Crystal Structure of Ribosylpyrimidin-2-one Dihydrate

SVEN FURBERG

Department of Chemistry, University of Oslo, Oslo 3, Norway

Ribosylpyrimidin-2-one crystallizes in space group $P2_12_12_1$, with $a = 17.968(2)$, $b = 13.520(3)$, $c = 4.944(1)$, $Z = 4$. The structure was derived from 1170 counter data and refined to $R = 0.037$. The glycosyl torsion angle is small (1.5°), giving rise to a long (1.511 Å) C1′−N1 bond. The ribose ring has nearly the ideal twist conformation, with C3′-*endo* C2′-*exo*. All hydroxyl hydrogen atoms take part in hydrogen bonds.

Continuing our studies of compounds related to nucleic acids [1] we have determined the crystal structure of the riboside of pyrimidin-2-one. Although the crystal structures of a large number of nucleosides and nucleotides are now known,[2,3] it would appear to be of interest to establish the conformational features of this substance, which may be considered the simplest nucleoside and the parent compound of the natural nucleosides. Its synthesis and properties have been described.[4,5]

EXPERIMENTAL, STRUCTURE ANALYSIS

A small sample of the compound was kindly supplied by Professor S. Laland, Department of Biochemistry, University of Oslo. It was recrystallized from a drop of water on a coverglass by slow evaporation. Needle-shaped crystals elongated along *c* were obtained. Weissenberg photographs showed the space group to be $P2_12_12_1$. Unit cell dimensions derived from diffractometer measurements are $a = 17.968(2)$, $b = 13.520(3)$, $c = 4.944(1)$ Å, $V = 1200.2$ Å^3. By flotation the density was found to be 1.45 g/cm^3. This indicates that two water molecules are present, the density corresponding to four units $C_9H_{12}N_2O_5.2H_2O$ being 1.46 g/cm^3. This was confirmed by the structure analysis.

The intensity measurements were made on a crystal of dimensions $0.07 \times 0.15 \times 0.35$ mm, using an automatic SYNTEX P1 diffractometer and monochromatic Mo$K\alpha$ radiation ($\lambda = 0.71069$ Å). The $\omega/2\theta <$ scan mode was employed. The scan rate was 1°/min and 1170

Table 1. Positional and thermal parameters ($\times 10^5$) for non-hydrogen atoms. The temperature factor is $\exp[-(B11h^2 + \cdots + B23kl)]$.

Atom	x	y	z	B11	B22	B33	B12	B13	B23
N1	24621(13)	72848(17)	49710(60)	141(8)	251(13)	2490(116)	−6(19)	83(59)	204(90)
C2	20380(17)	67391(25)	67933(79)	164(11)	398(19)	3018(168)	−27(26)	−227(90)	259(120)
N3	15631(14)	72301(21)	84461(67)	198(10)	567(20)	3178(156)	94(24)	337(73)	216(106)
C4	14893(21)	81945(31)	81680(101)	218(14)	621(28)	4813(39)	179(34)	232(108)	−970(159)
C5	18814(22)	87519(28)	63037(106)	281(14)	349(21)	6672(286)	75(32)	741(120)	−188(144)
C6	23711(20)	82720(24)	47153(94)	223(13)	340(20)	4870(231)	6(28)	224(110)	96(141)
O2	21161(12)	58332(16)	68568(60)	202(8)	368(14)	4906(150)	−43(16)	467(67)	732(83)
C1′	29841(15)	67137(22)	31554(73)	139(10)	263(16)	2464(150)	−72(23)	8(81)	−97(104)
C2′	36249(16)	62564(22)	47396(79)	142(10)	281(17)	2082(159)	−2(22)	145(75)	125(100)
C3′	41789(17)	71023(21)	47422(72)	148(11)	255(17)	2120(152)	−32(21)	−3(72)	−27(94)
C4′	40904(16)	75400(23)	19350(65)	145(10)	324(20)	2059(147)	−78(23)	65(71)	−104(103)
C5′	42763(22)	86268(25)	16625(88)	248(13)	359(20)	2796(186)	−114(28)	−66(99)	299(116)
O1′	33060(11)	73748(14)	12710(42)	175(7)	399(13)	2097(101)	−75(17)	−50(49)	324(69)
O2′	39363(13)	54601(16)	32306(58)	179(8)	264(11)	4681(137)	−9(18)	198(68)	−523(77)
O3′	49126(12)	67719(17)	53026(55)	155(8)	335(13)	3860(125)	−23(17)	−313(59)	215(83)
O5′	38876(15)	92012(17)	36044(59)	239(9)	319(14)	4412(151)	−53(19)	−89(73)	−554(84)
OW1	56910(17)	83194(24)	71095(69)	315(11)	485(19)	4121(161)	−48(24)	−733(76)	−253(103)
OW2	49489(18)	51997(21)	90355(67)	326(11)	456(17)	3313(136)	280(23)	222(72)	239(91)

