

Structures of furanosides: geometrical analysis of low-temperature X-ray and neutron crystal structures of five crystalline methyl pentofuranosides

Artem Evdokimov,^{a*} A. Joseph Gilboa,^b Thomas F. Koetzle,^c Wim T. Klooster,^c Arthur J. Schultz,^d Sax A. Mason,^e Alberto Albinati^f and Felix Frolow^g

^aProtein Engineering Section, Program in Structural Biology, NCI-Frederick Cancer Research and Development Center, PO Box B, Frederick, MD 21702, USA, ^bDepartment of Structural Biology, Weizmann Institute of Science, Rehovot 76100, Israel, ^cChemistry Department, Brookhaven National Laboratory, PO Box 5000, Upton, NY 11973, USA, ^dIPNS Division, Argonne National Laboratory, Argonne, IL 60439, USA, ^eInstitut Laue–Langevin, 38042 Grenoble CEDEX 9, France, ^fUniversità di Milano, Istituto di Chimica Farmaceutica, Milano 20131, Italy, and ^gGeorge S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel

Correspondence e-mail:
eudokima@mail.ncifcrf.gov

Crystal structures of all five crystalline methyl D-pentofuranosides, methyl α -D-arabinofuranoside (1), methyl β -D-arabinofuranoside (2), methyl α -D-lyxofuranoside (3), methyl β -D-ribofuranoside (4) and methyl α -D-xylofuranoside (5) have been determined by means of cryogenic X-ray and neutron crystallography. The neutron diffraction experiments provide accurate, unbiased H-atom positions which are especially important because of the critical role of hydrogen bonding in these systems. This paper summarizes the geometrical and conformational parameters of the structures of all five crystalline methyl pentofuranosides, several of them reported here for the first time. The methyl pentofuranoside structures are compared with the structures of the five crystalline methyl hexopyranosides for which accurate X-ray and neutron structures have been determined. Unlike the methyl hexopyranosides, which crystallize exclusively in the C_1 chair conformation, the five crystalline methyl pentofuranosides represent a very wide range of ring conformations.

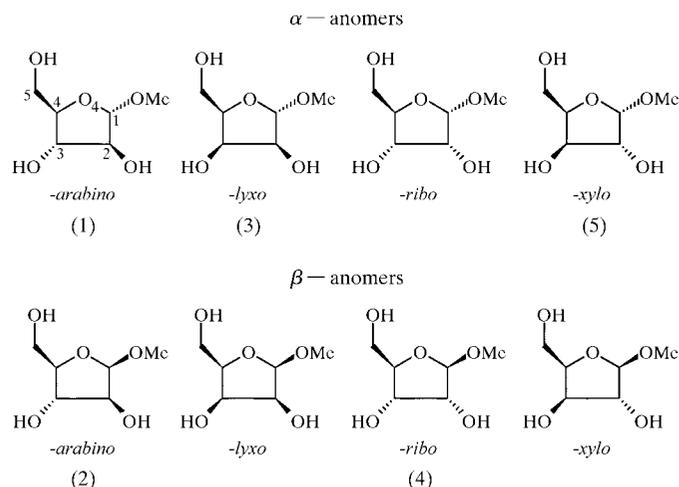
Received 9 August 2000
Accepted 8 November 2000

1. Introduction

The furanosides are of great chemical and biological importance, playing a major role in the structure and behavior of nucleic acids, antibiotics, and numerous oligo- and polysaccharides. In contrast to the pyranoside rings, in which bond lengths, bond angles and dihedral angles can be maintained at their minimum energy values in a well defined strain-free chair conformation, furanoside rings are strained in all conformations. Until 1996, structural data for the methyl pentofuranosides were limited to a single structure, that of methyl α -D-lyxofuranoside, determined by X-ray crystallography at room temperature (Groth & Hammer, 1968). In 1996, a room-temperature crystal structure was also reported for methyl β -D-ribofuranoside (Podlasek *et al.*, 1996). An accurate and self-consistent set of crystal structures of the methyl pentofuranosides, *i.e.* the simplest furanosides, can represent an important contribution to conformational analysis of the furanoside ring (Evdokimov *et al.*, 1999, 2000).

We have determined highly accurate and precise structures, by means of low-temperature X-ray and neutron crystallography, of the five crystalline methyl pentofuranosides: methyl α -D-arabinofuranoside (1), methyl β -D-arabinofuranoside (2), methyl α -D-lyxofuranoside (3), methyl β -D-ribofuranoside (4) and methyl α -D-xylofuranoside (5). The present work completes the full set of X-ray and neutron structures for all five crystalline compounds, representing seven independent highly accurate and precise structures for the methyl pentofuranosides. The geometrical and conformational data

for these compounds are analyzed and compared to those for the six methyl hexopyranosides whose crystal structures have been determined.



2. Materials and methods

2.1. Crystalline furanosides

The methyl pentofuranosides were prepared as described earlier (Evdokimov *et al.*, 1999; Wu & Serianni, 1991). Compound (2) crystallized upon cooling of the dry syrup with liquid nitrogen and was recrystallized from dry acetonitrile. Crystals suitable for neutron diffraction were grown by saturating acetonitrile with (2) at 318–328 K, cooling the solution to 303 K and nucleating with a microcrystal. Neutron-grade crystals of (5) (average size $2 \times 1 \times 1$ mm) were obtained in a similar manner.

The three hydroxyl protons of (3) were exchanged for deuterium by evaporation of a concentrated solution of the compound in D_2O . Neutron-grade crystals of deuterated (3) [referred to below as (3^D)] were obtained by seeding and slow cooling.

