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THE COMPOSITION AND CONFORMATION OF D-*threo*-3,4-HEXODIULOSE IN SOLUTION, AND THE X-RAY CRYSTAL STRUCTURE OF ITS $\beta\beta$ ANOMER*

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ABSTRACT

The crystal structure of D-*threo*-3,4-hexodiulose was determined, and it showed that the crystalline form is the $\beta\beta$ anomer. In solution, the $\alpha\alpha$ anomer is preponderant, although all of its hydroxyl groups are *cis* to each other. In the crystal, the diulose assumes the *endo,exo* conformation; in the aqueous solutions of both anomers, the *endo,endo* form preponderates, whereas the acetates in chloroform are mainly in the *exo,exo* conformation.

INTRODUCTION

The proportion of the α- and β-furanose forms of reducing sugars[1], and their conformations[2–4], in solution have been extensively studied, and are now fairly well understood. They are therefore predictable with reasonable accuracy.

The recently described D-*threo*-3,4-hexodiulose[5] (**1**), however, presents interesting problems. Having two keto groups, it will form two furanose rings (which are equivalent, the compound being symmetrical). Two anomeric forms are to be expected, namely, the $\alpha\alpha$ (**2**) and the $\beta\beta$ (**3**) forms. The $\alpha\beta$ form would contain two *trans*-fused, five-membered rings, a highly strained arrangement; this form has not been observed in the n.m.r. spectra. In furanoses, the anomer in which the anomeric hydroxyl group is *trans* to its hydroxyl neighbor is more stable than the *cis* anomer (exceptions are those having the *xylo* configuration of C-2, C-3, and C-4, for reasons which are well understood[2]). In the bicyclic system of the hexodiulose, however, other effects may be operative: in the bicyclo[3.3.0]octane system, *exo* substituents are more stable than *endo* substituents. We were unable to predict which would be the more stable anomer and therefore proceeded to determine experimentally the composition in solution.

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*Dedicated to the memory of Professor Edgar Lederer.

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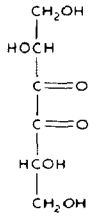
RESULTS AND DISCUSSION

The ^{1}H-n.m.r. spectrum of the hexodiulose (**1**) in deuterium oxide showed, indeed, the presence of two compounds in the ratio of ~2:1, but the values of the ^{1}H–^{1}H coupling constants (see later) were unsuited to allowing assignment of the anomeric configurations. To establish the identity of the two species seen in solution, complexing with lanthanide ions was tried. If a compound has three vicinal *cis*-hydroxyl groups on a five-membered ring, it will form a complex with cations[6]; if the cation is paramagnetic, a change of the chemical shifts in the n.m.r. spectrum will occur[7]. The $\alpha\alpha$ anomer (**2**) has the required geometry, but the $\beta\beta$ anomer (**3**) does not; hence, only the signals of **2** will shift on addition of a paramagnetic ion. It was found that the larger signals shifted on addition of 0.8 mol. equiv. of europium chloride (H-1 by 0.0054, H-1′ by −0.0031, and H-2 by −0.0018 p.p.m.), whereas the smaller signals were unaffected. Hence, the major form at equilibrium is the $\alpha\alpha$ anomer **2**.



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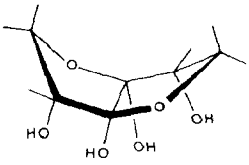
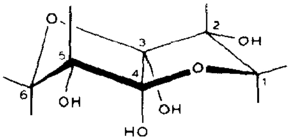


($^{6}EE^{1}$)

2a



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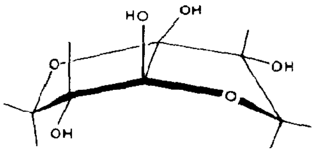
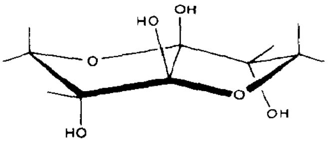
2b



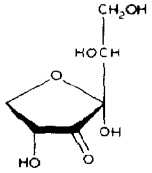
($_{6}EE_{1}$)

3a



($^{6}EE^{1}$)

3b



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The lanthanide-induced shifts are unusually small in this case. It was found that the hexodiulose complexes weakly: on a t.l.c. plate in the Ca^{2+} form[8], its R_F value is 0.70 (compared to 0.43 for methyl β-D-mannofuranoside). The rigidity of the molecule does not allow the close approach of O-2 to O-4 (or of O-3 to O-5) which is required for strong complexing. In the crystal structure[9] of methyl β-D-mannofuranoside · $CaCl_2$ · 4 H_2O, the distance between O-1 and O-3 is 285 pm; such a short distance is not possible in the hexodiulose.

