Carbohydrate Research, 127 (1984) 171–179
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CONFORMATIONAL DIFFERENCE IN THE SOLID STATE AND IN SOLUTION OF METHYL 2,3,4-TRIDEOXY-2,4-DI-*C*-METHYL-6-*O*-TRITYL-α-D-*lyxo*-HEXOPYRANOSIDE

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(Received March 7th, 1983; accepted for publication in revised form, July 5th, 1983)

ABSTRACT

The conformational difference of the title compound (**1**) in the solid state and in solution has been investigated by X-ray crystallography and high-field proton n.m.r. spectrometry. In the solid state, compound **1** adopts the $^4C_1$(D) conformation (**1a**), whereas **1** exists preferentially in the $^1C_4$(D) conformation (**1b**) in chloroform solution.

INTRODUCTION

Synthetic approaches to complex, optically active natural products from carbohydrate-derived synthons has become an active area of research because of the complete optical purity and unique chemical properties, especially the stereoselectivities of some reactions, of the carbohydrate molecule. Efficient utilization of such synthons requires precise determination of stereochemistry, for which n.m.r. analysis has been the most useful tool. However, conformational inversion or equilibrium of the sugar ring-system in solution often complicates the interpretation of n.m.r. spectra.

The title compound, methyl 2,3,4-trideoxy-2,4-di-*C*-methyl-6-*O*-trityl-(triphenylmethyl)-α-D-*lyxo*-hexopyranoside (**1**), has been synthesized from methyl α-D-glucoside, and employed by some workers[1] as the key intermediate for the syntheses of several natural products. The absolute stereochemistry of **1** was proved to be 1*S*,2*S*,4*R*,5*S* by conversions into known compounds. However, there has been some variance among proposals for the conformation of 1 based on n.m.r. spectrometry. Weiler *et al.*[1a], who first synthesized **1**, proposed that the compound assumed the $^4C_1$(D) conformation (**1a**) having 1,3-diaxial mehyl groups at C-2 and C-4. Fraser-Reid *et al.*[1b], in contrast, suggested the possibility of a conformational equilibrium (**1a**⇄**1b**) for **1**. It was considered that this ambiguity arose from

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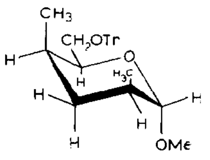
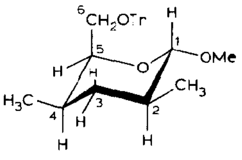


1a



1b

disagreement concerning interpretation of the unusual value (5.8 Hz) of the $J_{1,2}$ coupling constant.

In this work, we have determined the conformation of **1** in the solid state by X-ray crystallographic analysis and have investigated its conformational preference in chloroform solution by detailed examination of its high-field (400 MHz) proton-n.m.r. spectrum.

RESULTS AND DISCUSSION

X-Ray crystallographic analysis of **1** confirmed the proposed relative stereochemistry. The absolute stereochemistry was therefore established as 1*S*,2*S*,4*R*,5*S*, on the basis of the known absolute configurations of C-5 (D) and C-1 (α) of **1**, which were unchanged during transformations from the starting methyl α-D-glucoside. The stereoprojection (Fig. 1) shows that the compound adopts the $^4C_1$(D) conformation. These results agree with Weiler's n.m.r. assignment. Starting with the C-1–C-2 bond, the six endocyclic torsion-angles (e.s.d. values in parentheses) are +48.3°(4), −46.4°(5), +50.5°(4), −56.6°(3), +64.7°(3), and −59.8°(4); exocyclic torsion-angles for the ring protons are listed in Table I.

It was surprising that **1** exists with the unstable 1,3-diaxial arrangement of methyl substituents, because of the significant instability of compound **2a**, which has a partial structure analogous to **1** at C-1,2,3, and 4, and which is readily epimerized in acidic solution to give[2] 1:49 mixture of **2a** and **2b**.

