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Note

Structural analysis of methyl α-L-rhamnopyranoside in the solid state

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Methyl α-L-rhamnopyranoside [1] (**1**, methyl 6-deoxy-α-L-mannopyranoside), usually obtained by heating L-rhamnose monohydrate in acidic methanol, is an important synthetic intermediate and a partial structure of a growing family of pyranonaphthoquinone (benzoisochromanquinone) antibiotics such as nanaomycin D [2], kalafungin [3], granaticin [4] and medermycin [5] that have been shown to possess significant antimicrobial activities and potential antitumor activities [6]. Compound **1** is also considered a suitable starting material for the synthesis of branched-chain deoxy sugars [7], the essential components of many macrolide antibiotics.

Among the few crystallographic studies on methyl hexopyranosides, the crystal structures of methyl α-D-mannopyranoside [8], methyl α-D-glucopyranoside [9], and methyl α-D-altropyranoside [10] have been reported. In these compounds, there are significant conformational differences between the molecules in their crystal structures although they differ only in the configuration of their hydroxyl groups [11]. The molecules also differ in the conformation of their primary alcohol groups as well as in the hydrogen-bonding interactions in their crystal structures.

The structures of methyl 6-deoxy-α-D-idopyranoside [12] and methyl α-L-fucopyranoside [13] have recently been analyzed by X-ray crystallography and by NMR spectroscopy. Interestingly, these analyses indicated that, in the solid state, the pyranose ring of methyl 6-deoxy-α-D-idopyranoside adopts the $^1C_4$ conformation, but in solution it exists in an equilibrium between the $^1C_4$ form and another conformer, possibly the skew form $^2S_0$. However, the pyranose ring of methyl α-L-fucopyranoside adopts similar conformations, $^1C_4$, both in the solid state and in solution.

In the present work, we report on the 3D molecular structure of methyl α-L-rhamnopyranoside as determined by X-ray crystallography and compare its

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conformation in the crystal with that in solution as revealed by ^1H NMR spectroscopy [14].

1. Experimental

The sample of methyl α-L-rhamnopyranoside was kindly provided by Professor H.S. El Khadem from the late Dr. H.S. Isbell's collection of rare sugars at The American University, Washington DC. Suitable crystals for X-ray analysis were grown from ethyl alcohol at −10°C over a period of 72 h.

A colorless fragment with dimensions of 0.37 × 0.38 × 0.50 mm was used for the structure determination. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer equipped with graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) at 21°C. Unit-cell parameters were obtained from setting angles of 25 reflections having $19 < 2\theta < 25°$. The crystal data are summarized in Table 1. A total of 2127 reflections was measured by $\omega - 2\theta$ scans (one octant having $2 < 2\theta < 70°$) and variable scan rates (0.46–3.30 deg. min^{-1}), 2103 unique data were obtained; 1934 reflections with $I < 1\sigma(I)$ were used in the refinement. Crystal stability was monitored by recording three standard reflections every 10 000 s, and no significant variation was observed. The effects of absorption for this compound were very small and were neglected in our calculations. Systematic absences uniquely specified that the crystal belongs to orthorhombic space group $P2_12_12_1$ with $Z = 4$.

Table 1
Crystallographic data for methyl α-L-rhamnopyranoside (1)

Molecular formula	$C_7H_{14}O_5$
Molecular weight	178.2
Melting point (°C)	108–109
Crystal dimensions (mm)	0.37×0.38×0.50
Space group	$P2_12_12_1$
Cell dimensions (Å)	
a	7.5512(4)
b	8.2939(4)
c	13.3482(7)
Volume (Å^3)	836.0(1)
Z (molecules/cell)	4
F (000)	384
μ (cm^{-1})	1.13
Radiation (graphite monochromator)	Mo$K\alpha$
Calculated density (g cm^{-3})	1.416
Unique reflections	2103
Observed data	1934
S (166 variables)	1.911
Final residual factors	
R	0.031
R_w	0.038

Table 2
Atomic coordinates and isotropic [a] thermal parameters for methyl α-L-rhamnopyranoside (1)