Because the lanthanide-induced shifts are so small, additional confirmation of the configuration was sought. The hexodiulose crystallizes well. On the basis of its mutarotation, the $\beta\beta$ configuration was assigned[5] to the crystalline form on the assumption that Hudson's rule[10] is valid for this bicyclic system. To confirm this assignment, the crystal structure of **1** was determined by X-ray crystallographic analysis. This analysis, which is described in detail herein, confirmed that the crystalline anomer of **1** is the $\beta\beta$ form.

The ^{1}H-n.m.r. spectrum of the $\beta\beta$ anomer in deuterated dimethyl sulfoxide (Me_2SO-d_6; a solvent in which mutarotation is slow), immediately after dissolution, corresponded to that of the minor isomer at equilibrium. Signals of the $\alpha\alpha$ anomer appeared gradually. At equilibrium, the ratio of the $\alpha\alpha$ to the $\beta\beta$ anomer is 18:7 in Me_2SO-d_6, which is the same ratio found in deuterium oxide and in a 1:1 mixture of these two solvents. The $\alpha\alpha$ anomer is, therefore, more stable than the $\beta\beta$ anomer, even though it has four hydroxyl groups *cis* to each other; apparently, the circumstance of OH-2 and OH-5 being *exo* outweighs the *cis* interactions.

The n.m.r. spectrum in Me_2SO-d_6 also shows small signals of a third form (~4%) which is probably the monocyclic furanose isomer (**4**). This is not unexpected because equilibrated solutions of the pentuloses contain substantial proportions of the acyclic form[1]. These signals are at δ 6.56 (s, OH-3), 5.86 (s), 4.88 (d), 4.46 (t, OH-1), and 4.24–4.20 (CH). In aqueous (^2H_2O) solution, the monocyclic form was not detected.

The ^{13}C-n.m.r. spectrum of **1** in Me_2SO-d_6 shows signals of the $\alpha\alpha$ anomer at 107.80, 73.19, and 72.48 p.p.m.; and of the $\beta\beta$ anomer, at 107.55, 74.54, and 71.72 p.p.m.

The conformations of the hexodiulose. — Owing to the fusion of the two five-membered rings, most of the diulose molecule is rigid: C-2, C-3, C-4, and O-1 are nearly coplanar, and C-3, C-4, C-5, and O-6 are also nearly coplanar. Only C-1 and C-6 are mobile; they can lie above or below the plane of the furanose ring, either *exo* or *endo*. It would be expected that the *exo* form would be the more stable. Hence, the furanoses have an envelope (*E*) conformation, with the methylene group out of the plane; this conformation is not encountered among the monocyclic furanoses[2,4]. Twist (*T*) conformations adjacent to these *E* forms in the pseudorotational itinerary[11] may also occur; their endocyclic torsion angles are similar to those of the *E* forms, and the possibility of their presence does not affect the following discussion.

The coupling constants of the methylene protons clearly distinguish between the two possible *E* conformations. The Karplus equation[12], and experience with furanosides[2,4], indicates that the hydrogen atom *trans* to the oxygen atom on C-2 (or C-5) will have J ~5 Hz in either case; but the hydrogen atom *cis* to the oxygen atom will have $J_{1,2}$ ~1.5 Hz if it is *endo* (**2a**) and ~7.5 Hz if it is *exo* (**2b**) in the $\alpha\alpha$ anomer; for the $\beta\beta$ anomer, $J_{1,2}$ ~1.5 Hz defines the *exo* (**3b**), and ~7.5 Hz, the *endo* (**3a**), conformation. The tetraacetate[5] of the $\alpha\alpha$ form, with $J_{1,2}$ 7.5 Hz, and the tetraacetate of the $\beta\beta$ form, with $J_{1,2}$ 1.2 Hz, are both in the *exo,exo* conformations, $_6EE_1$ (**2b**) and $^6EE^1$ (**3b**), respectively, in C^2HCl_3.

