Conformational Features of Idopyranose Derivatives. The Molecular Structure of Methyl 1,2,3,4-Tetra-*O*-Acetyl-α-L-Idopyranuronate

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The molecular structure of the title compound has been determined by X-ray analysis. The structure was solved with the multisolution technique and the atomic parameters were refined by full-matrix least-squares refinement to an *R* value of 0.08 for 2 819 observed reflections. There are two molecules in the asymmetric unit. The bond lengths and bond angles of the pyranose rings are in good agreement within the limits of errors, except for the anomeric bond lengths. This is related to distinct conformations about the exocyclic anomeric bond which result in different respective orientations of the carbonyl O(62) and pyranic oxygen atoms. The conformation of each molecule is a normal $^1C_4$(L) chair slightly deformed towards the ^5H_O half chair. The molecular conformation of the title compound is compared to that of other idopyranose derivatives observed in the solid state.

2-Sulphated α-L-iduronic acid, glycosidically linked through position 4 to 2-deoxy-2-sulphamido-6-*O*-sulpho-α-D-glucopyranose, is the major repeating disaccharide unit of heparin.[1] The blood anticoagulant properties and biological activities of heparin are associated with its binding to Antithrombin III and other plasma proteins.[2] An understanding of how heparin functions at the molecular level requires detailed information about its geometry, which resides in the conformation of the 2 sulphated-α-L-iduronic acid component.

Discrimination between the two chair forms was possible through ^{1}H NMR studies,[3] which ruled out a substantial contribution of the $^4C_1$ form and predicted a slightly distorted $^1C_4$ chair conformation. Monocrystals of salts of methyl 4-*O*-methyl-2-*O*-sulpho-α-L-idopyranuronate could not be obtained until now. Hence an X-ray structural analysis of methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate has been undertaken in order to contribute to the understanding of the conformational transformations of idopyranose derivatives.

Experimental

Crystal Data.—$C_{15}H_{20}O_{11}$, M_w = 376.2, monoclinic, space group $P2_1$, a = 8.389(4), b = 21.572(9), c = 11.135(4) Å, α = 90.0°, β = 112.51(5)°, γ = 90.0°, V = 1 861.8 Å^3, Cu-K_α radiation, λ = 1.541 78 Å, D_c = 1 340 kg m^{-3}, Z = 4, F(000) = 792, μ(Cu-K_α) = 10.21 cm^{-1}. Colourless prismatic crystals were grown by cooling from ethanol. The crystal used for data collection had dimensions 0.14 × 0.1 × 0.3 mm.

Data Collection and Processing.—6 019 reflections of two asymmetric units of the reciprocal space were measured on a Philips PW 1100 diffractometer with graphite-monochromated Cu-K_α radiation by a θ − 2θ scan technique up to 2θ = 130°. Three check reflections were monitored every 120 min. Their intensity fluctuations were random. 2 918 symmetry-related pairs of intensities were averaged. The merging R value was 0.04. Out of 3 101 independent reflections, 2 819 had intensities $> 2\sigma(I)$. No correction was applied for absorption.

Structure Analysis.—The structure was solved with the multisolution technique.[4] The hydrogen atoms were located from a difference map. The weighting function was $w = 1/[\sigma^2(F_0) + 0.000\,26\ F_0^2]$. Full-matrix least-squares refinement[5] of the heavy atoms yielded anisotropically a final $R = (\Sigma||F_o| - |F_c||)/\Sigma|F_o|$ of 0.08. The weighted residual $R_w = \{[\Sigma w(|F_o| - |F_c|)^2]/\Sigma wF_o^2\}^{\frac{1}{2}}$ was 0.10. The scattering factors for the heavy atoms were taken from ref. 6 and for the hydrogen atoms from ref. 7. The residual electron density in the final difference map was within ±0.7 e Å^{-3}. Illustrations were prepared with ORTEP.[8]