The 400-MHz ^{1}H-n.m.r. spectrum of **1** (Fig. 2), shows vicinal spin-couplings for the ring protons that differ significantly from sets of J values calculated from the dihedral (torsion) angles in the solid state by using either the unmodified[3] or modified[4] Karplus equations. The difference between the observed and calculated values for $J_{1,2}$ is substantial and suggests that **1** exists either in a conformation dif-

TABLE I

TORSION ANGLES (DEGREES) OF PYRANOID-RING PROTONS IN COMPOUND **1** IN THE SOLID STATE (E S D VALUES IN PARENTHESES)

H-1–C-1–C-2–H-2	−86(3)	H-2–C-2–C-3–H-3A[a]	+80(3)
H-2–C-2–C-3–H-3B	−27(3)	H-4–C-4–C-3–H-3A	−72(3)
H-4–C-4–C-3–H-3B	+34(3)	H-4–C-4–C-5–H-5	−44(3)

[a] The geminal protons at C-3 for **1** were abbreviated as H-3A and H-3B, having axial and equatorial orientations in the solid state, respectively.

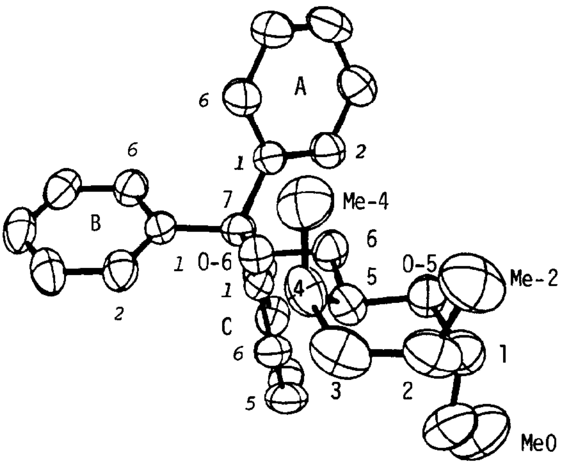
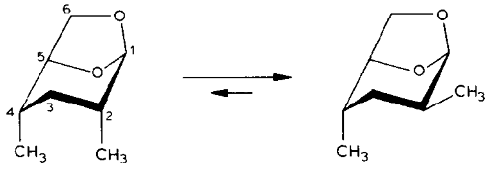


Fig. 1. Stereo-projection of compound **1**. (Hydrogen atoms are omitted for the sake of clarity.)



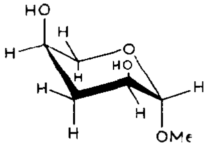
2a **2b**

ferent from that in the solid state or in a conformational equilibrium in $CDCl_3$ solution.

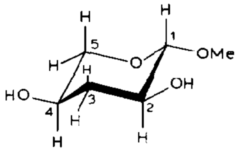
Further examination of the n.m.r. spectrum allowed conformational assignment for **1** in solution (Table II). The most characteristic feature of the spectrum was the two doublets of triplets at δ 1.01 and 1.74, assignable to H-3ax and H-3eq, respectively[5]. The equal values for $J_{2,3}$ and $J_{4,3}$ are characteristic of a chair or boat conformation, and not a skew or other flexible conformation. Inspection of Dreiding models suggested the chair conformation to be more plausible than a ($^{0,3}B$) boat (which would have a dihedral angle between H-4 and H-5 of ~0), because of the relatively small $J_{4,5}$ coupling (4.40 Hz). The large values for $J_{2,3ax}$ and $J_{4,3ax}$ indicates that H-3ax lies in axial–axial relationship with both H-2 and H-4. In addition, the $^{1}J_{C\text{-}1,H\text{-}1}$ value (159.7 Hz), indicates[6] the axial orientation for H-1. The foregoing data thus suggest that **1** adopts the $^{1}C_4$(D) conformation in solution.

