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STRUCTURE OF METHYL 6-DEOXY-α-D-IDOPYRANOSIDE

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ABSTRACT

The conformation of the pyranoid ring of the L-idopyranosyluronic acid residues of heparin and dermatan sulfate is a matter of controversy. X-Ray crystallographic analysis of methyl 6-deoxy-α-D-idopyranoside (**4**), which has the same relative arrangement of substituents on the pyranose ring, shows that it adopts the $^4C_1$ conformation having the four oxygen-containing substituents occupying axial positions and C-6 equatorial. The ring is slightly flattened, with torsion angles in the range of ±49.5 to 59.0(5)°. There are two intramolecular hydrogen bonds: O-2-H···O-4, 2.754(2) Å, and O-3-H···O-1, 2.874(2) Å, and the crystal structure is stabilized by an additional network of three intermolecular hydrogen-bonds. Analysis of the coupling constants obtained from the ^{1}H-n.m.r. spectrum of **4** suggests that, in solution, there is an equilibrium between the $^4C_1$ form and another conformer, possibly a skew form. These results are discussed in relation to recent studies of the conformation of L-iduronic acid residues in heparin and dermatan sulfate.

INTRODUCTION

Conformational analysis of the pyranose ring in idopyranose and its derivatives has been a topic of debate in the recent literature. Of the problems studied, one of the most controversial is the conformation of the α-L-iduronic acid residues in the glycosaminoglycans heparin and dermatan sulfate[1]. From fiber diffraction data obtained for dermatan sulfate, it was considered that the α-L-iduronic residues adopt the $^4C_1$ conformation, with the four oxygen-containing substituents occupying equatorial positions[2]. By contrast, vacuum-ultraviolet circular-dichroism measurements of dermatan sulfate[3], in both the solid and the solution phase, suggested that the favored conformation of the α-L-iduronic residues in the polymer chain is

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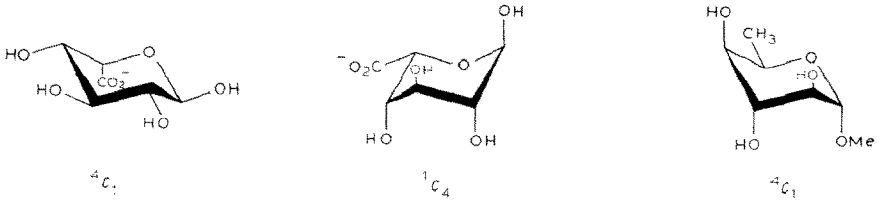
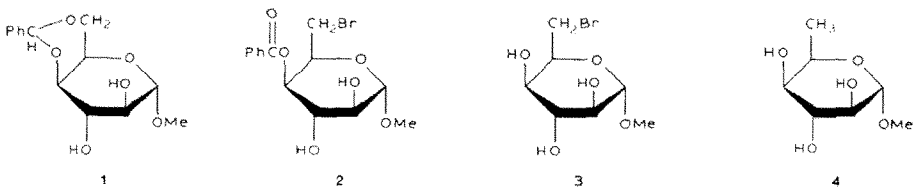


Conformations of α-L-iduronate (4)

$^1C_4$, with the oxygen-containing substituents in axial positions. Solution-phase n.m.r. analysis and force-field calculations also indicated that the favored conformation of α-L-iduronate in the monomeric form is $^1C_4$, with contributions from the skew form $^2S_0$ becoming significant for sulfated L-uronate residues in the heparin sequence[4]. Because the binding of heparin to the plasma protein antithrombin-III, the basis for its anticoagulant activity[5], may be dependent on the shape of the polymer chain, we need to know the conformation of the L-iduronate residues so as to understand the mechanism of action of heparin at the molecular level.

