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Structural analysis of methyl α-L-fucopyranoside by X-ray crystallography, NMR spectroscopy, and molecular mechanics calculations

D. Lamba [a,*], A.L. Segre [a], G. Fabrizi [b] and B. Matsuhiro [c]

[a] *Istituto di Strutturistica Chimica "G. Giacomello", C.N.R., Area della Ricerca di Roma, P.O. Box 10, I-00016 Monterotondo Stazione, Roma (Italy)*
[b] *Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università dell'Aquila, Via Assergi 6, I-67100 L'Aquila (Italy)*
[c] *Departamento de Quìmica, Universidad de Santiago de Chile, Casilla 5659, Santiago-2 (Chile)*

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ABSTRACT

The crystal and molecular structures of methyl α-L-fucopyranoside are reported. The sugar ring has the expected $^1C_4$ conformation. The ^{1}H NMR spectrum at 600 MHz was fully analysed. The conformation of the pyranose ring in solution, derived from $^3J_{HH}$ values, was very similar to that in the crystal. All these features have been rationalised through molecular mechanics calculations.

INTRODUCTION

L-Fucose is widely distributed in plant polysaccharides and animal glycans[1]. These include the fucans from brown-algal cell walls[2,3], and the hormonal, serum, and plasma glycoproteins[4]. L-Fucose is the immunodominant monosaccharide of many blood-group antigenic determinants[5]. Recent studies reported the occurrence of L-fucose in a carbohydrate tumor-associated antigen[6], in a glycosphingolipid[7], in the neutral glycopeptides from human neuroblastoma cells[8], in a glycopeptidolipid antigen of serovar 20 of the *Mycobacterium avium* serocomplex[9], and in the trisaccharide–protein conjugate of the phenolic glycolipid of *Mycobacterium tuberculosis*[10]. Bauman et al.[11] reported NMR and conformational studies of oligosaccharides substituted with L-fucopyranosyl residues. X-ray crystal structure determinations of a hydrated calcium bromide complex of α-D-fucose[12], of α-L-fucose[13], and of α-DL-fucose[14] have also been reported. In the present study, we have determined the crystal and molecular structures of methyl α-L-fucopyranoside. A ^{1}H NMR study at 600 MHz in D_2O has also been carried out with the aim

* Corresponding author.

of the complete assignment of the chemical shifts and $^3J_{HH}$ coupling constants that were not available from a previous study at 400 MHz because of the strongly coupled spectrum in the 3.80 ppm region due to protons H-2, H-3, and H-4[15].

EXPERIMENTAL

General.—Melting points (Kofler apparatus) are uncorrected. ^{1}H NMR spectra were recorded with a Bruker AX 600.14 MHz spectrometer. Optical rotations were determined at 23 ± 2°C with a Perkin–Elmer 241 polarimeter. Analytical TLC was carried out on Silica Gel 60 F_{264} (Merck) with detection by charring with 10% ethanolic phosphomolybdic acid. Column chromatography was performed on Kieselgel 60 (Merck, 70–230 mesh). L-Fucose was obtained from Sigma.

Synthesis.—The methyl α-L-fucopyranoside was synthesised according to Gardiner and Percival[16]. A solution of L-fucose (10.0 g) in anhyd MeOH (400 mL) was treated with acetyl chloride (6 mL) and left for 66 h at room temperature. The solution was neutralised with silver carbonate, the suspension filtered, and the filtrate concentrated under reduced pressure, giving a syrup (12.06 g). The crude product was chromatographed on silica gel. Elution was carried out with 95:5 EtOAc–MeOH, collecting fractions of 15 mL. Fractions 45–60 afforded a syrup (3.98 g) that showed a single spot in TLC, using the same mixture as eluent: $[\alpha]_D^{23}$ + 118.5° (*c* 1.5, MeOH); lit.[16] for methyl β-L-fucofuranoside, $[\alpha]_D^{23}$ + 112° (MeOH). Fractions 75–90 gave crystals (0.67 g) which were recrystallised from EtOAc; mp 125–126°C; $[\alpha]_D^{23}$ − 103.9° (*c* 1.39, MeOH); lit.[16] for methyl α-L-fucofuranoside, mp 127–128°C; $[\alpha]_D^{23}$ − 108° (MeOH). Fractions 91–109 gave crystals (0.34 g) which were recrystallised from EtOAc; mp 157–158°C; $[\alpha]_D^{23}$ − 188.03° (*c* 1.06, MeOH); lit.[16] for methyl α-L-fucopyranoside, mp 158–159°C; $[\alpha]_D^{23}$ − 191° (MeOH).