The X-ray crystallographic analysis of the $\beta\beta$ anomer shows that, in the

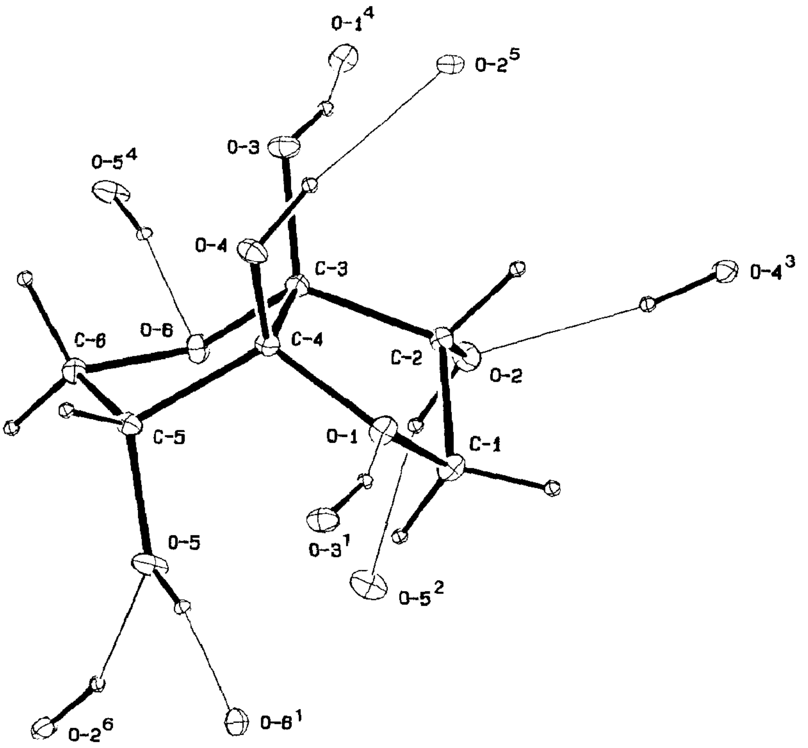

Fig. 1. ORTEP drawing of ββ-D-*threo*-3,4-hexodiulose (**3**). The superscript numbers indicate the symmetry code as defined in Table V.

crystal, the molecule has one methylene group *exo* and the other, *endo* (see Fig. 1). This conformation was not considered by Kuszmann and co-workers[5], although it is favored by its entropy, having no axis of symmetry. In view of this unexpected result, we then investigated, by ^{1}H-n.m.r. spectroscopy, the conformations of the two anomers in solution. In ^2H_2O, the spectrum of the ββ anomer could not be

TABLE I

PROTON CHEMICAL SHIFTS (P.P.M.) OF D-*threo*-3,4-HEXODIULOSE[a]

Proton	*αα Anomer* (**2**)				*ββ Anomer* (**3**)			
	D_2O	*D_2O–Me_2SO*-d_6	*Me_2SO*-d_6	*Acetate*[b] *in $CDCl_3$*	*D_2O*	*D_2O–Me_2SO*-d_6	*Me_2SO*-d_6	*Acetate in $CDCl_3$*
H-1	3.88	3.70	3.615	3.89	3.60	3.45	3.44	4.03
H-1'[c]	4.00	3.87	3.90	4.57	4.16	4.015	3.96	4.43
H-2	4.05	3.85	3.78	5.58	4.18	3.965	3.85	5.60

[a]Recorded with a Bruker AM-500 spectrometer. [b]Ref. 5. [c]H-1' is *trans* to O-2.