In the course of studies on the synthesis of carbohydrates found in antibiotics[6], methyl 6-deoxy-α-D-idopyranoside (**4**) was prepared and its structure was analyzed both by X-ray crystallography and by n.m.r. spectroscopy at 250 MHz. These analyses indicated that, in the solid state, the compound adopts the $^4C_1$ conformation (equivalent to the $^1C_4$ form for the L enantiomer). For the compound in solution, the coupling constants obtained from the ^{1}H-n.m.r. spectrum suggested the presence of an additional conformer, or significant distortion of the $^4C_1$ form, in agreement with results reported recently for other idose derivatives.



1 2 3 4

EXPERIMENTAL

General procedures. — Melting points were determined with a Thomas–Hoover melting-point apparatus, and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 337 grating spectrometer for KBr disks or thin films. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. ^{1}H-N.m.r. spectra were recorded at 90 MHz with a Varian EM-390 instrument. The 250-MHz spectrum of methyl 6-deoxy-α-D-idopyranoside was recorded with a Bruker WM 250 instrument by Mr. William C. Hutton of the University of Virginia. ^{13}C-N.m.r. spectra were recorded with a JEOL-PS 100P/EC-100 spectrometer.

Methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-idopyranoside (**2**). — A mixture of methyl 4,6-*O*-benzylidene-α-D-idopyranoside[7] (8.8 g, 31 mmol; dried over P_2O_5 for 4 d at 133–266 Pa), *N*-bromosuccinimide (6.6 g, 37 mmol; recrystallized from water and dried over P_2O_5), and barium carbonate (3.5 g) in dry carbon tetrachloride (500 mL) was boiled and stirred under reflux for 2.5 h. The mixture was filtered while hot, and the filtrate evaporated under diminished pressure to a syrup that was dissolved in dichloromethane. The solution was washed successively with dilute sodium hydrogensulfite solution, saturated sodium hydrogencarbonate solution, and water, dried (Na_2SO_4), and evaporated, to give 9.5 g (84%) of **2** as a chromatographically homogeneous syrup. A sample was purified by preparative thin-layer chromatography (silica gel 60, 1:24 methanol–chloroform), to give a colorless syrup that crystallized from dichloromethane–hexane. Compound **2** had m.p. 106.5–107.5°, $[\alpha]_D^{28}$ +104.1° (chloroform); ν_{max} 3500, 2925, and 1725 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 8.1–7.3 (m, 5 H, C_6H_5), 5.27 (m, 1 H, H-4), 4.87 (m, 1 H, H-1), 4.48 (m, 1 H, H-5), 4.00 (m, 1 H, H-3), 3.71 (m, 1 H, H-2), 3.55 (s, 3 H, OCH_3), 3.40 (d, 2 H, H-6), 2.56 (d, 1 H, O*H*), and 1.54 (d, 1 H, O*H*); ^{13}C-n.m.r. ($CDCl_3$): δ 164.5 (*C*=O), 133.7, 129.5, 129.1, 128.6, 102.1 (C-1), 71.8 (C-4), 68.8 (C-3), 67.9 (C-2), 66.5 (C-5), 55.9 (OCH_3), and 29.9 (C-6).

Anal. Calc. for $C_{14}H_{17}BrO_6$: C, 46.54; H, 4.71; Br, 22.16. Found: C, 46.28; H, 4.78; Br, 22.16.

Methyl 6-bromo-6-deoxy-α-D-idopyranoside (**3**). — A solution of **2** (9.4 g, 26 mmol) in anhydrous methanol (250 mL) containing 0.5M sodium methoxide (50 mL) was kept for 24 h at room temperature. The base was neutralized with AG-50 (H^+) resin, the mixture filtered, and the filtrate evaporated under diminished pressure to a syrup that was washed with ether (300 mL, used in portions), this was dissolved in water, and the solution extracted with chloroform. The extracts were combined and evaporated to give 4.0 g (59%) of syrupy **3**. A sample of the product was purified by column chromatography (silica gel, 1:24 methanol–chloroform), to give a colorless syrup that crystallized from dichloromethane–hexane. Compound **3** had the following characteristics: m.p. 68.5–70°, $[\alpha]_D^{25}$ +85.1° (chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 4.81 (s, 1 H, H-1), 4.23 (t, 1 H, H-5), 3.88 (m, 1 H), 3.75 (m, 1 H), 3.57 (d, 2 H, H-6), 3.50 (s, 3 H, OCH_3), and 3.37 (m, 1 H); ^{13}C-n.m.r. ($CDCl_3$): δ 101.8 (C-1), 69.3 (C-3), 69.3 (C-2), 67.6 (C-4), 67.1 (C-5), 55.7 (OCH_3), and 30.9 (C-6).

