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THE X-RAY CRYSTAL STRUCTURE OF DL-(1,3,5/2,4)-1,2,3,4-TETRA-ACETOXY-5-(ACETOXYMETHYL)CYCLOHEXANE*

STEVEN F. WATKINS, KHALIL A. ABBOUD, NHUAN P. NGHIEM, RONALD J. VOLL, AND EZZAT S. YOUNATHAN**

Departments of Chemistry and Biochemistry, Louisiana State University, Baton Rouge, LA 70803 (U.S.A.)

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ABSTRACT

The crystal and molecular structure of the pseudo-sugar DL-(1,3,5/2,4)-1,2,3,4-tetraacetoxy-5-(acetoxymethyl)cyclohexane ("pseudo-β-DL-glucopyranose pentaacetate") has been determined by X-ray diffraction and statistical-phasing procedures. The data were refined to $R = 0.049$ and $R_w = 0.054$ over 1543 reflections with I greater than $3\sigma(I)$. The racemic crystals are monoclinic, space group $P2_1/c$, $a = 11.580(2)$, $b = 8.276(1)$, $c = 22.031(2)$ Å, $\beta = 104.33(1)°$, $D_c = 1.26$ g/cm^3, with four molecules in the unit cell. The ring has a $^4C_1$(D), $^1C_4$(L) conformation, with puckering amplitude of 0.582(4) Å, a pseudorotation angle of −168.35°, and a *gg* orientation about the C-5–C-6 bond.

INTRODUCTION

Studies of carbohydrates have utilized many varied techniques during the past hundred years. Major advances are made when a structure is modified and the properties of the analog are compared to those of the original compound. In particular, meaningful information has been gained by the use of analogs of physiologically active sugars and their derivatives[1–3]. A useful modification is the replacement of an oxygen atom by a sulfur atom. Thus, the conversion of the 5-hydroxyl group of D-glucose into a thiol, to produce 5-thio-D-glucose has stimulated many studies of this interesting compound[4], and this general concept has encouraged making other replacements (by Se, P, or N; for a review, see ref. 5).

The term "pseudo-sugar" was suggested[6] for a sugar which has been modified by replacement of the ring-oxygen atom by a methylene group. The structure, which is trivially named pseudo-β-D-glucopyranose, occurs in the validamycin antibiotics as the related amine, validamine[7]. Pseudo-β-D-glucopyranose is correctly named (1*R*)-(1,3,5/2,4)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol. By virtue of their structure, pseudo-sugars are not able to

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**To whom correspondence should be addressed.

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tautomerize or anomerize; hence, they can be utilized as specific analogs of the α and β anomers of their corresponding parent sugars. Recently, pseudo-α- and pseudo-β-DL-glucose have been utilized to study the mechanism of D-glucose-stimulated insulin release by pancreatic islets[8].

In a previous study[9], we reported the X-ray crystal structure of 2,5-anhydro-D-mannitol, a structurally locked analog of the β-furanoses. We have used this analog extensively for metabolic studies[3] and discovered its hypoglycemic effect in diabetic animals[10]. In the work reported herein, we utilized X-ray diffraction to confirm the structure and to elucidate the conformation of DL-(1,3,5/2,4)-1,2,3,4-tetraacetoxy-5-(acetoxymethyl)cyclohexane **(1)** (pseudo-β-DL-glucopyranose pentaacetate) in the crystalline state. The data obtained were utilized to clarify the effect of this modification on the conformation of the pyranose ring of D-glucose.