Atom	x	y	z	B (Å²)
O-1	0.3895(1)	0.65641(9)	0.56966(6)	2.48(1)
O-2	0.3733(1)	0.2522(1)	0.47949(6)	2.68(1)
O-3	0.5820(1)	0.1955(1)	0.65145(6)	2.89(1)
O-4	0.3257(1)	0.2725(1)	0.80173(6)	3.24(2)
O-5	0.14884(9)	0.47880(9)	0.58302(5)	2.03(1)
C-1	0.3063(1)	0.5194(1)	0.53035(7)	1.97(1)
C-2	0.4421(1)	0.3838(1)	0.53584(7)	2.00(1)
C-3	0.4759(1)	0.3364(1)	0.64485(7)	1.93(1)
C-4	0.3023(1)	0.3016(1)	0.69778(7)	2.03(1)
C-5	0.1796(1)	0.4467(1)	0.68829(7)	2.01(1)
C-6	0.0009(2)	0.4220(2)	0.73695(9)	3.02(2)
C-7	0.3015(2)	0.8044(2)	0.5472(1)	3.27(2)
H-2OH	0.444(2)	0.192(2)	0.473(1)	4.3(4)
H-3OH	0.664(2)	0.203(2)	0.624(1)	3.6(3)
H-4OH	0.404(2)	0.230(2)	0.803(1)	4.9(4)
H-1	0.272(2)	0.534(2)	0.4650(9)	2.8(3)
H-2	0.553(2)	0.427(1)	0.510(1)	2.4(3)
H-3	0.533(2)	0.422(1)	0.6781(9)	1.9(2)
H-4	0.249(2)	0.215(2)	0.6669(9)	2.7(3)
H-5	0.253(2)	0.539(2)	0.7156(9)	2.4(3)
H-6a	0.021(3)	0.424(2)	0.815(1)	6.6(5)
H-6b	−0.074(2)	0.508(2)	0.720(1)	5.4(4)
H-6c	−0.043(2)	0.329(2)	0.713(1)	3.9(3)
H-7a	0.371(2)	0.888(2)	0.575(1)	4.9(4)
H-7b	0.287(3)	0.819(2)	0.472(1)	6.9(5)
H-7c	0.177(2)	0.795(2)	0.572(1)	6.4(5)

[a] Equivalent isotropic thermal parameters are given for nonhydrogen atoms. The definition of this quantity is $B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

The structure was solved by direct methods using the program MULTAN80 [15] that revealed the position of all nonhydrogen atoms. It was refined by full-matrix-least-squares-based upon F with weights $w = 4F_o^2[\sigma^2(I) + (0.02\ F_o^2)^2]^{-1}$ using the MolEN programs [16]. Nonhydrogen atoms were refined anisotropically. The hydrogen atoms were located from difference maps and were refined isotropically. Atomic coordinates and equivalent isotropic thermal parameters are given in Table 2 *. Final $R = 0.031$ for 1934 observed data (0.038 for all 2103 data), $R_w = 0.038$, and $S = 1.911$ for 166 variables. In the final cycle of refinement, the maximum shift was $< 0.01\sigma$, maximum residual density 0.23, minimum −0.14 eÅ^{-3}, and extinction coefficient $g = 5.5(2) \times 10^{-6}$ where the factor $(1 + gI_c)^{-1}$ was applied to F_c. All calculations were performed on a VAX 3600 computer. Atomic scattering factors were obtained from the International Tables for X-ray

* A table of structure factor amplitudes for this compound has been deposited with the Cambridge Crystallographic Data Centre and may be obtained on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

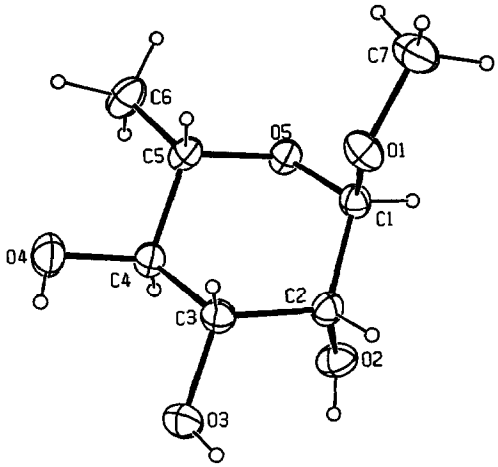

Fig. 1. Molecular structure and atomic numbering of methyl α-L-rhamnopyranoside (1). Nonhydrogen atoms are represented with 40% ellipsoids and hydrogen atoms with circles of arbitrary radius.

Crystallography [17]. The crystal structure is represented as an ORTEP [18] drawing (Fig. 1) which also shows the atom numbering in the molecule.