2.2. Neutron and X-ray diffraction studies of the methyl pentofuranosides

The X-ray diffraction structures of (1), (3), (4) and (5) as well as the neutron structures of (1) and (4) have been reported (Evdokimov *et al.*, 1999) and are available from the Cambridge Structural Database (CSD; Allen & Kennard, 1993; requisition codes 112946–112952).¹

The low-temperature (100 K) single-crystal X-ray structure of (2) and the neutron structures of (2), (3^D) and (5) at 20 K are reported here for the first time and were determined, as described below, by procedures generally similar to those reported earlier (Evdokimov *et al.*, 1999).

2.2.1. Methyl β -D-arabinofuranoside (2): X-ray and neutron data collection and analysis. A Nonius Kappa-CCD area detector was used for X-ray data collection of (2). The

data were processed using Nonius (1998) and *maXus* (Mackay *et al.*, 1998) software and the structure was solved and refined using *SHELXS97* and *SHELXL97* (Sheldrick, 1990, 1997; Sheldrick & Schneider, 1997). Full-matrix least-squares anisotropic refinement was performed with no restraints for all C and O atoms; H atoms were refined with isotropic displacement factors.

The neutron structure of (2) at 20 K was determined by time-of-flight measurements at the Intense Pulsed Neutron Source (IPNS) at the Argonne National Laboratory using a single-crystal diffractometer equipped with a position-sensitive 6Li -glass scintillation area detector (30×30 cm²; Schultz, 1987). Data collection and analysis procedures have been published previously (Schultz *et al.*, 1990). A crystal with approximate dimensions $2 \times 2 \times 1$ mm³ was covered with halocarbon grease, wrapped in aluminium foil and glued to an aluminium pin that was mounted on the cold stage of a Displex closed-cycle helium refrigerator (Air Products and Chemicals, Inc., Model CS-202) operating at 20 ± 0.1 K. An orientation matrix was initially obtained by an auto-indexing procedure using data obtained by searching a histogram for peaks (Jacobson, 1986). One unique octant of data, plus some additional reflections, were collected using wavelengths of 0.7–4.2 Å. Bragg reflections were integrated about their predicted locations and were corrected for the Lorentz factor, the incident spectrum and the detector efficiency. A wavelength-dependent spherical absorption correction was applied using cross-sections from Sears (1986) for the non-H atoms and from Howard *et al.* (1987) for the H atoms. Symmetry-related reflections were not averaged since different extinction factors are applicable to reflections measured at different wavelengths. The structure was refined using the *GSAS* program (Larson & Von Dreele, 1994). In the final refinement, a secondary extinction correction, Type II, was included, and all atoms were refined with anisotropic temperature factors. Table 1 summarizes the data collection, analysis and refinement parameters for this experiment.

2.2.2. Methyl α -D-xylofuranoside (5) and methyl α -D-lyxofuranoside (3^D): neutron data collection and analysis. Neutron diffraction experiments with (3^D) and (5) were performed at the Institut Laue–Langevin (ILL) using the thermal-beam instrument D19 equipped with a Displex cryorefrigerator (Archer & Lehmann, 1986) and a $4 \times 64^\circ$ position-sensitive detector (Thomas *et al.*, 1983). Reflections were integrated using the program *Retreat* (Wilkinson *et al.*, 1988) and corrected for absorption with the program *D19abs*, based on the ILL version of the *CCSL* system (Matthewman *et al.*, 1982). Refinement was performed with *SHELXL97* (Sheldrick, 1997; Sheldrick & Schneider, 1997) using anisotropic displacement parameters for all atoms. For (3^D), pairs of H and D atoms connected to O2, O3 and O5 were restrained to the same geometrical positions and the same atomic displacement parameters. Sums of occupancies of the related H and D atoms were restrained to unity, with starting individual deuterium occupancies of 0.5, which eventually refined to 0.7–0.8. For all atoms, the coherent scattering amplitudes were those tabulated by Sears (1992). Table 1 summarizes the data

¹Supplementary data for this paper are available from the IUCr electronic archives (Reference: AN0575). Services for accessing these data are described at the back of the journal.

Table 1
Experimental details.