EXPERIMENTAL

A sample of DL-(1,3,5/2,4)-1,2,3,4-tetraacetoxy-5-(acetoxymethyl)cyclohexane **(1)** was prepared according to the procedure published in the literature[7], and was recrystallized from absolute ethanol. A suitable crystal for X-ray diffraction was mounted on an Enraf-Nonius CAD4 diffractometer equipped with CuKα radiation and a graphite monochromator. The unit-cell constants shown in Table I were determined by least-squares refinement of 25 well-centered reflections ($30° < 2\theta < 32°$). All reflections within two octants ($+$ h, $+$ k, $+/-$ l) were measured with the $\omega/2\theta$ scan technique[11]. The intensities of standard reflections were measured periodically during data collection for the purpose of crystal decay

TABLE I

CRYSTAL DATA FOR DL-(1,3,5/2,4)-1,2,3,4-TETRAACETOXY-5-(ACETOXYMETHYL)CYCLOHEXANE

Formula	$C_{17}O_{10}H_{24}$
Formula weight	388.41
Cell constants	
a (Å)	11.580(2)
b (Å)	8.276(1)
c (Å)	22.031(1)
β	104.33(1)
Volume (Å)^3	2045.7(7)
Z (molecules/cell)	4
Density (g/cm^3)	1.26
Space group	$P2_1/c$
Crystal size (mm)	$0.3 \times 0.3 \times 0.36$
λ(CuKα) (Å)	1.54184
Minimum transmission	92.4%
Maximum transmission	99.88%
Reflections measured	2976
$I > 3\sigma(I)$	1543
$R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\alpha\|F_o\|$	0.049
$R_w = (\Sigma_w(\|F_o\| - \|F_c\|)^2/\Sigma_w\|F_o\|^2)^{1/2}$	0.054

TABLE II

ATOMIC COORDINATES OF DL-(1,3,5/2,4)-1,2,3,4-TETRAACETOXY-5-(ACETOXYMETHYL)CYCLOHEXANE

Atom	*x*	*y*	*z*
O-11	0.1268(2)	1.1114(3)	0.4747(1)
O-12	0.2469(3)	1.3175(4)	0.4691(2)
O-21	0.0766(2)	0.9144(3)	0.3720(1)
O-22	−0.0028(3)	0.6943(3)	0.4047(1)
O-31	−0.1707(2)	0.9178(3)	0.2993(1)
O-32	−0.0586(2)	0.8786(4)	0.2304(1)
O-41	−0.2679(2)	1.2310(3)	0.2780(1)
O-42	−0.4347(3)	1.1577(4)	0.3056(1)
O-61	−0.2935(2)	1.3507(3)	0.4280(1)
O-62	−0.4513(3)	1.5105(4)	0.3972(2)
C-1	0.0444(3)	1.1649(5)	0.4174(2)
C-2	−0.0152(3)	1.0150(5)	0.3858(2)
C-3	−0.1041(3)	1.0606(5)	0.3254(2)
C-4	−0.1952(3)	1.1787(5)	0.3380(2)
C-5	−0.1387(3)	1.3268(5)	0.3740(2)
C-6	−0.2341(4)	1.4386(5)	0.3882(2)
C-7	−0.0467(3)	1.2770(5)	0.4335(2)
C-11	0.2255(4)	1.1947(5)	0.4952(2)
C-12	0.3038(4)	1.1311(5)	0.5540(2)
C-21	0.0753(4)	0.7558(5)	0.3861(2)
C-22	0.1815(4)	0.6730(5)	0.3738(2)
C-31	−0.1399(3)	0.8400(5)	0.2520(2)
C-32	−0.2201(4)	0.6979(6)	0.2306(2)
C-41	−0.3875(4)	1.2161(6)	0.2677(2)
C-42	−0.4489(4)	1.2836(7)	0.2063(2)
C-61	−0.4044(4)	1.3983(6)	0.4267(2)
C-62	−0.4593(4)	1.2924(6)	0.4661(3)

and orientation control. Two strong reflections near $\chi = 90°$ were measured after data collection, using incremental ψ values of 10°; thus, a linear-decay correction and an empirical absorption correction, in addition to the standard Lp correction, were applied to the data.

The phasing model was obtained by direct methods procedures (MULTAN77)[12] which revealed the positions of all non-hydrogen atoms. The positions of all non-methyl hydrogen atoms were calculated by assuming sp^3 hybridization. The hydrogen atoms of each methyl group were found to be disordered, and the best model contains two sets of three half-hydrogen atoms related by a rotation of 60°.