TABLE II

PROTON-PROTON SPIN COUPLING CONSTANTS (Hz) FOR D-*threo*-3,4-HEXODIULOSE

Coupling constant	αα *Anomer* (**2**)				ββ *Anomer* (**3**)			
	D_2O	D_2O–Me_2SO-d$_6$	Me_2SO-d$_6$	*Acetate*[b] *in* $CDCl_3$	D_2O	D_2O–Me_2SO-d$_6$	Me_2SO-d$_6$	*Acetate in* $CDCl_3$
$J_{1,1'}$	10.2		9.3	10.0		9.0	8.8	8.3
$J_{1,2}$	2.5	2.6?	4.2	7.5		6.3	5.8	1.2
$J_{1',2}$	4.9	5.0?	5.7	5.0		6.1	5.7	5.0
$J_{H,OH}$			5.3				5.9	

[a]Ref. 5.

analyzed, owing to overlap of the H-1′ and H-2 signals, but the spectrum was first-order in 1:1 ^2H_2O–Me_2SO-d_6. In contrast, the spectrum of the αα anomer was first-order in ^2H_2O, but showed overlap in the solvent mixture. The chemical shifts are shown in Table I, and the coupling constants in Table II.

The $J_{1,2}$ value of 2.5 Hz indicates that the αα anomer is preponderantly in the *endo,endo* conformation (**2a**), in contrast to the behavior of its tetraacetate in C^2HCl_3. In Me_2SO-d_6, there is a mixture of the two conformations, or presence of the *exo,endo* conformation, or both; the coupling constants do not differentiate between these two possibilities. Similarly, the ββ anomer is mainly in the *endo,endo* form (**3a**) in water, and there is a mixture of conformations, or of the *exo,endo* conformation, or all three, in Me_2SO.

Clearly, for both anomers, the *endo* conformation is the more stable, although the energy difference is not large. The reason for this is not yet clear; it may be caused by the interaction of dipole moments. In the *endo,endo* conformation, the two dipole moments resulting from the C–O bonds in the rings are nearly anti-parallel; in the *exo,exo* form, they are at an angle to each other.

When the compounds are acetylated, and the acetates are dissolved in C^2HCl_3, the anomeric effect is greatly increased, and this seems to determine the conformational preference. In the *exo* anomers, the anomeric hydroxyl groups are farther out of the plane of the furanose rings than in the *endo* anomers; hence, the anomeric effect is more favorable in the former.

CRYSTAL STRUCTURE DETERMINATION

Crystal data. — $C_6H_{10}O_6$, M 178.1, orthorhombic, space group $P2_12_12_1$, *a* 5.669(1), *b* 9.678(1), *c* 12.995(2) Å, $V = 713.0(2)$ Å^3, $D_c = 1.66$ g.cm^{-3}, $Z = 4$, $\mu_{Mo} = 1.42$ cm^{-1}. The crystal (obtained from water–ethanol) was approximately equidimensional, mean size 0.2 mm, with the 16 faces of the forms {012}, {011}, {101}, and {110} present.

Structure determination. — Intensities for 779 reflexions were measured with an Enraf–Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode, using graphite-mono-

TABLE III

ATOMIC PARAMETERS (OTHER THAN HYDROGEN) FOR ββ-D-*threo*-3,4-HEXODIULO-3,6:4,1-DIFURANOSE (**3**)

Atom	*x/a*	*y/b*	*z/c*	B_{eq}[a]
C-1	0.7910(4)	0.3422(2)	0.3198(2)	2.36(4)
C-2	0.5321(4)	0.3814(2)	0.3076(2)	1.82(3)
C-3	0.5018(4)	0.4962(2)	0.3874(1)	1.77(4)
C-4	0.7540(4)	0.5576(2)	0.4005(2)	1.81(4)
C-5	0.8101(4)	0.5447(2)	0.5174(2)	2.10(4)
C-6	0.5677(4)	0.5174(2)	0.5617(2)	2.26(3)
O-1	0.9036(3)	0.4733(1)	0.3384(1)	2.29(4)
O-2	0.3693(3)	0.2710(2)	0.3617(1)	2.25(3)
O-3	0.3421(3)	0.5986(1)	0.3616(1)	2.49(4)
O-4	0.7806(3)	0.6932(1)	0.3721(1)	2.34(4)
O-5	0.9577(3)	0.4307(2)	0.5402(1)	2.95(4)
O-6	0.4486(3)	0.4349(1)	0.4847(1)	2.05(3)