Anal. Calc. for $C_7H_{13}BrO_5$: C, 32.70; H, 5.09; Br, 31.08. Found: C, 32.62; H, 5.11; Br, 31.02.

Methyl 6-deoxy-α-D-idopyranoside (**4**). — A mixture of syrupy bromide **3** (5.0 g, 19.4 mmol), triethylamine (5 mL), and W-2 Raney nickel (~0.25 teaspoonful of freshly prepared catalyst) in methanol (125 mL) was hydrogenated overnight at atmospheric pressure, the progress of the reaction being monitored by thin-layer chromatography (silica gel, 1:19 methanol–chloroform). Additional catalyst (0.5 teasponful) was added to the mixture during 2 d, after which it was filtered, the filtrate evaporated to a residue that was dissolved in methanol (100 mL), and the

solution stirred for 15 min at −5° with AG-50 H^+ resin (prewashed with methanol). The mixture was fiiltered, and the filtrate made neutral with lead carbonate. Solids were removed by filtration through celite and the filtrate was evaporated under diminished pressure to a syrupy residue. Trituration with ethyl acetate resulted in the crystallization of the remaining triethylamine hydrobromide, and left behind 3.6 g (59% from **1**) of syrupy **4**. Crystallization from dichloromethane–hexane gave prisms of **4**. Compound **4** had m.p. 96.0–97.5°, $[\alpha]_D^{25}$ +105.2° (acetone); ^{1}H-N.m.r. (250 MHz, Me_2SO-d_6): δ 5.04 (d, 1 H, O*H*), 4.74 (d, 1 H, O*H*), 4.64 (d, 1 H, O*H*), 4.38 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 3.98 (dq, 1 H, $J_{5,6}$ 6.5, $J_{4,5}$ 3.2 Hz, H-5), 3.47 (m, 1 H, $J_{3,4}$ 6.0 Hz, H-3), 3.28 (m, 1 H, H-4), 3.26 (s, 3 H, OCH_3), 3.23 (m, 1 H, $J_{2,3}$ 6.0 Hz, H-2), and 1.10 (d, 3 H, H-6); ^{13}C-n.m.r. (Me_2SO-d_6): δ 101.3 (C-1), 71.4 (C-4), 71.4 (C-3), 70.9 (C-2), 65.6 (C-5), 54.7 (OCH_3), and 14.8 (C-6).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.20; H, 7.94.

X-Ray crystallography. — Crystal data. Methyl 6-deoxy-α-D-idopyranoside, $C_7H_{14}O_5$, M = 178.2, orthorhombic, a = 6.997(3), b = 13.287(7), c = 9.249(5) Å, V = 859.9(12) Å^3, space group $P2_12_12_1$, D_m = 1.37 g.cm^{-3} [flotation, KI(aq)], Z = 4, D_c = 1.377 g.cm^{-3}, $F(000)$ = 384, μ (Cu$K\alpha$) 10 cm^{-1}.

The space group was determined from systematic absences $h = 2n + 1$ in $h00$, $k = 2n + 1$ in $0k0$, and $l = 2n + 1$ in $00l$ on 25° precession photographs of the principal equatorial zones, taken with Mo$K\alpha$ radiation. The unit cell dimensions were derived from the observed values of $\pm 2\theta$ for 20 strong high-order reflections, measured by diffractometry (Cu$K\alpha$ radiation, λ = 1.5418 Å).