By use of the unmodified Karplus equation[3], all possible dihedral angles were calculated from the observed J values. Comparison of the dihedral angles measured from the Dreiding model with these data also shows the $^{1}C_4$(D) conformation to be more feasible than other possible conformations.

Lemieux[7] discussed the $^{4}C_1 \rightleftharpoons {}^{1}C_4$ conformational equilibrium of methyl 3-deoxy-α-D-*erythro*-pentopyranoside (**3**) in terms of solvent effects on the basis of



3a



3b

^{1}H-n.m.r. analyses. As shown in Table II, the couplings between the ring protons of the $^1C_4$ conformer **3b** (in D_2O) are in good agreement with those of the compound **1** in $CDCl_3$, especially as regards the value of $J_{1,2}$.

In conclusion, n.m.r. evidence suggests that compound **1** in chloroform solution exists preferentially in the $^1C_4$(D) conformation (**1b**), but in the solid state adopts the inverted $^4C_1$(D) conformation (**1a**).

EXPERIMENTAL

*Methyl 2,3,4-trideoxy-2,4-di-C-methyl-6-O-trityl-α-*D-lyxo-*hexopyranoside* (**1**). — Compound **1** was obtained from methyl α-D-glucoside in nine steps according to the method of Fraser-Reid *et al.*[1b]. Upon evaporation of solvents, **1** immediately crystallized and was recrystallized from dichloromethane–light petroleum (b.p. 30–60°); m.p. 140–143°, $[\alpha]_D^{23}$ +30.9° (*c* 1.0, chloroform) (lit.[1a] m.p. 140–142°, $[\alpha]_D$ +27.0°; lit.[1c] m.p. 143–143.5°, $[\alpha]_D$ +30.4°). The spectral data were identical to those reported in the literature[1].

Anal. Calc. for $C_{28}H_{32}O_3$: C, 80.65; H, 7.68. Found: C, 80.73; H, 7.74.

X-ray crystallography. — (*a*) *Crystal data.* M = 416.5, orthorombic, plates along *a*-axis; space group $P2_12_12_1$, a = 11.268(1), b = 12.405(2), c = 16.967(3) Å; Z = 4, $D_c = D_m$ = 1.168 cm^{-1}; F(000) =896; μ(MoKα) = 0.80 cm^{-1}, λ(MoKα) = 0.70926 Å.

(*b*) *Data collection.* — A pure crystal of **1** (0.36 × 0.33 × 0.2 mm) was used with a computer-controlled, Rigaku four-circle diffractometer and graphite-monochromated MoKα radiation. Intensity data for 3064 unique reflections (2770 non-zero reflections) up to 55°(2θ) were collected at a temperature of 23 ±1° by using the $2\theta - \omega$ scan technique.

(*c*) *Structure determination.* — The molecular structure was solved by the direct method with the computer program[8] MULTAN 78. All non-hydrogen atoms except the methoxyl group and one of the *C*-methyl carbon atoms were first located on the E-map, and the positions of the residual carbon and oxygen atoms and all hydrogen atoms were determined by successive Fourier synthesis and differential Fourier synthesis. The atomic parameters were refined by the block-diagonal, least-squares method with the computer program[9] HBLSV. Thermal parameters for carbon and oxygen atoms were refined anisotropically, and hydrogen atoms were refined isotropically. The absolute stereochemistries at C-5 and C-1 were already established, based on the known absolute D and α configurations of the starting methyl α-D-glucoside[1b]. The least-squares function minimized was $\Sigma\omega(|F_0| -$

TABLE II

400 MHz-PROTON-N.M.R DATA FOR **1**, AND COMPARISONS OF SPIN-COUPLING CONSTANTS OBSERVED IN $CDCl_3$ SOLUTION WITH VALUES CALCULATED FROM DIHEDRAL ANGLES IN THE SOLID STATE, AND REPORTED FOR COMPOUND **3b**