NMR spectroscopy.—Recently, a ^{1}H and ^{13}C NMR study of the title compound has been reported[15] (400 MHz, D_2O at 70°C). The ^{1}H NMR spectrum was not fully assigned because of strong coupling in the 3.80-ppm region due to protons H-2, H-3, and H-4. We now report the complete assignment of the ^{1}H NMR spectrum at 600 MHz (3 mg/mL in D_2O; 27°C; internal standard, acetone 10^{-5} M, 2.225 ppm). Chemical shifts and *J* couplings are reported in Table I. The spectrum was acquired using 64 K scans with a total spectral width of 3600 Hz, a digital resolution of 0.05 Hz/point, and an acquisition time of 9 s. Resolution enhancement was achieved through a small Gaussian multiplication.

X-ray crystallography.—Evaporation of an ethyl acetate solution of the title compound yielded prismatic, transparent crystals. Weissenberg and oscillation photographs showed the crystal to be monoclinic, the space group being $P2_1$. A crystal (0.5 × 0.4 × 0.2 mm) was set on a four-circle Siemens R3m/V diffractometer equipped with graphite-monochromated Cu $K\alpha$ radiation. Accurate unit-cell parameters were obtained from a least-squares fit of 28 reflections with $77 \leq 2\theta \leq 94°$. The crystal data are given in Table II. The intensity data were collected in the θ–2θ scan mode; scan width, $2° + 0.14 \tan\theta$; scan rate, 1.5 to 14.65° · min^{-1};

TABLE I

^{1}H NMR data [a] (δ in ppm and J in Hz) (root mean square < 0.1 Hz)

Protons	δ	$^3J_{HH}$
H-1	4.919	
H-2	3.929	3.60
H-3	3.962	10.20
H-4	3.938	3.10
H-5	4.185	0.80
CH_3	1.378	6.70
O-CH_3	3.546	

[a] Assignment verified by homodecoupling, see Fig. 1.

background count time, half of total scan time; $\theta_{max} = 70°$; (*hkl* range: *h* 0 to 7, *k* 0 to 9, *l* −12 to 11). There was no significant intensity variation for the three check reflections 0 1 1, 1 1 0, 3 0 1, monitored every hundred. The data were corrected for Lorentz-polarisation effects; no absorption nor extinction corrections were made. A total of 1002 reflections were collected; merging equivalents gave 873