Table 2. Positional ($\times 10^3$) and thermal parameters for hydrogen atoms.

	x	y	z	B		x	y	z	B
H4	114(2)	849(2)	928(7)	3.6(8)	H16	415(2)	883(2)	-12(8)	2.8(8)
H5	180(2)	943(2)	601(8)	5.5(10)	H7	360(2)	503(3)	292(10)	6.6(12)
H6	268(2)	854(3)	333(8)	3.7(9)	H8	513(2)	723(3)	594(8)	4.5(11)
H11	268(1)	618(2)	222(6)	1.2(6)	H9	418(2)	950(3)	445(7)	2.9(10)
H12	349(1)	603(2)	648(7)	1.5(6)	H1	553(3)	887(3)	686(12)	7.9(16)
H13	402(1)	763(2)	610(6)	1.3(6)	H2	595(2)	829(4)	841(10)	5.6(14)
H14	437(1)	717(2)	60(6)	1.2(6)	H21	470(2)	538(3)	18(9)	3.9(12)
H15	482(2)	870(2)	192(7)	2.6(7)	H22	494(3)	566(3)	775(11)	6.6(13)

reflections with $2\theta < 70°$ and $I > 2\sigma(I)$ were measured. Three standard reflections were measured at intervals of 60 reflections and did not change significantly during the data collection. Corrections for absorption and extinction were not applied. The atomic form factors were those of Doyle and Turner,[6] except for hydrogen.[7]

The structure was solved by the MULTAN program and refined by full-matrix least-squares calculations. The weighting scheme was based on standard deviations from counter statistics and 2 % fluctuations in diffractometer stability. First only the heavy atom positions were refined, with isotropic temperature factors. On a difference Fourier map peaks corresponding to reasonable positions for all 16 hydrogen atoms were found. In the final refinement cycles anisotropic temperature factors were applied to the non-hydrogen atoms, isotropic ones to the hydrogen atoms. The value of R was 0.037, of R_w 0.031. In the final refinement the three strongest reflections (011, 020 and 301) were left out, apparently suffering from extinction errors (having F_{calc} about 10 % larger than F_{obs}). The calculations were carried out on CYBER-74, using the program assembly of Ref. 8. The parameters are given in Tables 1 and 2. They correspond to the R configuration at C1'. Fig. 1 shows the thermal ellipsoids.

A list of observed and calculated structure factors may be obtained from the author.

RESULTS AND DISCUSSION

The numbering of the atoms is shown in Fig. 1 and the bond lengths and angles in Table 3. They are in general agreement with those in other nucleosides.