2. Discussion

The study of the molecular structure of the title compound reveals that the L-rhamnopyranoside ring adopts the $^1C_4$ conformation with the four oxygen substituents arranged in the sequence $1a2a3e4e$ and with the 5-*C*-methyl group in the equatorial position. A least-squares plane through C-1, O-5, C-3, and C-4 shows average and maximum deviations of these atoms (from the plane) of 0.005(1) Å; C-2 is displaced by 0.649(1) Å above the plane and C-5 is 0.702(1) Å below it. The deviations of C-1 and C-4 from the plane defined by C-2, C-3, C-5, and O-5 are 0.644(1) and 0.694(1) Å, respectively.

The bond lengths, bond angles, and selected torsion angles in the molecule are listed in Table 3. The carbon–carbon bonds are between 1.511(2) and 1.529(1) Å with a mean of 1.520 Å, which is in good agreement with values reported for other carbohydrates [19–21]. The carbon–oxygen bond distances, however, show a greater variation and range between 1.400(1) and 1.449(1) Å with a mean value of 1.425 Å, which is not significantly greater than that seen in other pyranoside structures. As usual in the pyranosidic compounds, the C-1–O-1 bond [1.400(1) Å] is shorter than the O-5–C-1 bond [1.422(1) Å], and this difference is ascribed to the exo-anomeric effect. O–H Bond distances are in the range 0.69(2)–0.74(2) Å, while C–H bond distances are in the range 0.90(1)–1.06(2) Å and show no remarkable differences from the corresponding values in the two related structures, methyl 6-deoxy-α-D-idopyranoside [12] and methyl α-L-fucopyranoside [13].

Table 3
Bond lengths, bond angles, and selected torsion angles in methyl α-L-rhamnopyranoside (1)

Atoms	Length (Å)	Atoms	Length (Å)
O-1–C-1	1.400(1)	O-5–C-5	1.449(1)
O-1–C-7	1.427(1)	C-1–C-2	1.524(1)
O-2–C-2	1.424(1)	C-2–C-3	1.529(1)
O-3–C-3	1.420(1)	C-3–C-4	1.517(1)
O-4–C-4	1.419(1)	C-4–C-5	1.524(1)
O-5–C-1	1.422(1)	C-5–C-6	1.511(2)
Atoms	Angle (°)	Atoms	Angle (°)
C-1–O-1–C-7	114.21(9)	O-3–C-3–C-4	107.57(8)
C-1–O-5–C-5	112.90(7)	C-2–C-3–C-4	110.36(8)
O-1–C-1–O-5	112.46(8)	O-4–C-4–C-3	112.33(8)
O-1–C-1–C-2	106.19(8)	O-4–C-4–C-5	106.93(8)
O-5–C-1–C-2	111.36(8)	C-3–C-4–C-5	109.66(8)
O-2–C-2–C-1	107.12(8)	O-5–C-5–C-4	108.84(7)
O-2–C-2–C-3	111.54(8)	O-5–C-5–C-6	107.38(8)
C-1–C-2–C-3	110.34(8)	C-4–C-5–C-6	113.57(9)
O-3–C-3–C-2	111.39(8)		
Atoms	Angle (°)	Atoms	Angle (°)
O-5–C-1–C-2–C-3	−53.6(1)	C-3–C-4–C-5–O-5	59.2(1)
C-1–C-2–C-3–C-4	52.1(1)	C-1–O-5–C-5–C-4	−62.3(1)
C-2–C-3–C-4–C-5	−55.5(1)	C-5–O-5–C-1–C-2	59.8(1)
O-1–C-1–C-2–O-2	−169.2(1)	O-3–C-3–C-4–O-4	64.1(1)
O-2–C-2–C-3–O-3	52.6(1)	O-4–C-4–C-5–C-6	−59.2(1)

An average difference of the order of 5° is observed in the endocyclic torsion angles of the pyranose ring, in contrast with the corresponding angles in methyl α-D-mannopyranoside [8], which agree within less than 1°. The ring conformation of the latter has a perfect chair with puckering parameters [22] $\theta = 0.0°$, $\varphi = 0.0°$, and $Q = 0.556$ Å, whereas the puckering parameters for **1** are $\theta = 175.6(4)°$, $\varphi = 112(1)°$, and $Q = 0.574(5)$ Å. These differences may be attributed to the change in the nature of the C-6 substituent as well as to the distribution of the substituents around the ring, which gives rise to asymmetric intra- and inter-molecular interactions. The conformation of the methoxy group is *gauche–trans* with respect to the sugar ring, the C-7–O-1–C-1–O-5 and C-7–O-1–C-1–C-2 torsion angles being −73.6(1)° and 164.4(1)°, respectively.