Intensity data. — These were collected from a single-crystal prism, 0.3 mm on a side, recrystallized from a mixture of dichloromethane and hexane, and mounted on a Nicolet P3m diffractometer. Data were collected with monochromatic Cu$K\alpha$ radiation, by the $\omega - 2\theta$ method, for a single octant of reciprocal space ($0 \geq h \leq 7$, $0 \geq k \leq 14$, $0 \geq l \leq 10$) to $2\theta_{max}$ = 122°. The scan ranges were ±1.4° about the peak maximum, and scan speeds ranged from 2°.min^{-1} to 29.3° min^{-1}, so as to give a minimum of 10,000 counts in all scans run above the minimum speed. Backgrounds were measured at either extremity of the scan range for a total time equal to the scan time. The intensities of two symmetry-related reflections, measured as standards after every 50 measurement cycles, deviated from their mean intensity by <3% over the course of the experiment. Intensity significantly above background ($I \geq 2\sigma I$) was determined at 752 of the 787 reciprocal lattice points accessible to the instrument (95.6%). No absorption corrections were applied, and structure amplitudes were derived in the usual way.

Structure determination and refinement. — The phase problem was solved by routine appplication of the program MULTAN[8]. The known absolute configuration was adopted, hydrogen atoms were located from a difference electron-density map, and refinement was by the block-diagonal least-squares method. Anisotropic thermal parameters were adopted for the O and C atoms. The scattering factors for O and C were taken from Cromer and Waber[9], and those for H from Stewart *et al.*[10]. At convergence (Δ/σ max. ≤0.17, av. 0.03), the conventional unweighted and

weighted R values were 0.026 and 0.032*. The standard deviation of an observation of unit weight was 0.25. A final difference electron-density map was structurally featureless.

All calculations, except for MULTAN and ORTEP[11], were carried out using programs written in this laboratory for the AT & T 3B2 computer.

RESULTS AND DISCUSSION

In the synthesis of compound **4**, D-galactose was converted into methyl 4,6-*O*-benzylidene-α-D-idopyranoside (**1**) by the method of Sorkin and Reichstein[7]. Treatment of **1** with *N*-bromosuccinimide in carbon tetrachloride gave the 6-bromo 4-benzoate **2** in 84% yield. De-esterification of **2** to **3**, followed by catalytic reduction of **3**, gave compound **4** in 59% overall yield. A sample prepared by recrystallization from dichloromethane–hexane was used for X-ray crystallographic analysis.

Atomic coordinates and equivalent isotropic thermal parameters are given in Table I*. A labelled drawing indicating the atomic-displacement ellipsoids is shown as Fig. 1. Bond lengths, bond angles, and torsion angles involving the non-hydrogen atoms are shown diagrammatically in Fig. 2; they are in good agreement with corresponding values in comparable structures, and show no remarkable features. O–H bond distances are in the range 0.78–0.86(3) Å, and C–H bond distances are in the range 0.95–1.07(3) Å, except for C-7–H-7c which is 1.23(5) Å, indicating poor location of that H atom.

The D-idopyranoside ring adopts the $^4C_1$ conformation, with the four oxygen substituents in axial positions and with the 5-*C*-methyl group equatorial. A least-squares mean-plane through C-1, C-3, C-4, and O-5 shows average and maximum deviations of these atoms (from the plane) of 0.07 Å; C-2 is 0.614 Å below the plane and C-5 is 0.660 Å above it.

There is extensive hydrogen bonding in the crystal, as shown in Figs. 3 and 4. Five distinct hydrogen-bonds are formed, with the hydrogen atoms on O-2 and O-3 participating in three-center bonding, all OH groups acting as both donors and acceptors, and O-1 acting as a double acceptor. Two of the five bonds are intramolecular: O-2–H acts as a donor to O-4, with O···O = 2.754(2) Å and H···O = 2.00(2) Å; and O-3–H acts as a donor to O-1, with O···O = 2.874(2) Å, H···O = 2.40(2) Å. The remaining three bonds are intermolecular, and link the molecules in sheets parallel to the *ab* plane. The O-2–H group is also a donor to O-1 in a molecule at $0.5 - x, -y, z - 0.5$, with O···O = 2.882(2) and H···O = 2.41(2) Å; O-3–H is also a donor to O-2 at $0.5 - x, -y, 0.5 + z$, with O···O = 2.933(2) Å

*Tables listing observed and calculated structure amplitudes, anisotropic thermal parameters and certain least-squares mean-plane calculations are available from Elsevier SciencePublishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/411/*Carbohydr. Res.*, 191 (1989) 1–11.