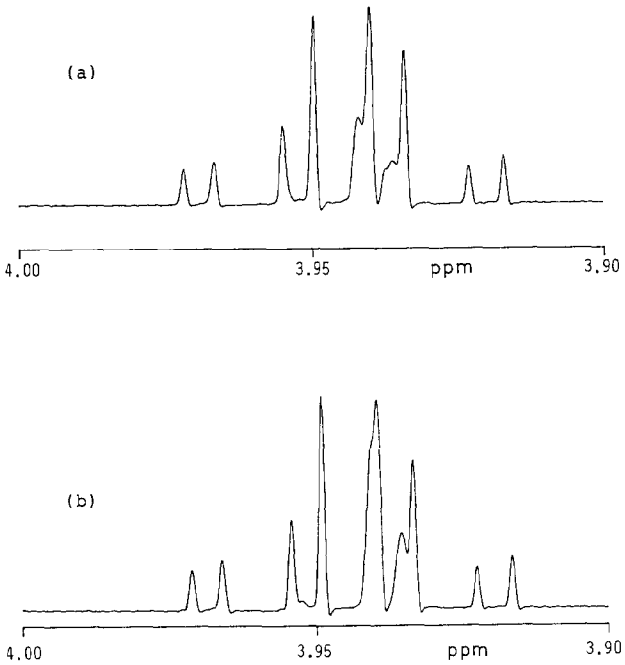

Fig. 1. (a) The 3.95-ppm region of the 600-MHz spectrum of methyl α-L-fucopyranoside; (b) homodecoupled on proton H-5.

TABLE II

Crystal data for methyl α-L-fucopyranoside

Molecular formula	$C_7H_{14}O_5$
Molecular weight	178.2
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	
a (Å)	5.839(2)
b	7.892(2)
c	10.074(3)
β (°)	102.61(2)
Cell volume (Å^3)	453.1(2)
Z	2
F (000)	192
μ (Cu $K\alpha$) (cm^{-1})	0.911
D_c (kg·m^{-3})	1.306

unique $R_{int} = 1.97\%$, of which 832 with $F_o \geq 4\sigma F_o$ were used for structural analysis. The structure was solved by direct methods, using the SHELXTL-Plus[17] package, and refined on F_o by full-matrix least-squares methods. All the hydrogen atoms were located in subsequent difference Fourier maps and included in the later refinement with fixed $U_{iso} = 0.08$ Å^2. The final R was 0.043, w$R = 0.068$, S = 0.98. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$, where $w = 1/\sigma^2(F_o) + 0.0049F_o$. Final Fourier synthesis was featureless with $-0.25 \leq \Delta\rho \leq 0.24$ e · Å^{-3}.

The atomic scattering factors were those in the SHELXTL-Plus package and are in the analytical form in the International Tables for X-ray Crystallography[18]. The PARST program[19] was used for geometry calculations.

TABLE III

Atomic coordinates and equivalent isotropic displacement coefficients (Å^2)

Atom	x/a	y/b	z/c	U_{eq} [a]
C-1	0.4311(5)	0.5156	0.3391(3)	0.395(9)
C-2	0.3275(4)	0.4578(5)	0.4580(3)	0.318(8)
C-3	0.0732(4)	0.4026(5)	0.4075(3)	0.329(8)
C-4	0.0549(5)	0.2707(6)	0.2956(3)	0.371(8)
C-5	0.1609(6)	0.3462(6)	0.1827(3)	0.455(10)
C-6	0.1596(11)	0.2268(8)	0.0651(5)	0.719(18)
C-7	0.4448(11)	0.7541(8)	0.2027(5)	0.668(17)
O-1	0.3265(4)	0.6696(5)	0.2916(3)	0.486(8)
O-2	0.3521(3)	0.5838(5)	0.5611(2)	0.377(7)
O-3	−0.0222(4)	0.3363(5)	0.5143(2)	0.411(8)
O-4	0.1619(4)	0.1140(5)	0.3433(2)	0.407(7)
O-5	0.4032(4)	0.3909(5)	0.2368(2)	0.458(8)

[a] $U_{eq} = 1/3\ \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$.

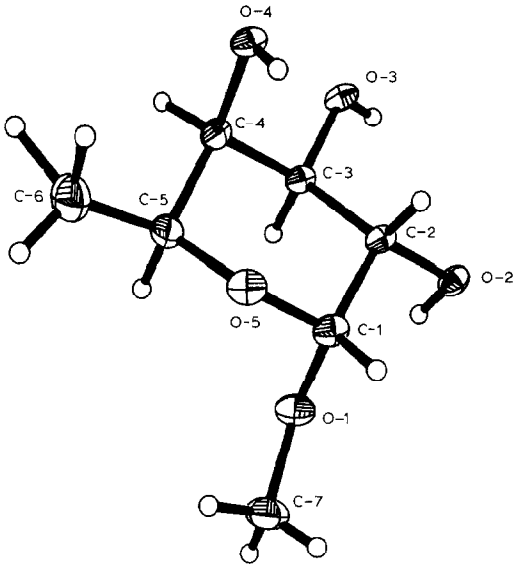

Fig. 2. Molecular conformation of methyl α-L-fucopyranoside.