The pyrimidine ring is essentially planar, as seen from Table 4. The attached atoms are slightly out of the plane. Similar deviations are commonly observed in related structures. The bond lengths and angles are not significantly different from those found in crystalline pyrimidin-2-one.[9]

Table 3. Bond lengths (Å) and bond angles (°). The estimated standard deviations are about 0.004 Å for bond lengths and 0.3° for bond angles involving non-hydrogen atoms, and 0.04 Å and $1-2°$ for those involving hydrogen atoms.

|			
C2-O2	1.233	C4-H4	0.92
N1-C2	1.392	C5-H5	0.94
N1-C6	1.351	C6-H6	0.96
C2-N3	1.355	C1'-H11	1.02
N3-C4	1.318	C2'-H12	0.94
C4-C5	1.383	C3'-H13	1.02
C5-C6	1.346	C4'-H14	0.97
N1-C1'	1.511	C5'-H15	0.99
C1'-C2'	1.524	C5'-H16	0.95
C2'-C3'	1.516	O2'-H7	0.86
C3'-C4'	1.517	O3'-H8	0.80
C4'-C5'	1.513	O5-H9	0.78
C4'-O1'	1.464	OW1-H1	0.81
O1'-C1'	1.415	OW1-H2	0.79
C2'-O2'	1.424	OW2-H21	0.76
C3'-O3'	1.419	OW2-H22	0.89
C5'-O5'	1.419		
N1-C2-O2	118.7	N3-C4-H4	116
N3-C2-O2	122.9	C5-C4-H4	120
N1-C2-N3	118.4	C6-C5-H5	119
C2-N3-C4	119.0	C4-C5-H5	124
N3-C4-C5	123.9	C5-C6-H6	128
C4-C5-C6	117.3	N1-C6-H6	112
C5-C6-N1	120.1	N1-C1'-H11	107
C6-N1-C2	121.2	O1'-C1'-H11	112
N1-C1'-O1'	108.8	C2'-C1'-H11	111
N1-C1'-C2'	111.8	C1'-C2'-H12	114
O1'-C1'-C2'	106.6	C3'-C2'-H12	114
C1'-C2'-C3'	101.0	C2'-C3'-H13	110
C2'-C3'-C4'	103.0	C4'-C3'-H13	108
C3'-C4'-O1'	104.3	C3'-C4'-H14	111
C4'-O1'-C1'	110.0	O1'-C4'-H14	106
C3'-C4'-C5'	115.9	C4'-C5'-H15	107
O1'-C4'-C5'	109.9	C4'-C5'-H16	108
C4'-C5'-O5'	111.3	C5'-O5'-H9	108
C4'-C3'-O3'	113.5	C3'-O3'-H8	107
C2'-C3'-O3'	111.9	C2'-O2'-H7	109
C3'-C2'-O2'	108.2	H1-OW1-H2	113
C1'-C2'-O2'	109.5	H21-OW2-H22	107
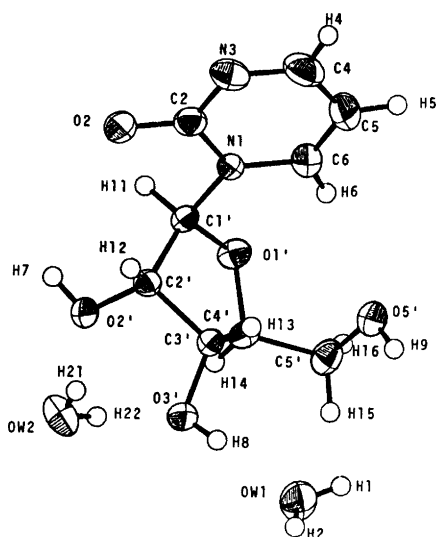
Fig. 1. Thermal ellipsoids at 50 % level (seen along *c*).

Table 4. Distances (Å) from the plane defined by the six pyrimidine ring atoms.

N1	0.016	O2	− 0.073
C2	− 0.024	C1′	− 0.028
N3	0.011	H4	− 0.011
C4	0.004	H5	− 0.089
C5	− 0.010	H6	− 0.009
C6	− 0.001	O1′	− 0.120
		C2′	1.247

Two main classes of furanose sugar conformations have been observed in crystal structures, C2′-*endo* C3′-*exo* and C3′-*endo* C2′-*exo*. Usually one atom is much more displaced than the other and the conformation is of the envelope type. In the present structure, however, a nearly ideal twist conformation occurs, the atom C3′ being displaced by 0.31 Å from the plane C1′ − O1′ − C4′ on the same side as C5′ (*endo*), whereas C2′ is at a distance of 0.32 Å from this plane on the other side of it. The ribose conformation is thus C3′-*endo* C2′-*exo*.[1] The torsion angles (Table 5) reflect the pseudo two-fold symmetry of the ring. As far as we know the present compound has a more pronounced C2′-*exo* character than any other of the more than one hundred β-ribofuranosides studied in the crystalline state up to now.