TABLE I

FRACTIONAL ATOMIC COORDINATES AND ISOTROPIC THERMAL PARAMETERS[a]

Atom	x	y	z	B_{eq}
O-1	$2164(2) \times 10^{-4}$	$1428(1) \times 10^{-4}$	$3837(2) \times 10^{-4}$	3.0
O-2	2445(2)	−888(1)	1840(2)	3.3
O-3	5401(2)	242(1)	4705(2)	3.2
O-4	6054(2)	−351(1)	937(2)	3.3
O-5	3365(2)	1268(1)	1483(1)	2.6
C-1	2209(3)	844(2)	2566(2)	2.4
C-2	2852(3)	−205(2)	2988(2)	2.4
C-3	4979(3)	−231(2)	3357(2)	2.4
C-4	6141(3)	277(2)	2183(2)	2.5
C-5	5374(3)	1321(2)	1863(2)	2.7
C-6	6352(4)	1835(2)	605(3)	4.0
C-7	1173(5)	2369(2)	3676(3)	5.1
HO-2	$342(3) \times 10^{-3}$	$-86(2) \times 10^{-3}$	$127(3) \times 10^{-3}$	4.1(5)
HO-3	453(4)	44(2)	514(3)	7.0(8)
HO-4	705(5)	−31(2)	44(3)	7.5(9)
H-1	81(3)	76(1)	211(2)	2.0(4)
H-2	218(3)	−45(2)	381(2)	3.4(5)
H-3	536(3)	−92(1)	341(2)	2.2(4)
H-4	750(3)	38(1)	258(2)	2.3(4)
H-5	550(3)	171(2)	274(2)	4.2(6)
H-6a	574(4)	254(2)	42(2)	5.4(6)
H-6b	598(4)	149(2)	−27(3)	4.3(5)
H-6c	777(4)	187(2)	86(3)	4.6(6)
H-7a	109(5)	262(3)	465(3)	7.4(8)
H-7b	195(5)	276(2)	296(3)	7.8(8)
H-7c	−44(3)	207(3)	338(5)	15.(2)

[a]Equivalent isotropic thermal parameters are given as $4(\Sigma_i\Sigma_j\beta_{ij}.\mathbf{a}_i.\mathbf{a}_j)/3$. Estimated standard deviations are given in parentheses, and are applicable to the least-significant digits quoted.

and H···O = 2.17(2) Å. Finally, O-4 is a donor to O-3 in a molecule at $1.5 - x, -y, z - 0.5$ with O···O = 2.733(3) Å and H···O = 1.91(2) Å. In their acceptor roles, O-1 receives from O-2 at $0.5 - x, -y, 0.5 + z$; O-2 receives from O-2 at $0.5 + x, -y, x - 0.5$; and O-3 receives from O-4 at $1.5 - x, -y, 0.5 + z$.

Analysis of the ^{1}H-n.m.r. spectrum of **4** strongly suggested that, in solution, the presence of an alternative conformer, or distortion of the pyranose ring from the $^4C_1$ form, becomes significant. Coupling constants obtained from the ^{1}H-n.m.r. spectrum of **4** are given in Table II, together with values reported for related compounds of interest. The *J* values observed for vicinal-proton couplings in compound **4** are incompatible with the exclusive presence of either the $^4C_1$ or $^1C_4$ form in solution, as they are intermediate between what would be expected on the basis of the Karplus[13] relationship and from comparison with *J* values observed for other monosaccharides. Vicinal-proton coupling constants for *gauche* orientations may range from 0.8 to 5.5 Hz, depending on the electronegativity and orientation of the substituents[14]. For monosaccharides in the pyranose form, a value of ~2.0 Hz is