	(2) X-ray	(2) neutron	(3 ^D) neutron	(5) neutron
Crystal data				
Chemical formula	C ₆ H ₁₂ O ₅	C ₆ H ₁₂ O ₅	C ₆ H ₁₂ O ₅	C ₆ H _{9.783} D _{2.217} O ₅
Chemical formula weight	164.16	164.16	164.16	166.2
Cell setting, space group	Orthorhombic, <i>P</i> ₂ ₁ ₂ ₁	Orthorhombic, <i>P</i> ₂ ₁ ₂ ₁	Monoclinic, <i>P</i> ₂ ₁	Orthorhombic, <i>P</i> ₂ ₁ ₂ ₁
<i>a</i> , <i>b</i> , <i>c</i> (Å)	5.906 (1), 10.845 (3), 12.154 (3)	5.901 (1), 10.791 (2), 12.151 (2)	6.2238 (2), 8.1389 (2), 7.3637 (2)	10.332 (3), 15.446 (2), 4.614 (1)
α , β , γ (°)	90, 90, 90	90, 90, 90	90, 101.1465 (17), 90	90, 90, 90
<i>V</i> (Å ³)	778.5 (2)	773.8 (2)	365.971 (18)	736.3 (3)
<i>Z</i>	4	4	2	4
<i>D</i> _x (Mg m ⁻³)	1.401	1.409	1.488	1.506
Radiation type	Mo <i>K</i> α	Neutron	Neutron	Neutron
Wavelength (Å)	0.71070	0.7–4.2	0.95284	0.95284
No. of reflections for cell parameters	600	All	1577	1949
θ range (°)	8–25	–	3–50	3–50
μ (mm ⁻¹)	0.123	–	2.56	2.14
Temperature (K)	100 (1)	20.0 (1)	20.0 (1)	20.0 (1)
Crystal form, colour	Rectangular prism, clear blank white	Rectangular prism, clear blank white	Rectangular block, clear blank white	Rectangular needle, clear blank white
Crystal size (mm)	0.4 × 0.1 × 0.1	2.0 × 2.0 × 1.0	3.5 × 1.12 × 1.11	6.7 × 1.3 × 1.1
Data collection				
Diffraction method	Nonius Kappa-CCD	IPNS SCD	ILL D19	ILL D19
Data collection method	φ scans	TOF Laue	ILL D19	ILL D19
Absorption correction	None	Sphere	Analytical	Analytical
<i>T</i> _{min}	–	–	0.699	0.6654
<i>T</i> _{max}	–	–	0.783	0.8287
No. of measured, independent and observed parameters	2313, 2313, 2219	4688, 4688, 2977	2323, 2323, 1949	2791, 2036, 1949
Criterion for observed reflections	<i>I</i> > 4 σ (<i>I</i>)	<i>I</i> > 3 σ (<i>I</i>)	<i>I</i> > 4 σ (<i>I</i>)	<i>I</i> > 4 σ (<i>I</i>)
<i>R</i> _{int}	0	0	0.0434	0.0395
θ _{max} (°)	30.91	61.00	50.12	52.07
Range of <i>h</i> , <i>k</i> , <i>l</i>	0 → <i>h</i> → 8 0 → <i>k</i> → 15 –16 → <i>l</i> → 17	0 → <i>h</i> → 8 0 → <i>k</i> → 15 0 → <i>l</i> → 17	–3 → <i>h</i> → 9 –5 → <i>k</i> → 13 –11 → <i>l</i> → 11	–4 → <i>h</i> → 17 –5 → <i>k</i> → 25 –2 → <i>l</i> → 7
No. and frequency of standard reflections	–	–	3 every 50 reflections	3 every 50 reflections
Refinement				
Refinement on	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.0273, 0.0764, 1.002	0.1, 0.117, 1.096	0.0399, 0.1024, 1.108	0.0415, 0.0853, 1.228
No. of reflections and parameters used in refinement	1365, 148	4688, 226	1619, 209	2036, 215
H-atom treatment	Mixed	All H-atom parameters refined	All H-atom parameters refined	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0517P)^2 + 0.0636P]$, where $P = (F_o^2 + 2F_c^2)/3$	$\Sigma F_o^2 = \Sigma F_c^2 + (0.002F_o^2)^2$; $w = 1.0/(\Sigma F_o^2)^2$; all single-crystal weights were scaled by $\text{Min}(F_o/F_c, F_c/F_o)^4$	$w = 1/[\sigma^2(F_o^2) + (0.0729P)^2 + 0.7096P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0141P)^2 + 4.2536P]$, where $P = (F_o^2 + 2F_c^2)/3$
(Δ/σ) _{max}	0.017	0.001	0.003	0.000
$\Delta\rho$ _{max} , $\Delta\rho$ _{min} (e Å ⁻³)	0.237, –0.199	–	–	–
Extinction method	None	GSAS (Larson & Von Dreele, 1994)	SHELXL97 (Sheldrick, 1997)	SHELXL97 (Sheldrick, 1997)
Extinction coefficient	–	0.0003 (1)	0.040 (6)	0.0161 (11)

Computer programs used: *maxus* (Nonius, 1998), *SHELXL97* (Sheldrick, 1997), custom software (Schultz, 1987), manual, ILL programs *Hklgen* and *Mad*, ILL program *Rafd19*. The largest positive and negative residual peaks in the neutron difference density maps were of the order 6–10% the height of typical atom peaks in the Fourier.

collection, analysis and refinement parameters for these experiments.

2.3. Crystal structures of the methyl hexopyranosides

Structural data for the six methyl hexopyranosides, methyl α -D-altropyranoside, methyl β -D-galactopyranoside, methyl

β -D-glucopyranoside, methyl α -D-mannopyranoside, methyl α -D-galactopyranoside and methyl α -D-glucopyranoside are from the CSD reference codes MALTPY, MEMANP, MGALPY (Gatehouse & Poppleton, 1971), MBDGAL (Sheldrick, 1977), MBDGPH10 (Jeffrey & Takagi, 1977), MGLUCP (Berman & Kim, 1968) for X-ray data and

MALTPY01 (Poppleton *et al.*, 1975), MBDGAL02, MGALPY01 (Takagi & Jeffrey, 1978), MEMANP11, MGLUCP11 (Jeffrey *et al.*, 1977) for neutron data.

2.4. Determination of furanose ring conformation

There are several conventions in use for describing the conformation of a five-membered ring to a good approximation (*e.g.* Altona & Sundaralingam, 1972; Cremer & Pople, 1975). We chose to use the system proposed by Marzec & Day (1993), which describes the *exact* geometry of any five-membered ring in terms of nine internal parameters: five bond lengths and four conformational variables. Two of the variables are the Cremer–Pople pseudorotation phase angle (\mathbf{P} , °) and the maximum deviation along the normal to the Cremer–Pople plane (\mathbf{q} , Å). The other two parameters, introduced by Marzec & Day (1993), are the distortion of the ring in the Cremer–Pople plane (\mathbf{s} , Å) and ($\mathbf{\Gamma}$, °), the direction of \mathbf{s} .

We have used the programs *BREAKRING* and *MAKERING* (Marzec & Day, 1993) to determine the values of \mathbf{P} , \mathbf{q} , \mathbf{s} and $\mathbf{\Gamma}$ from the Cartesian coordinates of the furanose rings; and to test the accuracy of ring structures reconstituted with average values of the five ring bond lengths and the ring parameters \mathbf{q} , \mathbf{s} and $\mathbf{\Gamma}$ set to 0 (*i.e.* the Cremer–Pople approximation).

3. Results and discussion

3.1. Crystal structures of the methyl pentofuranosides

Thermal motion ellipsoid (TME) plots and crystal packing diagrams for all five crystalline methyl pentofuranosides are shown in Figs. 1–3. In total there are seven independent furanose structures since (1) and (4) have two independent molecules in the asymmetric unit.