[a] B_{eq}(Å^2) is the isotropic equivalent of the anisotropic temperature factor.

chromatized molybdenum radiation (λ 0.7107 Å) and $2\theta_{max}$ of 50°. Data were corrected for absorption and, after removing systematic absences, 762 unique reflextions remained, of which 699 with $I > 3\sigma(I)$ were considered observed. These were used for least-squares refinement after structure solution by direct phasing and Fourier methods. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located in difference Fouriers, and given isotropic temperature parameters equivalent to those of the atoms to which they are bonded.

The final residuals R, R_w were 0.027 and 0.039. Reflexion weights used were $1/\sigma^2(F_0)$, with $\sigma(F_0)$ derived from $\sigma(I_0) = \{\sigma^2(I_0) + (0.04I_0)^2\}^{1/2}$. The weighted residual is defined as $R_w = (\Sigma w\Delta^2/\Sigma wF_0^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-Ray Crystallography[13]. Structure solution was by MULTAN-80 (ref. 14), and refinement used BLOCKLIS, a local version of ORFLS[15]. Cyber 172 and IBM3090 computers were used for all calculations.

An ORTEP drawing[16] of the structure of **3**, showing the atom numbering and the hydrogen bonds, is given in Fig. 1. Non-hydrogen atom parameters are listed in Table III, and bond lengths, angles and selected torsional angles in Table IV*. The two furanose rings are not equivalent. The C-1–C-4 ring is very close to the ideal $_1E$ form, with a phase angle[11] of 128.0° and an amplitude of 41.4° (the phase angle P is 126° for $_1E$); the C-3–C-6 ring, with a phase angle of 291.4° and an amplitude of 41.7°, is much closer to the $^1T_0$ (288°) than to the ^1E form (306°).

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*Tables of positional and anisotropic thermal parameters, and all bond distances, angles and torsional angles, as well as observed and calculated structure factors may be obtained from Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/416/*Carbohydr. Res.*, 194 (1989) 21–29.

TABLE IV

BOND LENGTHS (Å), BOND ANGLES (DEGREES), AND SELECTED TORSION ANGLES (DEGREES)

Bonds	*Bond lengths*	*Bonds*	*Bond lengths*
C-1–C-2	1.524(3)	C-6–O-6	1.447(3)
C-2–C-3	1.529(3)	O-6–C-3	1.429(2)
C-3–C-4	1.558(3)	C-2–O-2	1.417(2)
C-4–O-1	1.428(2)	C-3–O-3	1.384(2)
O-1–C-1	1.441(3)	C-4–O-4	1.371(2)
C-4–C-5	1.557(3)	C-5–O-5	1.416(3)
C-5–C-6	1.513(3)		
Bonds	*Bond angles*	*Bonds*	*Bond angles*
C-1–O-1–C-4	109.6(2)	C-2–C-3–C-4	104.4(2)
C-3–O-6–C-6	106.5(1)	O-1–C-4–O-4	109.2(2)
O-1–C-1–C-2	103.0(2)	O-1–C-4–C-3	105.4(1)
O-2–C-2–C-1	115.5(2)	O-1–C-4–C-5	112.6(2)
O-2–C-2–C-3	114.7(2)	O-4–C-4–C-3	115.9(2)
C-1–C-2–C-3	102.6(2)	O-4–C-4–C-5	108.5(2)
O-3–C-3–O-6	111.9(2)	C-3–C-4–C-5	105.3(2)
O-3–C-3–C-2	115.5(2)	O-5–C-5–C-4	112.8(2)
O-3–C-3–C-4	110.7(1)	O-5–C-5–C-6	108.7(2)
O-6–C-3–C-2	108.8(1)	C-4–C-5–C-6	101.5(2)
O-6–C-3–C-4	104.8(2)	O-6–C-6–C-5	104.9(2)
Bonds	*Torsion angles*	*Bonds*	*Torsion angles*
C-4–O-1–C-1–C-2	37.2(2)	C-3–O-6–C-6–C-5	−43.3(2)
O-1–C-1–C-2–C-3	−37.7(2)	O-6–C-6–C-5–C-4	34.9(2)
C-1–C-2–C-3–C-4	25.3(2)	C-6–C-5–C-4–C-3	−15.4(2)
C-2–C-3–C-4–O-1	−4.2(2)	C-5–C-4–C-3–O-6	−9.1(2)
C-3–C-4–O-1–C-1	−20.7(2)	C-4–C-3–O-6–C-6	31.9(2)
C-2–C-3–C-4–C-5	−123.4(2)	O-6–C-3–C-4–O-1	110.2(2)
O-2–C-2–C-3–O-3	−86.9(2)	O-4–C-4–C-5–O-5	−134.6(2)