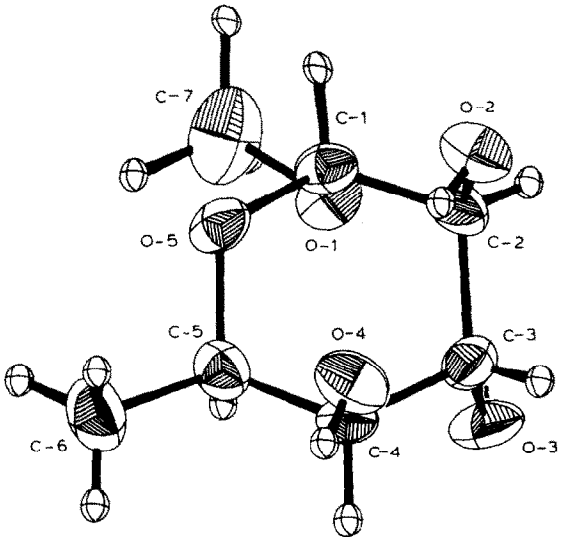


Fig. 1. ORTEP[11] view of the molecule, showing atomic-displacement ellipsoids (drawn to the 50% probability level) and numbering scheme adopted. Hydrogen atoms are drawn as spheres of arbitrary radius, and, in the Tables, are numbered to correspond to the atom of attachment.

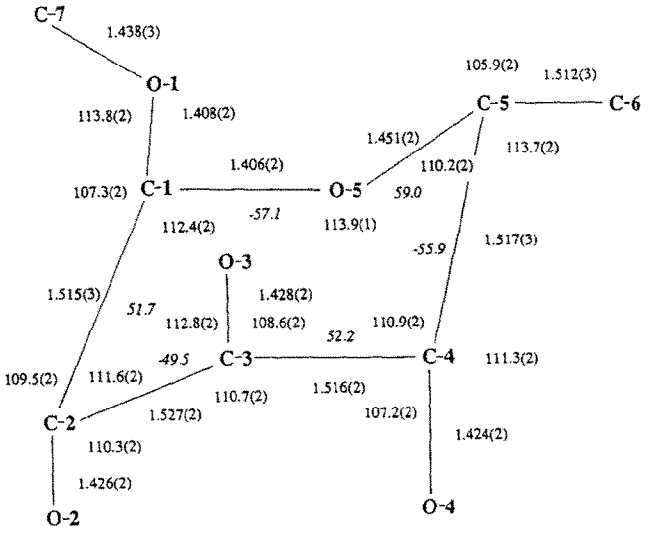


Fig. 2. Bond distances (Å), bond angles (°), and torsion angles (°) in the crystalline form of methyl 6-deoxy-α-D-idopyranoside.