Table 4
A comparison of torsion angles between methyl α-L-rhamnopyranoside vicinal protons derived from the ^{1}H NMR experiment (D_2O), the crystal structure, and molecular mechanics calculations (MMX)

Angle (°)	^{1}H NMR	X-ray	MMX
H-1–C-1–C-2–H-2	74	74(1)	65
H-2–C-2–C-3–C-3	53	48(1)	55
H-3–C-3–C-4–H-4	−164	−177(1)	−171
H-4–C-4–C-5–H-5	−164	−176(1)	−175

Table 5
Geometry of the hydrogen bonds in methyl α-L-rhamnopyranoside (1)

Number	O···O (Å)	O–H (Å)	H···O (Å)	O-H···O (deg)
1. O-2–H-O2···O-5 [a]	2.949(1)	0.74(2)	2.23(2)	168(2)
2. O-3–H-O3···O-2 [a]	2.843(1)	0.72(2)	2.13(2)	169(2)
3. O-4–H-O4···O-1 [b]	2.916(1)	0.69(2)	2.39(2)	135(2)
4. O-4–H-O4···O-3	2.860(1)	0.69(2)	2.44(2)	121(2)
	C···O (Å)	C–H (Å)	H···O (Å)	C-H···O (deg)
5. C-5–H-5···O-3 [c]	3.475(1)	1.01(2)	2.53(1)	156(1)
6. C-7–H-7b···O-4 [d]	3.474(2)	1.02(1)	2.54(2)	152(2)

Symmetry operations: $a = 0.5+x, 0.5-y, 1-z$; $b = 1-x, y-0.5, 1.5-z$; $c = 1-x, 0.5+y, 1.5-z$; $d = 0.5-x, 1-y, 0.5-z$.

The values of the torsion angles of the vicinal protons obtained by X-ray analysis have been compared with those previously obtained by NMR spectroscopy [14] through the Altona modification of the Karplus equation [23] and from molecular mechanics calculations (MMX) with PCMODEL [24] (Table 4). The values obtained from different methodologies were in close agreement, suggesting that methyl α-L-rhamnopyranoside adopts similar conformations both in the solid state and in solution.

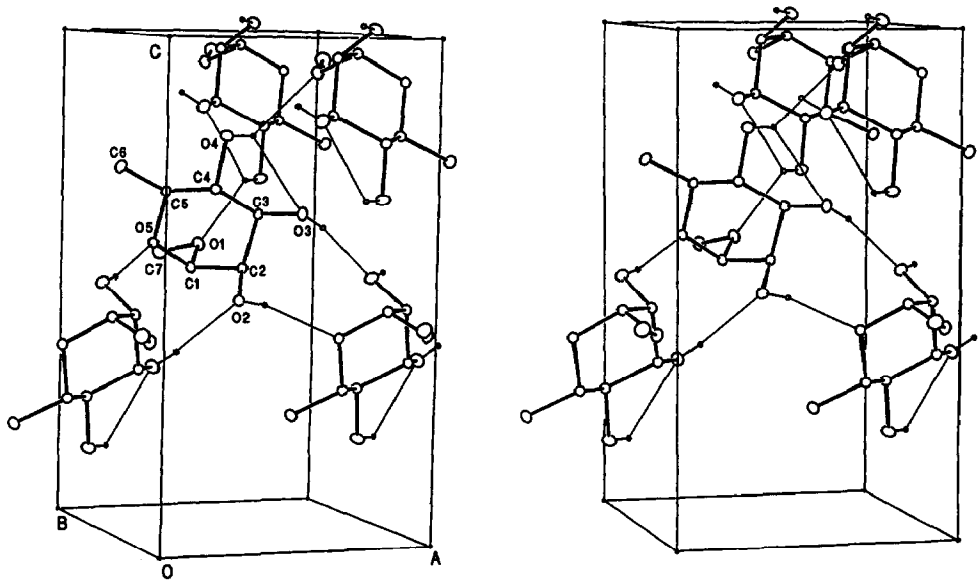

Fig. 2. Stereoview of the O-H···O hydrogen bonding scheme of methyl α-L-rhamnopyranoside (1). For clarity, hydrogen atoms not involved in hydrogen bonding are omitted.