3.2. Bond lengths

3.2.1. Ring bonds. The average bond lengths in pyranoside and furanose structures are essentially equal. Furanoside and pyranoside C–C bond lengths are 1.522 (4) *versus* 1.528 (8), respectively, for X-ray structures and 1.526 (3) *versus* 1.534 (6) Å for neutron structures; C–O bond lengths are 1.431 (9) *versus* 1.435 (12) Å (X-ray) and 1.425 (9) *versus* 1.435 (13) (neutron). The furanose bond lengths, however, have a somewhat larger spread, which may be attributed to the strain intrinsic to the five-membered ring. It should be noted that the available structural data for the pyranosides are based on measurements made at room temperature, whereas the furanose data are for 100 (X-ray) or 15–20 K (neutron).

3.2.2. O–H bonds. The X-ray values of the O–H bond lengths [0.83 (6) Å] are systematically shorter than those determined by neutron diffraction [0.969 (15) Å], and their standard uncertainty is much greater, as is the case for five of the six methyl hexopyranosides. The neutron values are tightly clustered around 0.97 Å. Thus, the empirical correction of O–H bond lengths from X-ray diffraction studies to a ‘standard’ value of 0.97 Å, applied successfully to the methyl hexopyr-

anosides (Jeffrey & Saenger, 1991, p. 108), is valid for the furanosides as well.

It is noteworthy that oxygen–deuterium distances in the neutron structure of (3^D) are not significantly different from the average O–H distances observed in the neutron structures of the other methyl pentofuranosides. This absence of systematic differences can be attributed to the fact that all

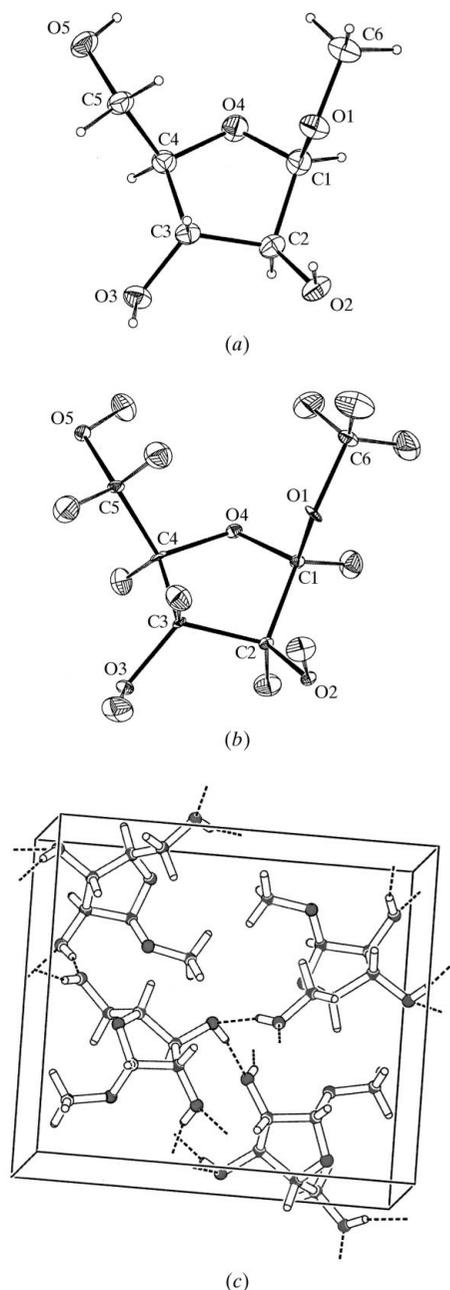


Figure 1 The eight methyl D-pentofuranosides. The compounds for which X-ray and neutron crystal structures are analyzed in this paper are identified by the appropriate numbers. (a) Thermal motion ellipsoid (TME) plot of the X-ray structure of methyl β -D-arabinofuranoside. Here and throughout the paper, ellipsoids represent 50% probability. H atoms are represented by empty circles of an arbitrary radius in the plots of the X-ray structures. Plots generated by *PLATON* (Spek, 2000). (b) TME plot of the neutron structure of methyl β -D-arabinofuranoside. (c) Methyl β -D-arabinofuranoside crystal packing diagram.

hydroxyls of the molecules are involved in strong hydrogen bonding which, together with the incomplete deuteration of (3^D), masks a small isotope effect. This small effect might be observed by comparing O—H and O—D bond lengths in very highly accurate neutron structures of (3) and (3^D) in which deuterium exchange is complete (e.g. Takusagawa & Koetzle, 1976).

3.3. Bond angles

Table 2 compares ring bond angles in the methyl pentofuranosides with those in the methyl hexopyranosides. These are significantly smaller in the methyl pentofuranosides than in the methyl hexopyranosides. Characteristic differences of C—C—C, C—C—O and C—O—C angles are ~ 8 , ~ 5 and $\sim 4^\circ$, respectively, suggesting that much of the strain of the five-membered ring is associated with bond angle compression. Among the three ring angle types, C—O—C is the least distorted. In the pyranosides, by contrast, the ring angles are close to their ideal values.

3.4. Hydrogen bonding

Hydrogen bonding in the methyl pentofuranoside crystals is extensive and strong (see Fig. 4) and is entirely intermolecular (Figs. 1c, 2b and 3b). No intramolecular hydrogen bonding is

observed in any of the crystals. Intramolecular hydrogen bonding is, however, an important stabilizing feature in isolated molecules of methyl pentofuranosides (Evdokimov *et al.*, 1999, 2000).