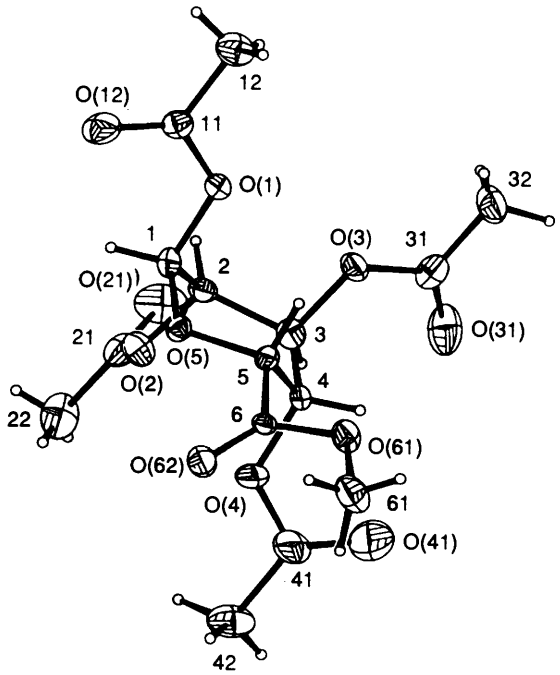

Figure 1. Perspective view and atomic numbering of the title compound.

Results and Discussion

The final atomic parameters, along with their esds, are given in Table 1. A perspective view of the title compound (**1**) with the atomic numbering is shown in Figure 1. The bond lengths and bond angles are displayed in Figure 2(*a*) and 2(*b*), respectively. The crystal structure, stabilized through C–H···O hydrogen bonds and through $CH_3\cdots O$ and $CH_3\cdots CH_3$ short

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for molecules **A** and **B**. The esds (in parentheses) apply to the last significant digit.

Molecule **A**	*x*	*y*	*z*
C(1)	8 215(9)	3 002(3)	6 151(7)
C(2)	7 815(9)	3 615(4)	6 645(7)
C(3)	6 456(9)	3 565(3)	7 207(7)
C(4)	6 642(8)	2 987(4)	8 045(7)
C(5)	6 962(8)	2 424(3)	7 379(6)
O(5)	8 431(5)	2 516(2)	7 041(4)
O(1)	6 774(6)	2 875(2)	4 946(5)
C(11)	7 101(10)	2 587(4)	3 992(8)
O(11)	8 526(9)	2 421(3)	4 103(6)
C(12)	5 516(12)	2 512(4)	2 813(9)
O(2)	9 433(6)	3 801(3)	7 616(5)
C(21)	9 825(12)	4 412(5)	7 765(9)
O(21)	8 811(12)	4 780(3)	7 106(8)
C(22)	11 416(15)	4 528(5)	8 840(12)
O(3)	4 817(6)	3 523(3)	6 145(5)
C(31)	3 451(11)	3 809(4)	6 205(9)
O(31)	3 621(10)	4 155(4)	7 119(10)
C(32)	1 868(11)	3 691(6)	5 112(11)
O(4)	8 083(6)	3 072(3)	9 268(5)
C(41)	7 834(15)	3 190(7)	10 304(10)
O(41)	6 315(14)	3 413(8)	10 183(8)
C(42)	9 474(15)	3 262(5)	11 494(9)
C(6)	7 401(8)	1 868(3)	8 264(6)
O(61)	5 924(6)	1 652(2)	8 335(5)
O(62)	8 792(6)	1 652(3)	8 843(5)
C(61)	6 139(11)	1 094(5)	9 086(10)
Molecule **B**			
C(1)	2 066(9)	1 278(3)	5 765(8)
C(2)	841(10)	1 384(3)	6 454(8)
C(3)	−135(8)	820(4)	6 567(7)
C(4)	966(8)	235(3)	6 936(6)
C(5)	2 040(9)	184(3)	612(6)
O(5)	3 072(6)	728(2)	6 226(5)
O(1)	1 068(8)	1 203(3)	4 419(5)
C(11)	1 435(17)	1 581(6)	3 587(9)
O(11)	2 500(12)	1 983(6)	3 926(9)
C(12)	134(2)	1 443(6)	2 255(11)
O(2)	1 774(6)	1 589(2)	7 763(4)
C(21)	2 229(9)	2 207(4)	7 941(9)
O(21)	2 160(6)	2 533(3)	7 068(6)
C(22)	2 741(11)	2 372(5)	9 304(9)
O(3)	−1 491(6)	652(3)	5 360(6)
C(31)	−3 050(10)	917(4)	5 068(10)
O(31)	−3 335(8)	1 294(4)	5 715(7)
C(32)	−4 273(13)	696(6)	3 778(11)
O(4)	2 162(6)	28(2)	8 253(4)
C(41)	1 634(12)	90(4)	9 174(8)
O(41)	229(9)	−119(4)	8 363(7)
C(42)	3 010(13)	193(6)	10 501(9)
C(6)	3 202(9)	−371(4)	6 548(7)
O(61)	4 855(7)	−256(3)	6 904(7)
O(62)	2 635(8)	−881(3)	6 493(6)
C(61)	5 968(14)	−811(5)	7 322(13)