The final model, refined by weighted, full-matrix, least-squares, contained 244 variables and incorporated the following features: anisotropic thermal parameters for all non-hydrogen atoms, fixed isotropic thermal parameters for hydrogen atoms, and a parameter which adjusts the weights for high-intensity effects (0.02). The atomic-scattering factors were those of Cromer and Mann[13]. The atomic coordinates are listed in Table II. The anisotropic thermal parameters

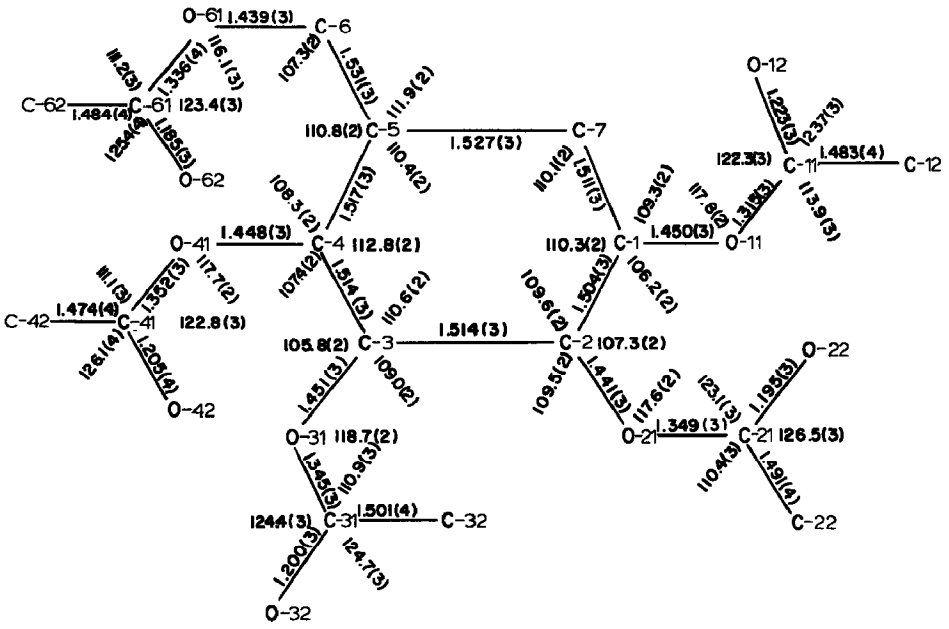

Fig. 1. Bond lengths (in Å; e.s.d. values in parentheses) and valence bond-angles (in degrees; e.s.d. values in parentheses) in DL-(1,3,5/2,4)-1,2,3,4-tetraacetoxy-5-(acetoxymethyl)cyclohexane.

and the observed and calculated structure-amplitudes are listed* in Tables III and IV.

RESULTS AND DISCUSSION

Bond lengths and angles are shown in Fig. 1, and selected torsion-angles are presented in Fig. 2. A stereoscopic view of the molecule is shown in Fig. 3. The crystal is racemic, as expected from the synthetic procedure, and the configuration of the ring substituents is the expected *β-gluco* (all-*trans*) sequence. For comparison purposes with D-glucopyranose, the ring-methylene carbon atom is numbered as C-7 in the data, and is in the same position as O-5 in a pyranose ring. The results for **1** were compared with the crystal structure[14] of *β*-D-glucopyranose pentaacetate (**2**).

All of the C–C bond-lengths in **1** agree with each other and with their corresponding bond lengths in **2**. The C–C average bond-length of 1.514(3) Å is in good agreement with the average in **2** [1.517(8) Å]. The endocyclic bond-angles all differ from the cyclohexane value of 111.5°, with the largest difference occurring at C-1–C-2–C-3 (−1.9°). When these angles are compared as between **1** and **2**, a significant difference is noted for C-1–C-2–C-3 (−3.9°) and C-3–C-4–C-5 (+3.1°).