Based on 58 crystal structures of pyranoses and pyranosides and one furanoside structure, Jeffrey & Mitra (1983) have developed a convenient classification of hydrogen-bonding patterns for crystalline monosaccharides. Type I hydrogen-bond networks are composed of an infinite chain not involving ring or glycosidic O atoms, except for weak three- or four-center bonds. Type II contains finite chains that terminate in the glycosidic or ring O atom. Type III networks contain infinite chains, formed from the majority of the hydroxyl groups, with a separate finite chain, terminating in a ring or glycosidic oxygen. Type IV networks incorporate ring and glycosidic O atoms by means of three-center hydrogen bonding, without disrupting the cooperative advantage of the infinite chain or closed loop. Hydrogen-bonding patterns in the methyl pentofuranosides, with the exception of (4), fall into classes I and III.

Representatives of type I are: (1), with a single infinite hydrogen-bond chain, involving all the hydroxyls of both of the independent molecules in the asymmetric unit (Fig. 4a); (2), with a single infinite hydrogen-bond chain (Fig. 4b); (5), with a single infinite hydrogen-bond chain (Fig. 4c).

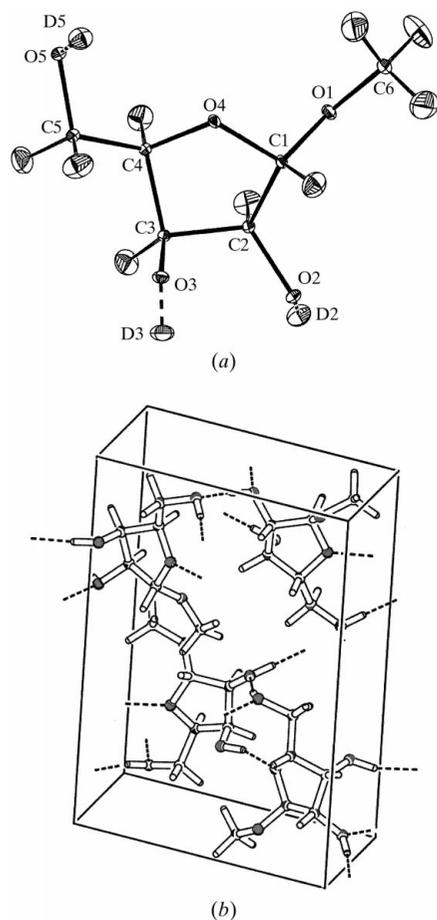


Figure 2
(a) TME plot of the neutron structure of methyl α -D-lyxofuranoside (3).
(b) Methyl α -D-lyxofuranoside (3) crystal packing diagram.

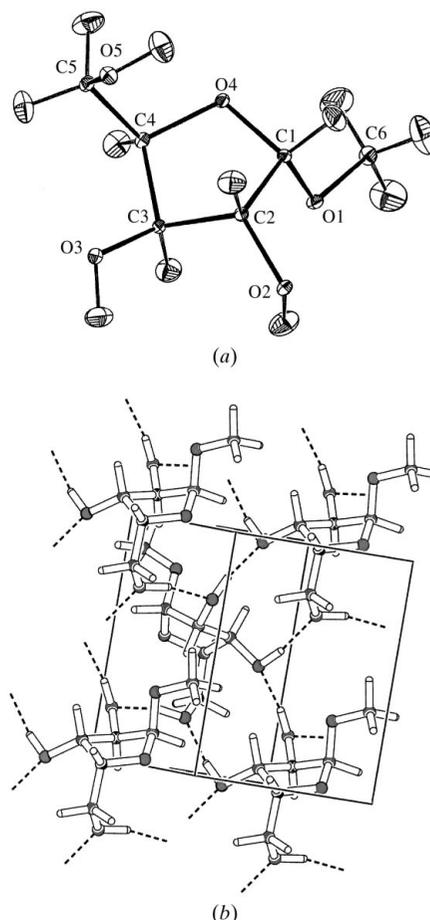


Figure 3
(a) TME plot of the neutron structure of methyl α -D-xylofuranoside (5).
(b) Methyl α -D-xylofuranoside (5) crystal packing diagram.

Table 2

Average bond lengths for ring atoms of methyl pentofuranosides and methyl hexopyranosides.

E.s.d.'s of the average bond angles of a stated type are given in parentheses. The average experimental uncertainty for angles is 0.3° for X-ray structures of furanosides and 0.2° for neutron structures of furanosides; the spread ($^\circ$) and number of data points are in square brackets.

Angle	Furanoside ($^\circ$)	Pyranoside ($^\circ$)
C—C—C (X-ray)	102.3 (1.1) [4.4, $n = 14$]	110.4 (1.0) [4.8, $n = 21$]
C—C—C (Neutron)	102.14 (1.1) [4.7, $n = 14$]	110.4 (0.8) [4.2, $n = 15$]
C—C—O (X-ray)	105.1 (1.2) [4.0, $n = 14$]	109.9 (0.8) [3.9, $n = 14$]
C—C—O (Neutron)	105.2 (1.2) [4.3, $n = 14$]	110.4 (0.6) [2.7, $n = 10$]
C—O—C (X-ray)	108.6 (1.0) [3.6, $n = 7$]	112.8 (1.4) [3.4, $n = 7$]
C—O—C (Neutron)	108.7 (1.4) [4.6, $n = 7$]	113.4 (0.8) [2.8, $n = 5$]

Type III is represented by (3^D), where an infinite chain composed of hydroxyls 2 and 5 is accompanied by a single-link finite chain formed by hydroxyl 3 and the ring oxygen (Fig. 4*d*).

Hydrogen bonding in (4) does not fall under any of the categories introduced by Jeffrey & Mitra (1983) and is more complex than the schemes encountered in any other monosaccharide. This novel pattern is shown in Fig. 4(*e*). An infinite chain made of repetitions of hydroxyl 3*A* is accompanied by a separate one-link finite chain formed by hydroxyl 2*A* and the ring oxygen O4*B* (*A* and *B* are the two independent molecules in the unit cell). An additional infinite chain is formed by hydroxyls 3*B* and 5*A* with a finite chain bifurcating off hydroxyl 5*A* to hydroxyl 2*B*. This chain is three-membered, involving hydroxyls 5*A*, 3*B*, 2*B* and 5*B* and terminating at the anomeric oxygen O1*A*.