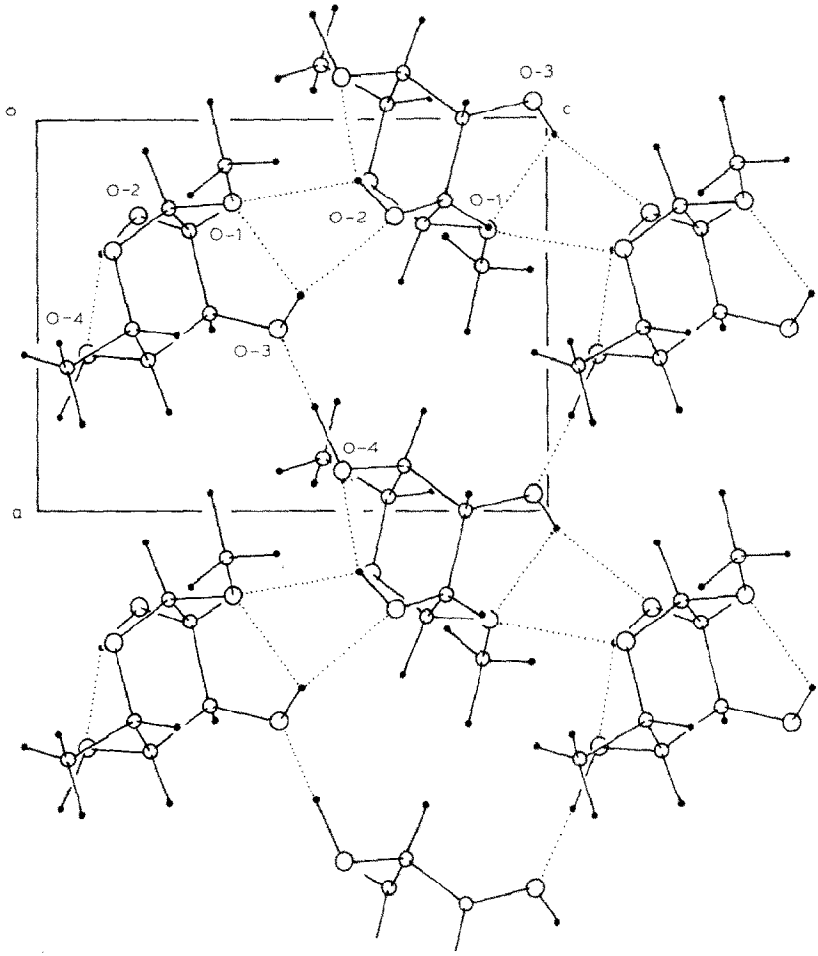


Fig. 3. View of a sheet of hydrogen-bonded molecules in the crystal, seen in partial projection down *b*. The hydrogen bonds are indicated by dotted lines.

typical for *gauche* orientations, whereas diaxial couplings are usually[15] ~8–9 Hz. As shown in Table II, values observed for **4** are similar to those reported for methyl α-D-idopyranosiduronate (**6**) but slightly different from those reported for compounds **5** and **7**, which also show long-range "W-couplings" between H-2 and H-4 in each case. These long-range couplings indicate[16] that **5** and **7** adopt standard chair conformations, namely, $^1C_4$ in **5** and the equivalent $^4C_1$ in **7**. By contrast, the coupling data for **4** and **6** reflect either an equilibrium between forms, or a conformationally stable form having distorted geometry. The observed temperature-dependence of coupling constants in **6** seems to favor the former interpretation. In recent n.m.r. studies[15] of idose, an equilibrium between chair and skew forms of the pyranose ring was proposed. Skew forms have also been considered to be important in conformational analyses of other idopyranose derivatives[17].

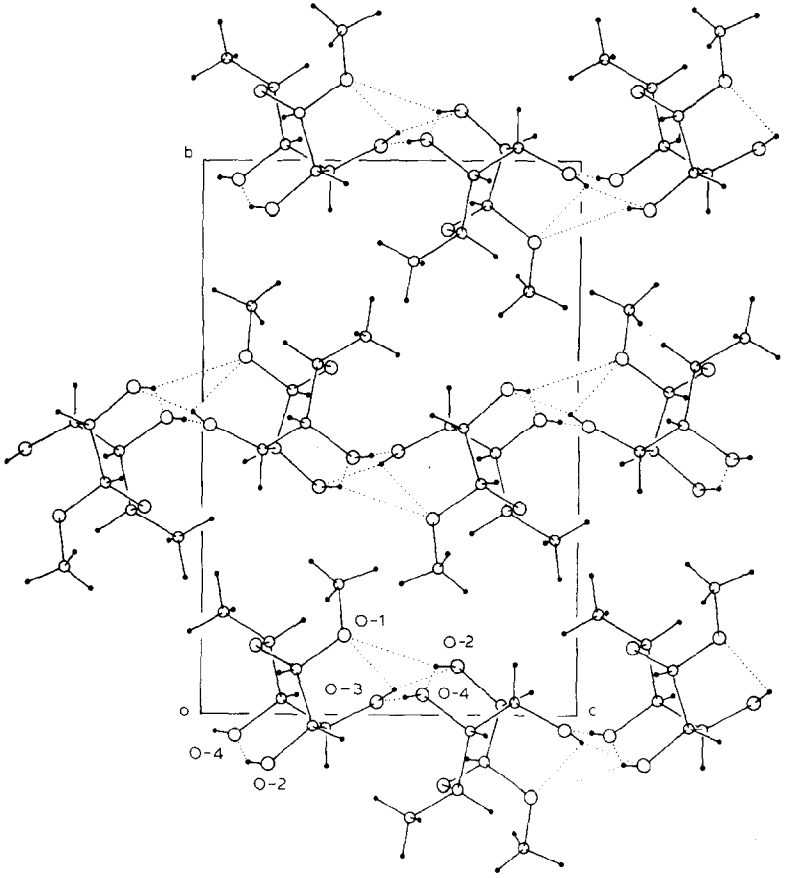
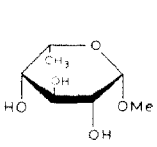