*Tables III and IV have been deposited with, and can be obtained from, Elsevier Science Publishers B.V., B.B.A. Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/351/*Carbohydr. Res.*, 158 (1986) 7–12.

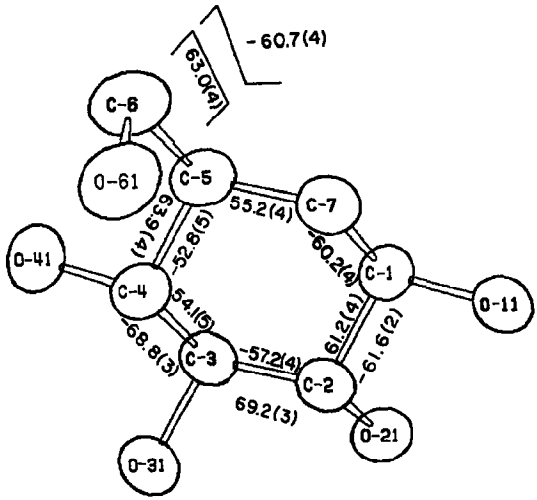

Fig. 2. Selected torsion-angles (in degrees; e.s.d. values in parentheses) in DL-(1,3,5/2,4)-1,2,3,4-tetra-acetoxy-5-(acetoxymethyl)cyclohexane.

The ring torsion-angles are similarly in agreement, and closer to the values for the perfect cyclohexane ring, except for a significant difference observed in angle C-4–C-5–C-7–C-1 in **1**, when compared to its counterpart angle C-4–C-5–O-5–C-1 in **2**. This angle in **1** is 10.7° smaller, indicating the existence of considerable flattening of the ring near C-7 in **1**.

Bond lengths and angles of all five acetyl groups of **1** are in good agreement with those of **2**. The least-squares planes of all five acetyl groups were calculated. Only C-11 was shifted significantly [0.019(4) Å] from the plane; all other acetyl groups were found to be planar. All the secondary acetate groups lie in their expected, equatorial positions, with the carbonyl group coplanar with the ring-methine hydrogen atom[15]. The 1-acetate groups of **1** and **2** are in similar

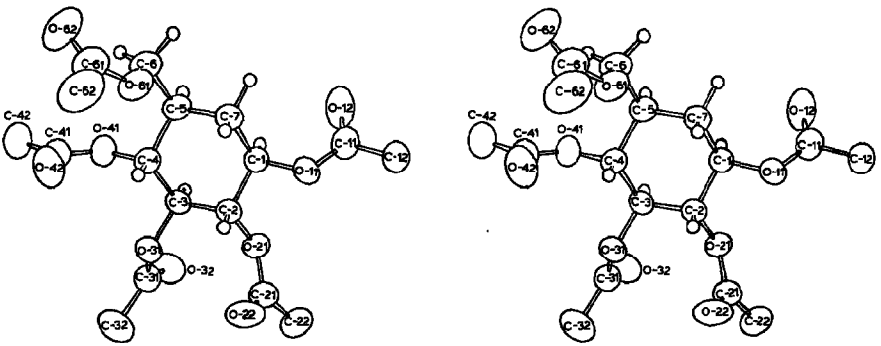

Fig. 3. Stereoscopic view of DL-(1,3,5/2,4)-1,2,3,4-tetraacetoxy-5-(acetoxymethyl)cyclohexane.

orientations. In contrast, the 6-acetate of **1** is near the *gg* position, whereas in **2**, it is near the *gt* position.

The least-squares plane passing through carbon atoms 2, 3, 5, and 7 places carbon atoms 1 and 4 at positions 0.631(4) Å below and 0.707(4) Å above the plane, respectively. This indicates that the ring is in a $^4C_1$(D), $^1C_4$(L) conformation. The ring also has a puckering amplitude of 0.582(4) Å and a pseudorotation angle[16] (ϕ) of $-168.35°$.

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