The average O—H...O hydrogen-to-acceptor distance in infinite cooperative hydrogen-bond chains in the neutron structures of the methyl pentofuranosides is 1.76 (4) Å, close to the value of 1.80 (7) Å reported by Jeffrey & Saenger (1991) for methyl pyranosides and related structures. Due to the absence of cooperativity, hydrogen bonds participating in finite chains are longer than those participating in infinite chains, as expected (Jeffrey & Saenger, 1991).

3.5. Ring conformation in the crystalline methyl pentofuranosides

The conformational parameters of the five-membered rings of the methyl pentofuranosides according to the Marzec–Day (Marzec & Day, 1993) convention, calculated from the experimental coordinates of the ring atoms (neutron data) by the program *BREAKRING*, are shown in Table 3. A wide range of pseudorotational phase angle, \mathbf{P} , is evident whereas the other conformational parameters, \mathbf{q} , \mathbf{s} and $\mathbf{\Gamma}$, are clustered about their average values. The average value of \mathbf{s} is rather small, consequently, the value of $\mathbf{\Gamma}$ tends to be poorly determined.

3.5.1. Comparison of ring conformation in methyl β -D-ribofuranoside and complex ribofuranosides. The ring conformation of methyl β -D-ribofuranoside (4) ($\mathbf{P} = 340^\circ$) is very different from the conformations observed for the majority of ribo- and deoxyribofuranoside rings in RNA, DNA and nucleosides/tides ($\mathbf{P} = 18^\circ$ and $\mathbf{P} = 180^\circ$). This is attributable to the influence of the bulky anomeric substituents in nucleosides and nucleotides, as well as to conformational effects imposed by nucleic acid secondary and tertiary structure. However, the experimental values of \mathbf{q} , \mathbf{s} and $\mathbf{\Gamma}$ observed for the rings in the present study are close to the average values of more than 1000 RNA/DNA and nucleoside and nucleotide sugar rings, as reported earlier (Altona & Sundaralingam, 1972; Marzec & Day, 1993).

3.6. Eclipsed bonds

Since the ring oxygen in furanosides has no exocyclic substituents, the 'northern' sector in the pseudorotational itinerary from $\mathbf{P} = 340^\circ$ to $\mathbf{P} = 20^\circ$, corresponding to ring conformations from E_2 through 3T_2 to 3E , is characterized by minimal eclipsing of ring substituents. As \mathbf{P} increases to 90° , eclipsing becomes progressively more serious. The *mm* symmetry of the planar projection of the furanoside ring generates a second region of minimal eclipsing near the south pole, encompassing roughly $\mathbf{P} = 160^\circ$ to $\mathbf{P} = 200^\circ$ (2E through 2T_3 to E_3), as well as a second region of maximal eclipsing centered on $\mathbf{P} = 270^\circ$. Analysis of many hundreds of crystal structures of ribo- and deoxyribofuranosides (Marzec & Day, 1993) reveals a pronounced preference for ring conformations

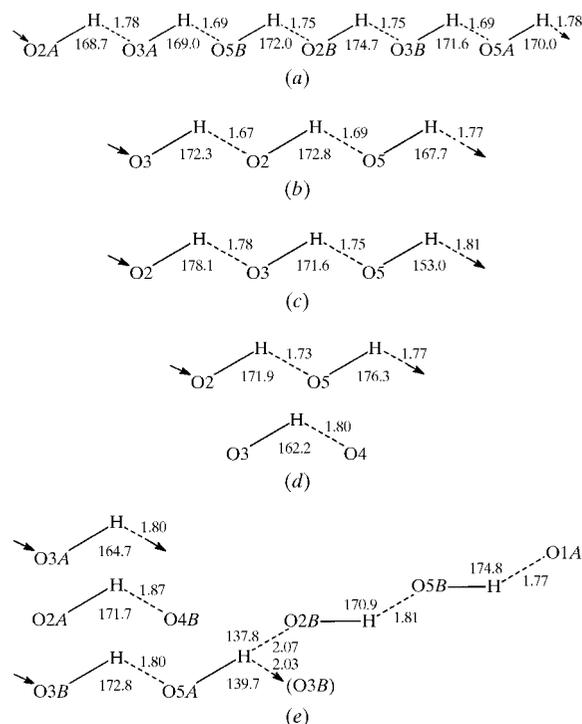


Figure 4 Hydrogen-bonding patterns in (a) methyl α -D-arabinofuranoside (1), (b) methyl β -D-arabinofuranoside (2), (c) methyl α -D-xylofuranoside (5), (d) methyl α -D-lyxofuranoside (3) and (e) methyl β -D-ribofuranoside (4).

Table 3

Conformational parameters for the five-membered rings of the five crystalline methyl pentofuranosides.

Conformational parameters are according to the convention of Marzec & Day (1993), as described in the text.

Compound	\mathbf{P} ($^{\circ}$)	Ring form	\mathbf{q} (\AA)	\mathbf{s} (\AA)	$\mathbf{\Gamma}$ ($^{\circ}$)
(1) Ring A^{\dagger}	54.4	E_4	0.39	0.34	89
(1) Ring B^{\dagger}	58.4	E_4	0.38	0.39	84
(2)	325.8	1T_2	0.39	0.34	77
(3)	27.0	3E	0.43	0.35	56
(4) Ring A^{\dagger}	336.7	E_2	0.35	0.31	102
(4) Ring B^{\dagger}	348.5	E_2	0.38	0.29	85
(5)	159.5	2E	0.40	0.25	81
		Average	0.38 (2)	0.32 (3)	81 (8)

\dagger Compounds (1) and (4) have two independent molecules per asymmetric unit.

in the regions of minimal eclipsing near the north and south poles. Table 3 shows the same general trend for the crystalline methyl pentofuranosides, the outstanding exceptions being the conformations of the two independent structures of methyl α -D-arabinofuranoside (1). These structures ($\mathbf{P} = 54.4, 58.4^{\circ}$), unlike the other methyl pentofuranosides, are in a region of serious eclipsing. It is noteworthy that energy minimization of an isolated molecule of methyl α -D-arabinofuranoside (1) (Evdokimov *et al.*, 1999) shows that, also in the absence of lattice forces, these highly eclipsed ring conformations are close to energetic minima.

