}$ and $^3J_{H1'C2}$ is -142° (typical *anti*), and -97° (high *anti*), respectively. The glycosidic angle in oximinouridine **1** observed in the chloroform solution and in X-ray structure are thus quite qualititatively comparable (vide infra).

A careful inspection of coupling constants of the sugar protons shows a unique four bond coupling between H2'-H4' ($^4J_{2'4'}$ = 1.5 Hz). Such effective four-bond coupling through H-C-C-C--H have been normally confined to a planar zig-zag configuration (W-path) arising from rigid systems[6]. Such rigid system for oximinouridine **1** is in fact evident from its temperature independent NMR data (-20 ° to 50 °C) and planar C3' with respect to its three substituents found in the X-ray structure (vide infra). To the best of our knowledge, this is the first example of four-bond H1', H4' coupling which did not arise through the homoallylic coupling as in 2',3'-unsaturated nucleosides[8].

The complete X-ray structure of oximinouridine **1** is shown in Figure 2. Table 2 gives positional coordinates, and Table 3 details the important geometric characteristics of the nucleoside part of the structure and its oxime substituent. The furanose ring adopts a C2' *endo* pucker with a phase angle of pseudorotation P of 154° and a maximum angle of pucker τ_m of -31°. The glycoside angle, of -123.1(3)°, is in the high *anti* range and the conformations around C4'-C5' bond are g^+, g^-.The oxime group itself has a C=N bond length of 1.259(4)Å close to the norm[9] of 1.281Å, and C-O length of 1.414(3)Å is in excellent agreement with the standard value of 1.416Å. The oxygen atom (O1) is *trans* with respect to C3'-C2' bond which means that the oxime is in *anti* conformation. The hydrogen atom attached to O1 is also *trans* with respect to its point of attachment (C3') on the furanose ring.

The atttachment of the oxime group to C3' has resulted in a slight shortening of the C3'-C4' bond from its average value[10] of 1.523Å. The C2'-C3'-C4' bond angle has increased by over 6°, although it is still far from a standard sp^2 bond angle. It is overall apparent that the oxime group has resulted in few changes to the furanose ring geometry that are of significance.

Comparison of X-ray crystal structure with the above NMR results in general shows good agreement, with the high *anti* glycosidic angle being found both in solution and in the

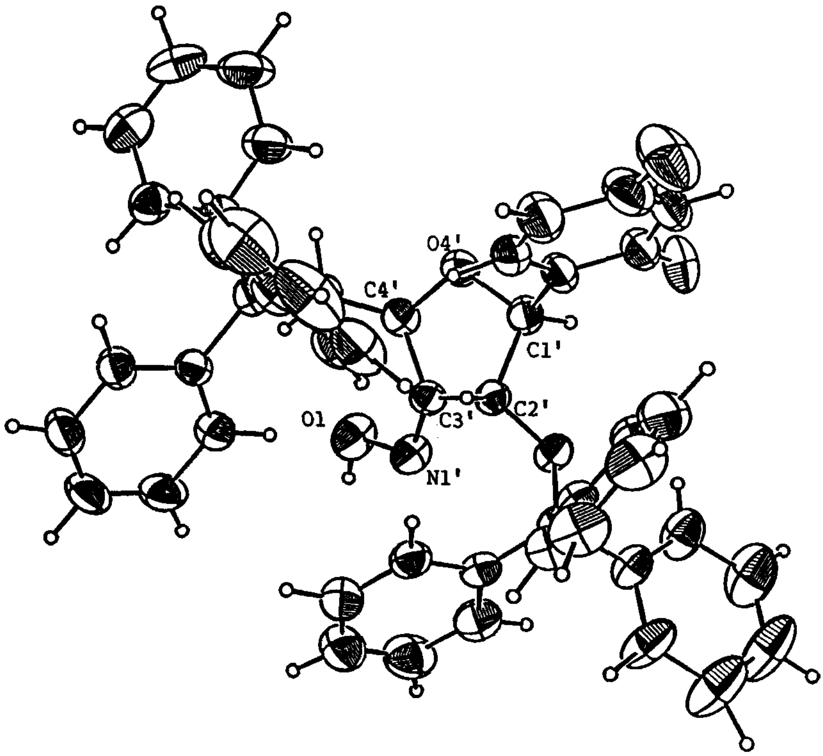

Figure 2. Crystal Structure of 2',5'-Bis-(O-trityl)-3'-oximinouridine (**1**).

crystal, as in the conformation about C4'-C5'. The sugar pucker (C2'-*endo*) is qualititatively identical in both cases.