Fig. 4. Molecular packing in the crystal, seen in projection down *a*. Hydrogen bonds are indicated by dotted lines.

TABLE II

VICINAL COUPLING-CONSTANTS (Hz) FOR METHYL 6-DEOXY-α-D-IDOPYRANOSIDE AND OTHER IDOPYRANOSIDES

Compound	*Reference*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	*Solvent*	*T (degrees)*
4		4.5	6.0	6.0	3.2	Me_2SO	20
5	12	2.0	5.0	5.0	3.0	D_2O	
6	16	3.3	5.5	5.5	3.0	D_2O	15
		4.0	6.0	6.0	3.5	D_2O	40
7	16	1.9	3.5	3.5	2.3	D_2O	40
8	4	1.8	3.34	3.44	2.22	D_2O	23
9	4	3.95	7.54	3.56	3.13	D_2O	23



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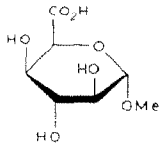

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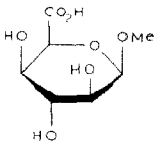

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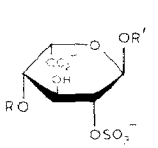

8 R = R′ = Me

9

9 R = 0-(2-deoxy-2-sulfamido-6-0-sulfo-α-D-glucopyranosyl)-(1→4)-0-(β-D-glucopyranosyluronic acid)-(1→4)-(2-deoxy-2-sulfamido-3,6-di-0-sulfo-α-D-glucopyranosyl)

R′ = 2-deoxy-2-sulfamido-6-0-sulfo-α-D-glucopyranose residue

On the basis of n.m.r. analysis and force-field calculations for methyl 4-*O*-methyl-2-*O*-sulfo-L-idosiduronic acid (**8**) and oligosaccharides containing α-L-iduronate residues, *e.g.*, **9**, it was concluded that the pyranose ring of α-L-iduronate adopts mainly (>90%) the $^1C_4$ conformation in the monomer **8**, and that the skew form $^2S_0$ becomes an important contributor to the conformation of the iduronate residues in the heparin oligosaccharide[4]. Results obtained for the oligosaccharide were considered sufficient to preclude a substantial contribution of the $^4C_1$ form to the conformer population.

In conclusion, we have shown that the pyranose ring of methyl 6-deoxy-α-D-idopyranoside exists in the $^4C_1$ conformation in the solid state, equivalent to the $^1C_4$ conformation for the L-enantiomer. Analysis of the vicinal-proton coupling constants observed in the ^{1}H-n.m.r. spectrum of the compound, and comparison of these values with those reported for other idose derivatives, suggest that an equilibrium exists in solution between the $^4C_1$ form an another conformer, possibly the skew form $^2S_0$. Whereas our results do not necessarily rule out the $^4C_1$ form for the L-iduronate residues in heparin or in dermatan sulfate, they do clearly suggest that the alternative $^1C_4$ form is accessible to the monomer of that species. Together with the other results quoted, ours strengthen the case for a critical re-examination of the fiber-diffraction model.

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