contacts, is illustrated in Figure 3. Tables of hydrogen atom co-ordinates, thermal parameters, bond lengths, bond angles and equations of least squares planes have been deposited at the Cambridge Crystallographic Data Centre (CCDC).*

There are two molecules in the asymmetric unit. The bond lengths and bond angles of the pyranose rings in the two molecules agree within the limits of errors, except for the C(5)–O(5)–C(1)–O(1) bond sequence. In molecule **A**, the O(5)–C(1) bond [1.404(9) Å] is shorter by 3- and 5σ than the

* For details, see 'Instructions for Authors (1990)', *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

Table 2. Torsional angles/°. The esds (in parentheses) refer to the last significant digit.

Ring angles	Molecule **A**	Molecule **B**
O(5)–C(1)–C(2)–C(3)	−46.4(6)	−45.7(7)
C(1)–C(2)–C(3)–C(4)	41.4(7)	42.5(7)
C(2)–C(3)–C(4)–C(5)	−45.9(7)	−46.0(6)
C(3)–C(4)–C(5)–O(5)	55.1(6)	55.6(6)
C(4)–C(5)–O(5)–C(1)	−62.8(6)	−62.2(6)
C(5)–O(5)–C(1)–C(2)	57.5(6)	55.5(7)
Exocyclic Angles		
C(5)–O(5)–C(1)–O(1)	−60.8(7)	−63.2(7)
O(5)–C(1)–O(1)–C(11)	−92.9(7)	−114.2(9)
C(2)–C(1)–O(1)–C(11)	145.3(8)	125.2(9)
O(62)–C(6)–C(5)–O(5)	18.3(6)	−176.6(9)
O(62)–C(6)–C(5)–C(4)	−101.7(8)	60.7(7)
O(61)–C(6)–C(5)–O(5)	−163.5(7)	−0.6(7)
O(61)–C(6)–C(5)–C(4)	76.5(7)	−123.3(8)
C(61)–O(61)–C(6)–C(5)	−176.1(8)	179.5(8)
C(61)–O(61)–C(6)–O(62)	−5.6(7)	−4.2(8)
C(1)–O(1)–C(11)–O(11)	1.2(7)	−3(1)
C(2)–O(2)–C(21)–O(21)	1.3(8)	−13.9(7)
C(3)–O(3)–C(31)–O(31)	6.4(8)	3.4(8)
C(4)–O(4)–C(41)–O(41)	−20(1)	0.0(7)
C(1)–O(1)–C(11)–C(12)	−178(1)	−176(1)
C(2)–O(2)–C(21)–C(22)	175(1)	165(1)
C(3)–O(3)–C(31)–C(32)	−176(1)	180(1)
C(4)–O(4)–C(41)–C(42)	180(1)	−178(1)