In conclusion, this is the first example of a sugar-rigid nucleoside in which the rigidity of pentofuranose moiety comes from the inherent sp^2 character of an endocyclic carbon (*i.e.* C3') in contrast with other sugar-rigid structures (excluding the conformationally rigid aglycone-sugar fused nucleosides[9]) in which the strain originates from the fusion of a three-, four- or a five-membered ring across the ν_2 torsion of the sugar ring (see for example, [3.1.0]-fused-2',3'-modified-β-D-nucleosides as 2',3'-anhydro-, 2',3'-epimino- or 2',3'-dideoxy-2',3'-α-methylene uridine)[7].

Experimental

^{1}H-NMR spectra were recorded in deuterochloroform (~5 mM) using a Brucker AMX 500 spectrometer with TMS as internal standard. Single crystals were obtained from a 1:1

Table 2. Positional Parameters and Their Estimated Standard Deviations for Oximinouridine **1**.

Atom	*x*	*y*	*z*	B(Å^2)
O1	0.5135 (3)	0.695	0.6650 (2)	4.91 (5)
O2'	0.6741 (2)	0.9191 (1)	0.5430 (1)	3.20 (4)
O2	0.3754 (3)	1.0844 (1)	0.4596 (1)	4.78 (5)
O4	0.4728 (4)	1.2995 (2)	0.6715 (2)	7.71 (8)
O4'	0.3341 (2)	0.9264 (1)	0.6579 (1)	3.78 (4)
O5'	0.4885 (2)	0.8953 (1)	0.8409 (1)	3.04 (4)
N1'	0.5940 (3)	0.7640 (2)	0.6330 (2)	3.73 (6)
N1	0.4398 (3)	1.0519 (2)	0.6177 (2)	3.34 (5)
N3	0.4112 (3)	1.1909 (2)	0.5692 (2)	4.41 (6)
C1A	0.6099 (3)	0.8250 (2)	0.9843 (2)	3.04 (6)
C1B	0.5889 (4)	0.9799 (2)	0.9722 (2)	3.49 (7)
C1D	0.9045 (3)	0.8548 (2)	0.6197 (2)	3.20 (6)
C1C	0.3496 (3)	0.8972 (2)	0.9819 (2)	3.26 (6)
C1F	0.8939 (4)	0.9339 (2)	0.4607 (2)	3.57 (6)
C1'	0.4386 (3)	0.9622 (2)	0.5978 (2)	3.21 (6)
C1E	0.8741 (3)	1.0178 (2)	0.6047 (2)	3.12 (6)
C2'	0.5889 (3)	0.9171 (2)	0.6232 (2)	2.77 (6)
C2B	0.5661 (5)	1.0219 (2)	1.0579 (3)	5.27 (9)
C2'A	0.8379 (3)	0.9304 (2)	0.5608 (2)	3.02 (6)
C2D	0.9213 (3)	0.8542 (2)	0.7202 (2)	3.63 (7)
C2A	0.6496 (4)	0.8183 (2)	1.0838 (2)	3.67 (7)
C2F	0.7975 (4)	0.9390 (3)	0.3776 (2)	4.91 (8)
C2	0.4057 (4)	1.1076 (2)	0.5424 (2)	3.96 (7)
C2E	1.0043 (4)	1.0333 (2)	0.6664 (2)	4.01 (7)
C2C	0.2965 (4)	0.8341 (2)	1.0381 (2)	3.86 (7)
C3A	0.7493 (4)	0.7569 (2)	1.1202 (2)	4.42 (8)
C3D	0.9722 (4)	0.7837 (3)	0.7711 (2)	4.83 (8)
C3F	0.8579 (5)	0.9484 (3)	0.2884 (3)	7.0 (1)
C3B	0.6475 (5)	1.0939 (3)	1.0855 (3)	7.1 (1)
C3E	1.0404 (4)	1.1150 (2)	0.6953 (3)	5.14 (9)
C3'	0.5315 (3)	0.8322 (2)	0.6513 (2)	2.98 (6)
C3C	0.1485 (4)	0.8363 (3)	1.0622 (3)	5.18 (9)
C4'	0.3809 (3)	0.8433 (2)	0.6895 (2)	3.18 (6)
C4D	1.0044 (4)	0.7117 (3)	0.7226 (3)	5.8 (1)
C4A	0.8075 (4)	0.7003 (2)	1.0609 (3)	4.86 (8)
C4C	0.0533 (4)	0.8993 (3)	1.0298 (3)	5.50 (9)
C4	0.4590 (5)	1.2235 (2)	0.6609 (3)	5.20 (9)
C4F	1.0090 (5)	0.9524 (3)	0.2835 (3)	7.3 (1)
C4E	0.9504 (5)	1.1811 (2)	0.6640 (3)	5.51 (9)
C4B	0.7506 (5)	1.1248 (2)	1.0274 (3)	6.9 (1)
C5A	0.7699 (4)	0.7061 (2)	0.9626 (3)	4.70 (8)
C5D	0.9863 (4)	0.7104 (2)	0.6236 (3)	5.61 (9)
C5'A	0.5067 (3)	0.8971 (2)	0.9459 (2)	2.99 (6)
C5	0.4860 (5)	1.1605 (2)	0.7343 (2)	4.94 (8)
C5F	1.1074 (5)	0.9451 (3)	0.3657 (3)	7.0 (1)
C5B	0.7721 (4)	1.0858 (2)	0.9412 (3)	5.72 (9)
C5E	0.8231 (4)	1.1669 (2)	0.6012 (3)	5.16 (9)
C5'	0.3781 (3)	0.8379 (2)	0.7969 (2)	3.22 (6)
C5C	0.1041 (4)	0.9623 (3)	0.9746 (3)	5.9 (1)
C6F	1.0483 (4)	0.9369 (3)	0.4543 (2)	5.55 (9)
C6D	0.9389 (4)	0.7818 (2)	0.5722 (2)	4.51 (8)
C6	0.4753 (4)	1.0799 (2)	0.7118 (2)	3.88 (7)
C6A	0.6716 (4)	0.7691 (2)	0.9243 (2)	3.85 (7)
C6B	0.6941 (4)	1.0116 (2)	0.9157 (2)	4.20 (7)
C6E	0.7861 (4)	1.0852 (2)	0.5717 (2)	4.00 (7)