The molecules are linked in the crystal by a network of hydrogen bonds. It involves all three hydroxyl groups. OH-2 and OH-3 act both as donors and acceptors, whereas OH-4 acts as a donor only, and it is incorporated as a symmetrical bifurcated interaction. One acceptor in the bifurcated interaction is intramolecular (O-3), while the other is intermolecular. The ring oxygen, O-5, and the glycosidic oxygen, O-1, are also included in the hydrogen bonding as acceptors. In addition, two C-H ··· O hydrogen bonds with well-defined metrical properties [25,26] occur in the present structure. These involve C-5 and C-7 act as hydrogen bond donors and O-3 and O-4 as hydrogen bond acceptors, respectively. The relevant bond distances and angles are listed in Table 5 and a stereoview of the O-H ··· O hydrogen bonding interactions are shown in Fig. 2.

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References

[1] E. Fischer, *Ber.*, 28 (1895) 1158–1159.
[2] S. Omura, H. Tanka, Y. Okada, and H. Marumo, *J. Chem. Soc., Chem. Commun.*, (1976) 320–321.
[3] H. Hoeksema and W.C. Krueger, *J. Antibiot.*, 29 (1976) 704–709.
[4] W. Keller-Schierlien, M. Brufani, and S. Barcza, *Helv. Chim. Acta*, 51 (1968) 1257–1268.
[5] H. Ogura and K. Furuhata, *9th Int. Congr. of Heterocycl. Chem.*, Tokyo, August 1983, *Abstr.* No. S-IV-6.
[6] H.W. Moore, *Science*, 197 (1977) 527–532.
[7] H. Grisebach, *Adv. Carbohydr. Chem. Biochem.*, 35 (1978) 81–126.
[8] B.M. Gatehouse and B.J. Poppleton, *Acta Crystallogr., Sect. B*, 26 (1970) 1761–1765.
[9] H.M. Berman and S.H. Kim, *Acta Crystallogr., Sect. B*, 24 (1968) 897–904.
[10] G.A. Jeffrey, R.K. McMullan, and S. Takagi, *Acta Crystallogr., Sect. B*, 33 (1977) 728–737.
[11] B.J. Poppleton, G.A. Jeffrey, and G.J.B. Williams, *Acta Crystallogr., Sect. B*, 31 (1968) 63–76.
[12] R.M. Giuliano, R.F. Bryan, P. Hartley, S. Peckler, and M.K. Woode, *Carbohydr. Res.*, 191 (1989) 1–11.
[13] D. Lamba, A.L. Segre, G. Fabrizi, and B. Matsuhiro, *Carbohydr. Res.*, 243 (1993) 217–224.
[14] A. De Bruyn, M. Anteunis, R. De Gussem, and G.S. Dutton, *Carbohydr. Res.*, 47 (1976) 158–163.
[15] P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq, and M.M. Woolfson, MULTAN80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data, Universities of York, UK and Louvain, Belgium.
[16] C.K. Fair, MolEN, An Interactive Structure Solution Procedure, Enraf-Nonius, Delft, The Netherlands, 1990.
[17] D.T. Cromer and J.T. Waber, *International Tables for X-Ray Crystallography*, Vol. IV, Tables 2, 2B, and 2.3.1, The Kynoch Press, Birmingham, UK, 1974 (current distributor, Kluwer Academic Publishers, Dordrecht).

[18] C.K. Johnson, ORTEP II, Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[19] G.A. Jeffery and A.D. French, *Chem. Soc. Spec. Publ.*, 6 (1978) 183–223.
[20] F.H. Allen, *Acta Crystallogr., Sect. B*, 42 (1986) 515–522.
[21] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, (1987) S1–S19.
[22] D. Cremer and J.A. Pople, *J. Am. Chem. Soc.*, 97 (1975) 1354–1358.
[23] C.A.G. Hasnoot, F.A.A.M. De Leeuw, and C. Altona, *Tetrahedron*, 36 (1980) 2783–2792.
[24] PCMODEL version 4.3, Serena Software, Box 3076, Bloomington, IN 47402-3076, USA.
[25] R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 104 (1982) 5063–5070.
[26] T. Steiner and W. Saenger, *J. Am. Chem. Soc.*, 114 (1992) 10146–10154.