Table 5. Some torsion angles (°).

C6 − N1 − C1′ − O1′	− 1.5
C4′ − O1′ − C1′ − C2′	− 12.6
C3′ − C4′ − O1′ − C1′	− 12.1
O1′ − C1′ − C2′ − C3′	31.9
C4′ − C3′ − C2′ − C1′	− 38.3
O1′ − C4′ − C3′ − C2′	31.8
O5′ − C5′ − C4′ − C3′	− 52.3
O5′ − C5′ − C4′ − O1′	65.6
H9 − O5′ − C5′ − C4′	123
H8 − O3′ − C3′ − C2′	− 154
H7 − O2′ − C2′ − C3′	− 168

The conformation around C4′ − C5′ is *gauche-gauche* (Table 5), as is commonly found in nucleosides. Around C5′ − O5′ the conformation is close to eclipsed, presumably due to crystal forces.

It is well-known that the glycosyl torsion angle C6 − N1 − C1′ − O1′ is correlated to the type of pucker of the sugar.[2,3] The angular ranges are roughly 0 − 40° for C3′-*endo* sugars and 40 − 70° for C2′-*endo* sugars. The value of 1.5° observed in the present compound is on the low side of the C3′-*endo* range. This is presumably related to the high degree of C2′-*exo* pucker of the ribose. Two other compounds, deoxycytidine hydrochloride[10] and deoxycytidine 5″-phosphate monohydrate,[11] which have been reported to have similar torsion angles (0 and − 6°, respectively), also have an unusually high degree of C2′-*exo* pucker, C2′ being displaced by 0.24 and 0.22 Å, respectively, from the C1′ − O1′ − C4′ plane. It is to be expected that C2′-*exo* pucker is rather strongly correlated with torsion angle, as the effect of this type of puckering is to bring the base in an axial position with respect to the mean sugar ring plane and thus generally in closer contact with sugar atoms. The favourable range of rotation around C1′ − N is probably small for β-ribofuranosides with pronounced C2′-*exo* pucker (torsion angle about 0°). Features of this conformation include approximately equal distances between O2 and hydrogen atoms H11 and H12 (2.54 and 2.48 Å, respectively), and also between H6 and oxygen atoms O1′ and O5′ (see below). Interestingly, the glycosyl bond is found to be unusually long in all three compounds, 1.511 Å in the present one and 1.508(3) and 1.510(3) Å, respectively, for the two deoxycytidine derivatives men-

tioned above. This has been explained by repulsive forces between the electrons in the bonds N1−C6 and C1′−O1′.[10] The general correlation between glycosyl torsion angle and bond length C1′−N has been noted earlier.[12]

The small torsion angle C1′−N implies that O1′ lies nearly in the pyrimidine plane. The distances from O1′ to C6 and H6 are short, 2.682 and 2.19 Å, respectively. C6−H6 appears to be bent towards O1′, the angle N1−C6−H6 being only 112°, but this effect may not be real. H6 is also in contact with O5′ (2.34 Å) and the distance C6···O5′ is short, 3.050 Å. The existence of a weak hydrogen bond C6−H6···O5′ has been suggested in several nucleoside structures,[13,14] but it does not appear reasonable to classify the interaction in the present structure in this way, as the angle at H6 is 130°.

The hydrogen bonding scheme and the arrangement of the molecules is shown in Fig. 2.