Table 4 gives the absolute values of eclipsed torsion angles smaller than 30° between pairs of adjacent ring substituents, for all five crystalline methyl pentofuranosides. As stated above, with the exception of (1), there are no seriously eclipsed substituents. This may be contrasted to the DFT predictions for the isolated molecule of methyl α -D-lyxofuranoside (3), where several stable structures have seriously eclipsed substituents (Evdokimov *et al.*, 2000). In those cases, however, intramolecular hydrogen bonds compensate for the strain attributable to eclipsing.

Notwithstanding the absence of intramolecular hydrogen bonds in the crystalline methyl pentofuranosides, the gas-phase ring conformations are generally similar to those observed in crystal structures, with the outstanding exception of methyl α -D-lyxofuranoside (3), for which the pseudorotation angle of the minimized structure differs from that of the crystal structure by 100° (Evdokimov *et al.*, 1999). A recent theoretical study of the conformational space of methyl α -D-lyxofuranoside (3) (Evdokimov *et al.*, 2000) suggests, however, that the ring conformation of the crystal structure is actually quite close to that of a stable gas-phase structure. In this case, the orientation of O2H in the crystal drives the minimization to a different region of conformational space in order to form an intramolecular O2—H \cdots O4 hydrogen bond (see Fig. 2a).

3.7. Application of accurate crystal structures to conformational analysis of the furanosides

Some accurate crystal structures of the methyl pentofuranosides have been used to evaluate the adequacy of DFT methods using a variety of exchange-correlation functionals

Table 4

Eclipsed torsion angles (less than or equal to 30°) for ring substituents in the five crystalline methyl pentofuranosides.

The average e.s.d. of the torsion angles is 31° .

Compound	Atoms defining torsion angle	Angle ($^{\circ}$)
(1) Ring A^{\dagger}	H2—C2—C1—O1	1
(1) Ring A	O2—C2—C1—H1	2
(1) Ring A	H2—C2—C3—O3	28
(1) Ring B^{\dagger}	H2—C2—C1—O1	2
(1) Ring B	O2—C2—C1—H1	3
(1) Ring B	H2—C2—C3—O3	27
(2)	O3—C3—C4—H4	18
(2)	H3—C3—C4—C5	18
(3 ^D)	H2—C2—C1—O1	25
(3 ^D)	O2—C2—C1—H1	30
(4) Ring A^{\dagger}	H3—C3—C4—C5	26
(4) Ring A	O3—C3—C4—H4	23
(5)	O3—C3—C4—C5	26
(5)	H3—C3—C4—H4	26

\dagger Compounds (1) and (4) have two independent molecules per asymmetric unit. Ring B in (4) has no eclipsed bonds.

and a sequence of basis sets, in terms of their ability to predict accurate values for 'hard' structural parameters such as bond lengths and bond angles (Evdokimov *et al.*, 1999). It was shown that DFT with the B3LYP exchange-correlation functional used and a basis set of at least double- ξ -plus-polarization quality (such as cc-PVDZ) produced bond lengths and bond angles which agree with the low-temperature neutron diffraction values to within their experimental uncertainty.

Subsequently (Evdokimov *et al.*, 2000), this DFT approach was used to study the conformational space of one of the methyl pentofuranosides, methyl α -D-lyxofuranoside, (3) in the present study. Energy minimization was performed on a set of starting models with six different ring conformations generated by means of the procedure proposed by Marzec & Day (1993) and implemented in the program *MAKERING*. Given a set of five ring bond distances, a pseudorotation phase angle, \mathbf{P} , and three additional conformational variables, \mathbf{q} , \mathbf{s} and $\mathbf{\Gamma}$, *MAKERING* calculates *exact* coordinates of the ring atoms. The present study has allowed us to simplify the procedure because the average experimental bond distances together with the average values of three of the conformational variables, \mathbf{q} , \mathbf{s} and $\mathbf{\Gamma}$ (Table 3) can be used to reproduce all the crystal structures to within their average experimental uncertainties. (Indeed, equally satisfactory geometries are obtained by setting two of the variables, \mathbf{s} and $\mathbf{\Gamma}$, to zero (Evdokimov *et al.*, 2000). As in the Cremer & Pople (1975) approximation, this leaves only one adjustable parameter, the pseudorotation phase angle, \mathbf{P} , to be assigned any value from 0 to 359° . in order to calculate ring coordinates for a reasonable starting model with any ring conformation desired. This procedure should be equally useful for scanning the conformational space of the remaining four crystalline methyl pentofuranosides, as well as that of other furanosides, and in particular the three methyl furanosides, methyl α -D-ribofuranoside, methyl β -D-lyxofuranoside and methyl β -D-xylofuranoside, that are not amenable to crystallization.

4. Conclusions

Highly accurate low-temperature X-ray diffraction structures of methyl β -D-arabinofuranoside (2) and neutron structures of methyl α -D-lyxofuranoside (3) and methyl α -D-xylofuranoside (5) complete the full set of structures of the crystalline methyl pentofuranosides. Comparison of the geometric parameters of the furanoside ring with those of the pyranoside ring demonstrates 4–8° distortion of ring bond angles from their nearly ideal values in pyranosides, while no significant bond difference in average bond lengths is evident. These geometric data provide the basis for in-depth theoretical studies of compounds containing furanoside rings. Crystalline methyl pentofuranosides form extensive cooperative networks of hydrogen bonds, which with the exception of the complicated pattern formed by (4) fall into the classification introduced by Jeffrey & Mitra (1983) for the hydrogen-bond networks in pyranosides.