Final fractional coordinates and U_{eq} values of the heavy atoms are listed in Table III *.

DISCUSSION

The configuration, the conformation, and the atom-numbering scheme are shown in Fig. 2. The molecular geometry is listed in Table IV. Bond lengths and valence angles conform to those of the three related structures: $CaBr_2$–α-D-fucose[12], α-L-fucopyranose[13], and α-DL-fucopyranose[14]. As usual in the pyranosidic compounds, the C-1–O-1 bond [1.397(4) Å] is shorter then the C-1–O-5 bond [1.402(4) Å] and this difference is ascribed to the exo-anomeric effect. The fucopyranoside ring adopts a $^1C_4$ conformation, Q = 0.577(3) Å, θ = 175.5(4)°, and ϕ = 90(4)°, as described by the Cremer and Pople puckering parameters[20]. 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 the C-7–O-1–C-1–C-2 torsion angles being −70.1(4)° and 166.5(4)°, respectively. The values of the torsion angle of vicinal protons obtained by X-ray analysis have been compared with those obtained by NMR spectroscopy from $^3J_{HH}$ values through the Altona modification of the Karplus equation[21] and from molecular mechanics calculations (MMX) with PCMODEL[22]

* Anisotropic thermal vibration parameters U_{ij} of the heavy atoms, the coordinates and U_{iso} values of the H atoms, and lists of F_o and F_c structure factors have been deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, Netherlands. Reference should be made to No. BBA/DD/533/*Carbohydr. Res.*, 217–224.

TABLE IV

Molecular geometry and hydrogen-bonding network

Bonds			
O-1–C-1	1.397(4)	O-5–C-1	1.408(4)
O-1–C-7	1.412(7)	C-1–C-2	1.525(5)
O-2–C-2	1.422(5)	C-2–C-3	1.524(4)
O-3–C-3	1.415(4)	C-3–C-4	1.521(5)
O-4–C-4	1.412(5)	C-4–C-5	1.530(5)
O-5–C-5	1.444(4)	C-5–C-6	1.512(7)
Angles			
O-1–C-1–O-5	112.6(2)	C-3–C-4–O-4	113.0(3)
C-2–C-1–O-5	111.3(2)	C-3–C-4–C-5	108.1(3)
C-2–C-1–O-1	108.1(3)	C-5–C-4–O-4	111.8(3)
C-1–C-2–O-2	111.7(2)	C-4–C-5–O-5	109.7(3)
C-1–C-2–C-3	110.4(2)	C-4–C-5–C-6	110.0(4)
C-3–C-2–O-2	112.3(2)	C-6–C-5–O-5	106.0(3)
C-2–C-3–O-3	111.6(2)	C-1–O-1–C-7	113.0(4)
C-2–C-3–C-4	110.4(2)	C-1–O-5–C-5	113.2(3)
C-4–C-3–O-3	109.5(3)		
Torsion angles (°)			
Endocyclic		Exocyclic	
O-5–C-1–C-2–C-3	−53.5(3)	O-1–C-1–C-2–O-2	−55.0(3)
C-1–C-2–C-3–C-4	53.5(4)	O-2–C-2–C-3–O-3	−59.1(4)
C-2–C-3–C-4–C-5	−56.3(4)	O-3–C-3–C-4–O-4	−55.4(4)
C-3–C-4–C-5–O-5	59.4(4)	O-4–C-4–C-5–C-6	53.8(5)
C-4–C-5–O-5–C-1	−62.4(4)	C-6–C-5–O-5–C-1	174.0(3)
C-5–O-5–C-1–C-2	58.8(4)	C-6–C-5–C-4–C-3	178.8(8)
		C-7–O-1–C-1–O-5	−70.1(4)
		C-7–O-1–C-1–C-2	166.5(4)