All seven hydroxyl hydrogen atoms are engaged in the formation of hydrogen bonds, the structural characteristics of which are given in Table 6. One of the water molecules is taking part in four hydrogen bonds, tetrahedrally distributed, whereas the other is engaged in three such bonds. The water molecules are associated mainly with the sugar hydroxyl groups rather than with the C=O group. This appears to be the case in most nucleoside hydrates. In addition, one hydrogen bond is formed to N3.

REFERENCES

1. Furberg, S. and Aas, J. B. *Acta Chem. Scand. A 29* (1975) 713.
2. Arnott, S. and Hukins, D. W. L. *Biochem. J. 130* (1972) 453.

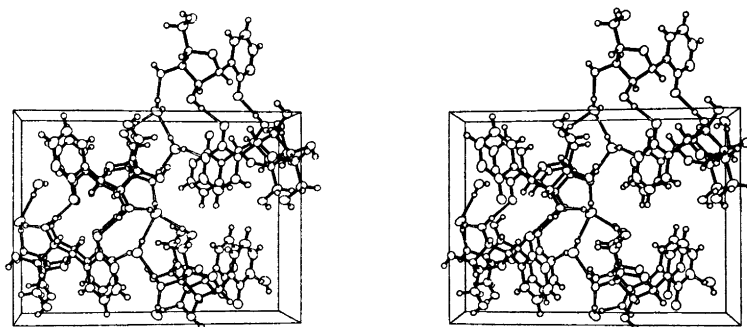*Fig. 2.* Stereoscopic view of the structure in the *c* direction.

Table 6. Hydrogen bonds A−H···B with distances (Å) and angles (°).

	A···B	A−H	H···B	∠A−H−B
O2′−H7···O2(II)	2.664(3)	0.86(4)	1.81(4)	173(5)
O3′−H8···OW1(I)	2.671(4)	0.80(4)	1.87(4)	174(4)
O5′−H9···OW(2) III)	2.749(4)	0.78(3)	1.98(3)	168(4)
OW1−H1···OW(2) (III)	2.847(5)	0.81(4)	2.04(4)	174(5)
OW1−H2···N3(IV)	2.799(5)	0.79(5)	2.03(5)	163(5)
OW2−H21···O2′(V)	2.781(4)	0.76(4)	2.04(4)	163(4)
OW2−H22···O3′(I)	2.816(4)	0.89(5)	1.93(5)	173(4)

Symmetry codes
(I)   x,y,z
(II)   1/2−x,1−y,−1/2+z
(III)   1−x,1/2+y,3/2−z
(IV)   1/2+x,3/2−y,2−z
(V)   x,y,1+z

3. Sundaralingam, M. *Jerusalem Symp. Quantum Chem. Biochem. 5* (1973) 417.
4. Funakoski, R., Masachika, I. and Ukita, T. *Chem. Pharm. Bull. 9* (1961) 406.
5. Øyen, T. B. *Biochim. Biophys. Acta 186* (1969) 237.
6. Doyle, P. A. and Turner, P. S. *Acta Crystallogr. A 24* (1968) 390.
7. Stewart, R. F., Davidson, E. R. and Simpson, W. T. *J. Chem. Phys. 42* (1965) 3175.
8. Dahl, T., Gram, F., Groth, P., Klewe, B. and Rømming, C. *Acta Chem. Scand. 24* (1970) 2232.
9. Furberg, S. and Solbakk, J. *Acta Chem. Scand. 24* (1970) 3230.
10. Subramanian, E. and Hunt, D. J. *Acta Crystallogr. B 26* (1970) 303.
11. Viswamitra, M. A., Reddy, B. S., Lin, G. H.-Y. and Sundaralingam, M. *J. Am. Chem. Soc. 93* (1971) 4565.
12. Lin, G. H.-L., Sundaralingam, M. and Arora, S. K. *J. Am. Chem. Soc. 93* (1971) 1235.
13. Furberg, S., Petersen, C. S. and Rømming, C. *Acta Crystallogr. 18* (1965) 313.
14. Green, E. A., Rosenstein, R. D., Shiono, R. and Abraham, D. J. *Acta Crystallogr. B 31* (1975) 102.