Conformational flexibility of the furanosides results in a wide variety of the pseudorotational phase angles found in their crystal structures. Using the Marzec–Day (1993) parameterization with the geometric parameters taken from the present study it is possible to accurately construct furanoside rings using a single parameter (the pseudorotational phase angle), which greatly simplifies the approach to the modelling of these compounds (Evdokimov *et al.*, 2000).

We thank Professor Israel Goldberg (Department of Chemistry, Tel-Aviv University) for access to the Kappa-CCD X-ray diffractometer. We acknowledge the help of Ms Martha Miller and Dr Robert Henning of the IPNS staff. Work at Argonne National Laboratory was supported by the US Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences, under Contract No. W-31-109-ENG-38. Work at Brookhaven National Laboratory was carried out under Contract DE-AC02-98-CH10886 with the US Department of Energy, Office of Basic Energy Sciences. We are grateful to Mr John Archer for technical support at ILL. AE acknowledges a Doctoral Fellowship of the Feinberg Graduate School, WIS. We express our gratitude to Dr Loren Day of New York University for the source code of the *BREAKRING* and *MAKERING* programs and for helpful advice.

References

Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 1, 31–37.
 Altona, C. & Sundaralingam, M. (1972). *J. Am. Chem. Soc.* **94**, 8205–8212.
 Archer, J. & Lehmann, M. S. (1986). *J. Appl. Cryst.* **19**, 456–459.

Berman, H. M. & Kim, S. H. (1968). *Acta Cryst.* **B24**, 897–904.
 Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
 Evdokimov, A. G., Gilboa, A. J., Koetzle, T. F., Klooster, W. T. & Martin, J. M. L. (1999). *J. Phys. Chem. A*, **103**, 744–753.
 Evdokimov, A. G., Gilboa, A. J. & Martin, J. M. L. (2000). *J. Phys. Chem. A*, **104**, 5291–5297.
 Gatehouse, B. M. & Poppleton, B. J. (1971). *Acta Cryst.* **B27**, 871–877.
 Groth, P. & Hammer, H. (1968). *Acta Chem. Scand.* **22**, 2059–2062.
 Howard, J. A. K., Johnson, O., Schultz, A. J. & Stringer, A. M. (1987). *J. Appl. Cryst.* **20**, 120–123.
 Jacobson, R. A. (1986). *J. Appl. Cryst.* **19**, 283–287.
 Jeffrey, G. A., McMullan, R. K. & Takagi, S. (1977). *Acta Cryst.* **B33**, 728–737.
 Jeffrey, G. A. & Mitra, J. (1983). *Acta Cryst.* **B39**, 469–480.
 Jeffrey, G. A. & Saenger, W. (1991). *Hydrogen Bonding in Biological Structures*. Berlin: Springer-Verlag.
 Jeffrey, G. A. & Takagi, S. (1977). *Acta Cryst.* **B33**, 738–743.
 Larson, A. C. & Von Dreele, R. B. (1994). *GSAS*. Los Alamos National Laboratory, Los Alamos, NM.
 Mackay, S., Gilmore, C. J., Edwards, C., Tremayne, M., Stuart, N. & Shankland, K. (1998). *maXus*. University of Glasgow, Scotland, Nonius BV, Delft, The Netherlands, and MacScience Co. Ltd, Yokohama, Japan.
 Matthewman, J. C., Thompson, P. & Brown, P. J. (1982). *J. Appl. Cryst.* **15**, 167–171.
 Marzec, C. J. & Day, L. A. (1993). *J. Biomol. Struct. Dyn.* **10**, 1091–1102.
 Nonius (1998). *Kappa-CCD Reference Manual*. Nonius BV, Delft, The Netherlands.
 Podlasek, C. A., Stripe, W. A., Carmichael, I., Shang, M., Basu, B. & Serianni, A. S. (1996). *J. Am. Chem. Soc.* **118**, 1413–1422.
 Poppleton, B. J., Jeffrey, G. A. & Williams, G. J. B. (1975). *Acta Cryst.* **B31**, 2400–2405.
 Schultz, A. J. (1987). *Trans. Am. Cryst. Assoc.* **23**, 61–65.
 Schultz, A. J., Van Derveer, D. G., Parker, D. W. & Baldwin, J. E. (1990). *Acta Cryst.* **C46**, 276–279.
 Sears, V. F. (1986). *Methods of Experimental Physics*, edited by K. Sköld and D. L. Price, Vol. 23, p. 521. Orlando, Florida: Academic Press.
 Sears, V. F. (1992). *Neutron News*, **3**, 26–27.
 Sheldrick, B. (1977). *Acta Cryst.* **B33**, 3003–3006.
 Sheldrick, G. M. (1990). *Acta Cryst.* **A46**, 467–473.
 Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
 Sheldrick, G. M. & Schneider, T. R. (1997). *Methods Enzymol.* **277**, 319–343.
 Spek, A. L. (2000). *PLATON*. Utrecht University, The Netherlands.
 Takagi, S. & Jeffrey, G. A. (1978). *Acta Cryst.* **B35**, 902–907.
 Takusagawa, F. & Koetzle, T. F. (1976). *Acta Cryst.* **B35**, 2126–2134.
 Thomas, M., Stansfield, R. F. D., Berneron, M., Filhol, A., Greenwood, G., Jacobe, J., Feltn, D. & Mason, S. A. (1983). *Position-Sensitive Detection of Thermal Neutrons*, edited by P. Convert and J. B. Forsyth, p. 344. London: Academic Press.
 Wilkinson, C., Khamis, H. W., Stansfield, R. F. D. & McIntyre, G. J. (1988). *J. Appl. Cryst.* **21**, 471–479.
 Wu, J. & Serianni, A. S. (1991). *Carbohydr. Res.* **210**, 51–54.