D-H ··· A	D ··· A (Å)	D-H (Å)	H ··· A (Å)	< (D-H ··· A) (°)
O-4–H–O4 ··· O-2 [b]	2.801(3)	0.81(7)	2.06(6)	152(6)
O-2–H–O2 ··· O-3 [a]	2.761(5)	0.81(7)	1.99(7)	160(6)
O-3–H–O3 ··· O-4 [a]	2.835(5)	0.75(7)	2.12(8)	161(6)

Symmetry code: [a] $-x, +y+1/2, -z+1$. [b] $-x+1, +y-1/2, -z+1$.

(Table V). The values obtained from different methodologies compare very well, suggesting that methyl α-L-fucopyranoside adopts similar conformations both in the solid state and in solution. The crystal packing projected along the *a* axis is

TABLE V

Torsion angles (°) between fucopyranosidic vicinal protons derived from the NMR experiment (D_2O), the crystal structure, and molecular mechanics calculations (MMX)

Angles	^{1}H NMR	X-ray	MMX
H-1–C-1–C-2–H-2	−53	−50	−53
H-2–C-2–C-3–H-3	170	175	174
H-3–C-3–C-4–H-4	−53	−58	−53
H-4–C-4–C-5–H-5	59	60	55

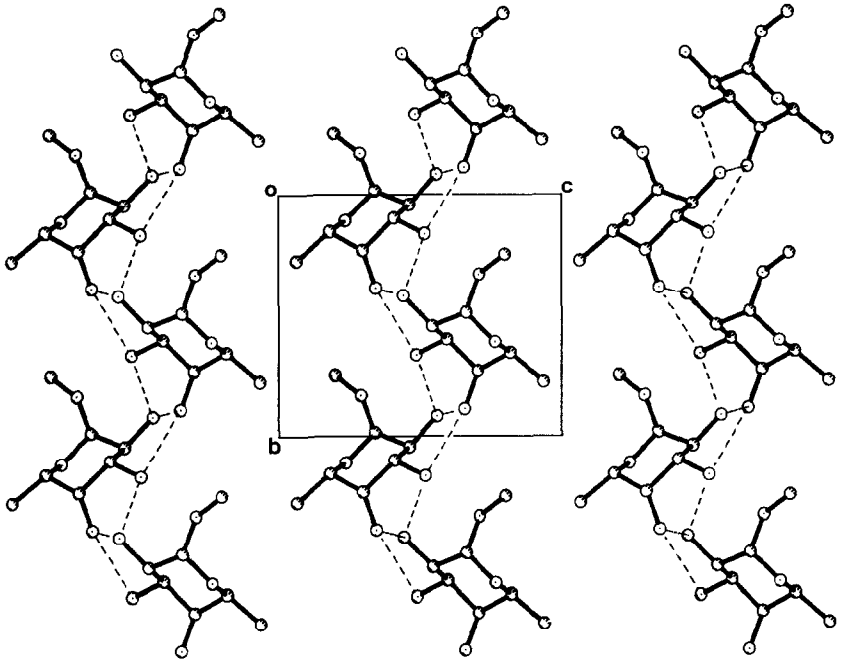

Fig. 3. Packing diagram viewed along *a*.

shown in Fig. 3. The net of hydrogen bonds involve all the hydroxyl groups which act both as donors and acceptors (Table IV). A stable arrangement is achieved through a two-fold screw axis operation parallel to the crystallographic axis *b*, which produces a "molecular chain". The chain–chain non-bonded interactions are dominated by Van der Waals contacts involving the CH_3 and OCH_3 groups.

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