C(5)–O(5)[1.433(9) Å] and C(1)–O(1) [1.447(7) Å] bonds, respectively. The same trend was observed in 1,2,3,4,6-penta-*O*-acetyl-α-D-idopyranose[9] (**2**). This is in agreement with the anomeric bond length distribution usually observed in α-anomers of pyranoses.[10] The conformation about the anomeric bonds is $-g,-g$, the C(5)–O(5)–C(1)–O(1) and O(5)–C(1)–O(1)–C(11) torsion angles being −60.8(7) and −92.5(7)° in molecule **A** and −63.2(7) and 114.2(9)° in molecule **B**, respectively. In molecule **B**, the back-donation of the O(5) lone-pair electrons is not observed, the O(5)–C(1) bond [1.441(9) Å] being 2.5σ longer than the C(1)–O(1) bond [1.419(9) Å]. The O(5)–C(1)–O(1)–C(11) torsion angle of −114.2° brings the lone-pair electrons of O(5) and O(1) into an almost synaxial position, causing dipole repulsion and restraining the back-donation of the O(5) lone-pair.

These observations are in agreement with the relative orientation of the carboxy groups and pyranic oxygens in each molecule of the asymmetric unit. In molecule **A**, where due to the lone-pair delocalisation the O(5) atom has a partial positive charge, the carbonyl oxygen is *cis* with respect to O(5). The O(62)–C(6)–C(5)–O(5) and O(61)–C(6)–C(5)–O(5) torsion angles are 18.3(6) and −163.5(7)°, respectively. A similar conformation was observed in the methyl ester of α-D-galacturonic acid.[11] In molecule **B**, where the O-5 atom would have a partial negative charge the carbonyl oxygen is *trans* with respect to O(5). The O(62)–C(6)–C(5)–O(5) and O(61)–C(6)–C(5)–O(5) torsion angles are −176.6(9) and −0.6(7)°, respectively.

Due to the high thermal parameter of O(41), the geometry of the acetate group bound to C(4) in molecule **A** is subject to error and has not been taken into account in the following discussion. The average of the bond lengths [excluding the C(1)–O(1) bonds] and bond angles calculated for seven acetate groups are in good agreement with the corresponding mean values given by Luger and Paulsen[12] and Oliver and Strickland.[13] For each acetate group the CH_3–O–C = O moiety is planar (χ^2 in the range 0–11).

The C–CH_3 bonds are *anti*-parallel and the C=O bonds *syn*-parallel to the C_i–O_i bonds. Consequently the C_i–O_i–C_{i1}–C_{i2}