TABLE V

HYDROGEN BONDING

Hydrogen bond	*Symmetry code*	*O · · · O (Å)*
O-1 · · · H-O-3^{1}	$1 = 1 + x, y, z$	2.78
O-2-H · · · O-5^{2}	$2 = -1/2 + x, 1/2 - y, 1 - z$	2.74
O-2 · · · H-O-4^{3}	$3 = 1 - x, -1/2 + y, 1/2 - z$	2.70
O-3-H · · · O-1^{4}	$4 = -1 + x, y, z$	2.78
O-4-H · · · O-2^{5}	$5 = 1 + x, 1/2 + y, 1/2 - z$	2.70
O-5 · · · H-O-2^{6}	$6 = 1/2 + x, 1/2 - y, 1 - z$	2.74
O-5-H · · · O-6^{1}		2.88
O-6 · · · H-O-5^{4}		2.88

The C–O distances display the expected variations as shown, for the aldopyranoses, by Jeffrey and co-workers[17]. Owing to their partial double-bond character, the anomeric C–O bonds (C-3–O-3 and C-4–O-4) are considerably shorter than

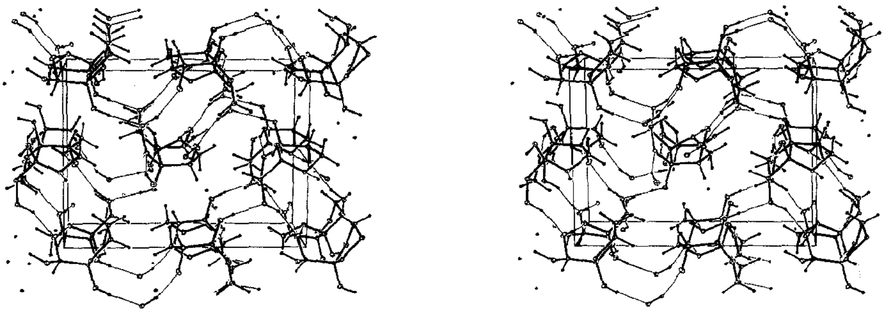

Fig. 2. Stereoview of the crystal packing of **3**, viewed approximately along the *a* axis.

the normal C-2–O-2 and C-5–O-5 bonds. In turn, the C-3–O-6 and the C-4–O-1 bonds are slightly, and the C-6–O-6 and the C-1–O-1 bonds considerably, longer.

The molecules are arranged in columns parallel to the *a* axis. Each molecule is hydrogen-bonded to six other molecules; the bonding pattern is described in Table V. Two hydrogen bonds connect each molecule to each of its neighbors in the column, two to molecules of an adjacent column, and one each to two other columns. The crystal packing is shown in Fig. 2. The anomeric oxygen atoms are hydrogen donors; the ring-oxygen atoms can, of course, only act as hydrogen acceptors; and O-2 and O-5 are both donors and acceptors.

The hydrogen atoms on O-3 and O-5 provide links to adjacent molecules in the column; hence, the C-5–O-5 and C-3–O-3 bonds are nearly antiparallel. On the other hand, O-2 provides links to other columns; hence, the C-2–O-2 bond points outwards. Thus, the hydrogen bonds provide the reason for the two furanose rings' being in different conformations.

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