C6C	0.2510 (4)	0.9616 (2)	0.9510 (3)	5.09 (8)
H1	0.565 (6)	0.651 (4)	0.647 (3)	15 (2)*
H1'	0.413 (3)	0.956 (2)	0.524 (2)	2.2 (5)*
H2'	0.638 (3)	0.944 (2)	0.684 (2)	3.8 (6)*
H2B	0.483 (4)	0.999 (3)	1.108 (3)	9 (1)*
H2D	0.896 (3)	0.907 (2)	0.753 (2)	3.4 (6)*
H2A	0.605 (3)	0.855 (2)	1.126 (2)	4.7 (7)*
H2F	0.689 (4)	0.941 (2)	0.376 (2)	5.7 (8)*
H2E	1.073 (3)	0.986 (2)	0.686 (2)	5.0 (8)*
H2C	0.356 (3)	0.788 (2)	1.063 (2)	4.2 (7)*
H3	0.390 (4)	1.229 (2)	0.520 (2)	6.6 (9)*
H3A	0.768 (4)	0.758 (2)	1.188 (2)	5.6 (8)*
H3D	0.980 (4)	0.781 (2)	0.847 (2)	7.0 (9)*
H3F	0.792 (4)	0.956 (3)	0.238 (2)	8 (1)*
H3E	1.144 (4)	1.122 (2)	0.734 (2)	5.9 (8)*
H3C	0.121 (4)	0.793 (2)	1.102 (2)	6.5 (9)*
H3B	0.624 (5)	1.124 (3)	1.149 (3)	13 (2)*
H4D	1.030 (4)	0.659 (3)	0.761 (3)	9 (1)*
H4A	0.880 (4)	0.659 (2)	1.088 (2)	5.8 (8)*
H4C	-0.055 (4)	0.896 (2)	1.049 (2)	7.0 (9)*
H4F	1.050 (4)	0.959 (3)	0.227 (3)	9 (1)*
H4E	0.978 (4)	1.238 (2)	0.683 (2)	7 (1)*
H4B	0.810 (5)	1.179 (3)	1.052 (3)	11 (1)*
H4'	0.312 (3)	0.802 (2)	0.660 (2)	2.9 (6)*
H5D	1.008 (4)	0.660 (3)	0.580 (3)	9 (1)*
H5	0.521 (4)	1.176 (2)	0.799 (2)	6.4 (9)*
H5F	1.227 (5)	0.963 (3)	0.351 (3)	10 (1)*
H5B	0.846 (4)	1.107 (2)	0.900 (2)	6.9 (9)*
H5E	0.754 (4)	1.212 (2)	0.572 (2)	6.7 (9)*
H5C	0.030 (4)	1.011 (3)	0.949 (2)	9 (1)*
H5A	0.806 (3)	0.671 (2)	0.917 (2)	5.1 (8)*
H6D	0.924 (3)	0.783 (2)	0.501 (2)	3.3 (6)*
H6	0.494 (3)	1.032 (2)	0.756 (2)	4.3 (7)*
H6A	0.653 (3)	0.775 (2)	0.850 (2)	4.4 (7)*
H6B	0.713 (3)	0.978 (2)	0.858 (2)	3.1 (6)*
H6E	0.712 (3)	1.076 (2)	0.525 (2)	3.4 (6)*
H6C	0.293 (4)	1.008 (2)	0.916 (2)	7.0 (9)*
H6F	1.126 (4)	0.933 (3)	0.514 (3)	9 (1)*
H5'1	0.410 (3)	0.779 (2)	0.818 (2)	5.1 (8)*
H5'2	0.270 (3)	0.855 (2)	0.814 (2)	3.3 (6)*