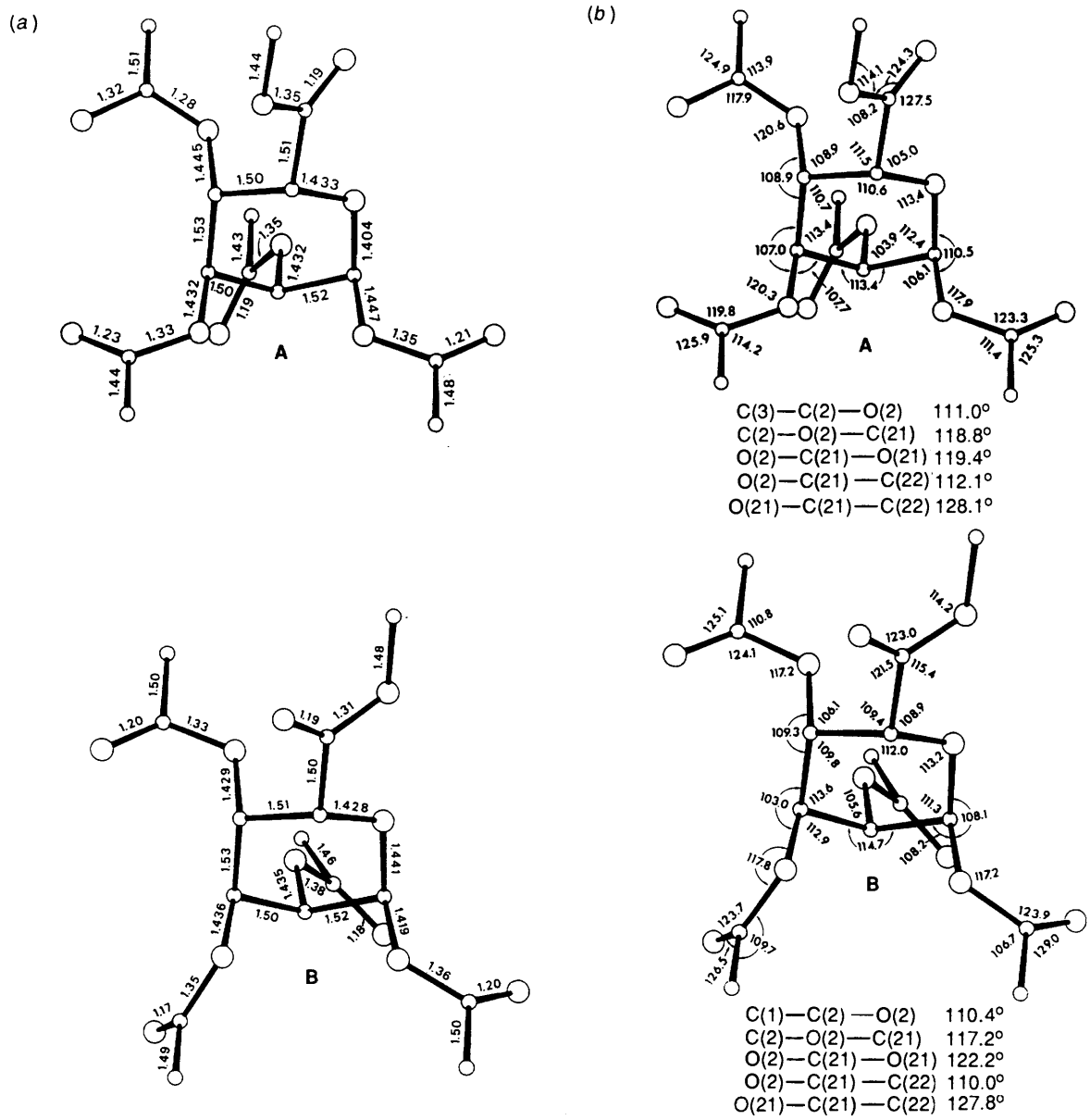

Figure 2. (*a*) Bond lengths/Å. The esds are 0.01 Å for C–C, C–O, C=O, and 0.009 Å for C_{sp^3}–O. (*b*) Bond angles/°. The esds are 0.6° for C–C–C and C–C–O; 0.7° for O–C–O; and 0.9° for CH_3–C–O.

Table 3. Polar parameters of puckering. The esds (in parentheses) refer to the last significant digit.

Compound	(1)A	(1)B	(2)	(3)	(4)
Q/Å	0.51(1)	0.51(1)	0.489(7)	0.609(8)	0.575(5)
θ/°	169(1)	170(1)	8.8(8)	7(1)	175.4(6)
φ/°	143(1)	140(1)	316.2(8)	106(1)	187.0(6)

and C_i–O_i–C_{i1}–O_{i1} torsion angles vary from 165–180° and from 0–14°, respectively. Short intramolecular interactions exist between the carbonyl oxygens of the acetate groups and the hydrogen atoms, both being bound to the same ring carbon atom [2.30 ⩽ d ⩽ 2.58 Å < d > 2.41(9) Å]. The dihedral angles between the least-squares planes [passing through the C(2), C(3), C(5), and O(5) atoms of the pyranose ring] and the acetate groups [bound to C(1) and C(4)] are 85 and 88° in molecule **A** and 88 and 85° in molecule **B**, respectively. Due to the repulsion of the synaxial acetate groups, those linked to C(2) and C(3) form—with the best planes of the pyranose rings—an angle of 68 and 77° in molecule **A** and 73 and 62° in molecule **B**.

Conformation.—The torsion angles, along with their esds are given in Table 2. The polar puckering parameters[14] are shown in Table 3. The 1,2,3- and 4-*O*-acetyl groups in (**1**) and (**2**) are in the axial position and the 6-methyl esters and the 6-*O*-acetyl group are in the equatorial position. Due to 1,3 *syn*-diaxial interactions of the acetyl groups the pyranose rings are flattened. The smallest value of the torsion angles is observed at the C(2)–C(3) bonds [41.4, 42.5 and 40.9° in molecules (**1**)**A**, (**1**)**B** and (**2**), respectively]. The torsion angles, together with the polar puckering parameters, suggest that the normal $^1C_4$(L) and $^4C_1$(D) chair conformations are deformed towards ^5H_O [for (**1**)] and $^OH_5$ [for (**2**)] half chairs.[15]

In the idopyranosyl part of 2-acetamido-1,3,6-tri-*O*-acetyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-L-idopyranosyl)-α-D-

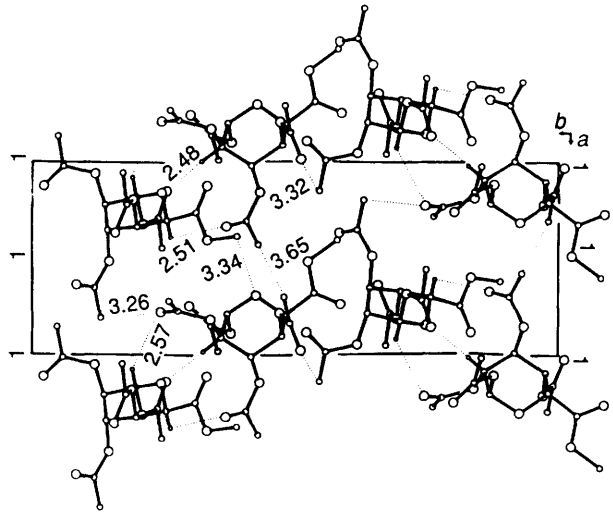

Figure 3. Molecular packing of the title compound viewed along *c* (distances/Å).

glucopyranose[16] (**3**) and in methyl 2,4-bis(*N*-acetyl-*N*-benzoylamino)-3,6-di-*O*-benzoyl-2,4-dideoxy-α-D-idopyranoside[17] (**4**) the normal chair conformation is reversed: $^4C_1$(L) for (**3**) and $^1C_4$(D) for (**4**).

The substituents attached to C(1)–C(4) are in equatorial positions whereas those at C(5) are axial.

The α-D- and α-L-idopyranoses are highly flexible compounds, the estimated free energy difference between the $^1C_4$ and $^4C_1$ chair conformations being 0.5 kcal mol^{-1}.[18]

Force-field calculations[3] for methyl 4-*O*-methyl-2-*O*-sulpho-α-L-idopyranuronate resulted in three comparable energy minima (at $\varphi = 270$ and $\theta = 0$, 180 and 90°) on the two dimensional $E(\theta, \varphi)$ energy map (θ and φ being polar puckering parameters as defined by Cremer and Pople),[14] indicating three possible conformers: the $^4C_1$ and $^1C_4$ chair forms and the $^1T_5$ twist–boat. Along the boat–twist–boat pseudorotational path ($\theta = 90°$), three additional minima were observed at $\varphi = 30$, 150 and 330° corresponding to $^3T_1$, ^2T_O and $^OT_2$ conformations, respectively which are at a higher energy level, by at least 4 kcal mol^{-1}, than the $^1T_5$ conformation. Augé and David[19] suggested the ^2T_O twist–boat conformer to be considered for the interpretation of the unusual coupling constants observed for idopyranose derivatives.

The anomeric effect, the 1,3-diaxial interactions, the crystal field in the solid state or the hydrogen bonds formed with the solvent molecules in solution can all easily induce a deformation of the chair conformation or even invert it. Hence, in oligosaccharides such as heparin, heparan, and dermatan the idopyranuronic residue may easily adjust its conformation to the steric and electronic requirements of the surrounding sugars. Nevertheless, the twist–boat conformation has not been observed in the solid state until now. When idopyranose or idopyranuronic acid is kept by itself or bound to another pyranose chair conformations, more or less deformed towards half-chairs were detected.

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