* Starred atoms were refined isotropically

EtOH/H_2O mixture. Cell dimensions were obtained by least-squares refinement of Θ values from 25 reflections measured on an Enraf-Nonius CAD4 Turbo diffractometer. They are: $\underline{a}$ = 8.918(1), $\underline{b}$ = 15.921(2), $\underline{c}$ = 13.917(2)Å and β = 95.80(1)°. Systematic absences O$\underline{k}$O, $\underline{r}$ = 2N+1, together with the subsequent successful structure analysis, confirmed the space group as $\underline{P}2_1$ (No. 5). The unit cell contains two molecules of $C_{46}H_{40}O_6N_4$, with a calculated density of 1.23 gm cm^{-3}. Intensity data were collected on the diffractometer for a crystal of approximate dimensions 0.20 x 0.10 x 0.03 mm, using graphite-monochromated Cu-K_α radiation (λ = 1.54051Å). An ω-2Θ scan technique was

Table 3. Major geometries and conformation features of the Crystal Structures of Oximinouridine **1**.

(a) Bond lengths (Å)

C1'-C2'	1.530(4)	C3'-N1'	1.259(4)
C1'-O4'	1.432(4)	N1'-O1	1.414(3)
C1'-N1	1.453(4)	C4'-C5'	1.500(4)
C2'-O2'	1.412(3)	C2'-C3'	1.511(4)
C3'-C4'	1.504(4)	C4'-O4'	1.443(4)

(b) Bond angles (°)

C1'-O4'-C4'	110.0(2)	O4'-C1'-C2'	106.5(2)
C1'-C2'-C3'	99.7(2)	O4'-C1'-N1	105.8(2)
C1'-C2'-O2'	109.6(2)	C2'-C1'-N1	115.3(2)
C3'-C2'-O2'	116.2(2)	C3'-C4'-O4'	104.0(2)
C2'-C3'-C4'	108.9(2)	C3'-C4'-C5'	116.7(2)
C2'-C3'-N1'	123.4(3)	O4'-C4'-C5'	108.8(2)
C4'-C3'-N1'	127.1(3)	C3'-N1'-O1	111.2(3)

(c) Torsion angles (°)

O4'-C1'-C2'-C3'	30.7(3)	C2'-C3'-C4'-O4'	15.9(3)
C1'-C2'-C3'-C4'	-28.3(3)	C3'-C4'-O4'-C1'	4.8(3)
C4'-O4'-C1'-C2'	-23.3(3)	O4'-C1'-N1-C2	-123.1(3)
O5'-C5'-C4'-C3'	52.8(3)	C3'-N1'-O1-H1	177.8(7)
O5'-C5'-C4'-O4'	-64.4(3)	C4'-C3'-N1'-O1	-8.0(4)

Phase angle of pseudorotation (P):	154°
Maximum Puckering amplitude (ν_m):	-31°
Sugar pucker description:	C2'-*endo*

(d) Least-squares planes. Derivation from the planes are in Å

*N1'	0.019(2)	C3'	0.0
*C3'	-0.046(3)	N1'	0.0
*C2'	0.013(3)	O1	-0.021(2)
*C4'	0.014(3)	C2'	0.040(3)
*O1	0.0	C4'	0.167(3)

Atoms marked (*) were included in the calculation of the plane used, with a maximum scan time per reflection of 90 sec and a maximum scan rate of 3.33°/min. Data were collected in the range $1.5 < \underline{\Theta} < 65°$, and $O \leq \underline{h} \leq 10$, $O \leq \underline{k} \leq 17$ and $-15 \leq \underline{l} \leq 15$. A periodic check was kept on crystal stability and orientation; no significant decay was observed during the data collection. a total of 3240 unique reflections were measured, of which 2806 had $\underline{I} > 3\sigma(\underline{I})$ and were used in the subsequent refinement.

The structure was solved by direct methods, together with tangent formula recycling procedures and difference Fourier syntheses. It was refined by full-matrix least-squares methods. The positions of all hydrogen atoms were located in a series of Fourier syntheses. Their positional and isotropic temperature factores were included in the latter stages of refinement. A weighting scheme of the form $\underline{w} = 1[\sigma^2(\underline{F}) + (0.04\underline{F})^2]$ was used. The final least-squares cycle had an $\underline{R} = 0.0284$ and $\underline{R}_w = 0.0262$ with a maximum shift/error of <0.1. A final difference Fourier map did not have any peaks outside the values of $\pm$ 0.2eÅ^{-3}.

Scatteirng factors were taken from International Tables for X-Ray Crystallography (1974), Vol. IV). All calculations were performed with the MOIEN computer package (Delft Instruments, Holland 1990).

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