Atom	*H-1*	*H-2*	*H-3*A	*H-3*B	*H-4*	*H-5*	*H-6*	*H-6'*	*Me-2*	*Me-4*	*MeO*	*Trityl*
δ *(p.p.m.)*[a]	*4 26d*	*1.65m*	*1.01dt*	*1.74dt*	*1.89m*	*4.09dt*	*3.28dd*	*3.06dd*	*0.96d*	*0.70d*	*3.48s*	*7.2–7.6*
J (Hz)	1,2[b]	2,3ax	2,3eq	3ax,3eq	4,3ax	4,3eq	4,5	56	5,6'	6,6'	2,Me-2	4,Me-4
	5.76	9.28	5.37	13.18	9.28	5.37	4.40	7.32	4.40	9.77	6.84	7.32
J calc.[c]	−0.27	−0.11	6.37		0.41	5.45	4.07					
J calc.[d]	1.48	2.09	9.84		2.60	7.28	5.53					
J[e]	6.0	8.9	4.5		8.9	4.5						

[a] Signal multiplicity: s, singlet; t, triplet; m, complex multiplet; d, doublet of triplets; and so on. [b] The magnitudes of $J_{1,2}$ observed (100 MHz) for **1** in CCl_4 and $CDCl_3$–CD_3OD (1:1) were 4.5 and 6.0 Hz, respectively. [c] **By use of the Karplus equation[3], $J_{H,H'} = 4.22 - 0.5\cos\phi + 4.5\cos2\phi$, where ϕ is the dihedral (torsion)** angle as observed for **1** in the solid state. [d] By use of the modified Karplus equation[4], $J_{H,H'} = 7.8 - 1.0\cos\phi + 5.6\cos2\phi)(1 - 0.1\Delta X)$, where ΔX is an electronegativity term $= \Sigma_1^4 (X_n - X_H)$ for the system $R^1R^2CH\text{-}CHR^3R^4$; using the values for X of H = 2.1, C = 2.5, −O- = 3.3. [e] For compound **3b**; see ref. 7.

TABLE III

NON-HYDROGEN ATOMIC COORDINATES ($\times$ 10^4) (E S D VALUES IN PARENTHESES) AND THERMAL PARAMETERS ($\times$ 10^2)

Atom	*X*	*Y*	*Z*	*Beq*
C-1	1106(3)	11103(3)	7555(2)	558(17)
C-2	96(3)	11109(3)	6963(2)	584(18)
C-3	−137(3)	9956(3)	6671(2)	626(19)
C-4	977(3)	9301(3)	6434(2)	507(16)
C-5	1853(3)	9395(3)	7123(2)	419(13)
C-6	3084(3)	8914(2)	6989(2)	396(13)
C-7	3960(2)	7148(2)	6918(2)	349(11)
C(MeO)	1511(4)	10718(5)	8909(3)	872(29)
O(MeO)	676(2)	10687(3)	8276(1)	655(14)
O-5	2103(2)	10516(2)	7288(1)	434(9)
O-6	2911(2)	7809(2)	6801(1)	372(8)
C-Me-2	317(4)	11913(4)	6302(3)	803(25)
C-Me-4	1513(4)	9583(4)	5641(2)	673(21)
C-A-1	5017(3)	7676(2)	6493(1)	354(11)
C-A-2	5864(3)	8295(3)	6880(2)	428(13)
C-A-3	6739(3)	8841(3)	6457(2)	529(16)
C-A-4	6781(3)	8764(3)	5644(2)	562(17)
C-A-5	5917(4)	8181(3)	5258(2)	543(18)
C-A-6	5044(3)	7646(3)	5670(2)	456(13)
C-B-1	3663(3)	6036(2)	6579(2)	351(11)
C-B-2	2479(3)	5720(3)	6524(2)	421(13)
C-B-3	2212(3)	4680(3)	6258(2)	507(16)
C-B-4	3101(3)	3968(2)	6043(2)	494(15)
C-B-5	4268(3)	4299(3)	6086(2)	474(14)
C-B-6	4554(3)	5332(2)	6359(2)	428(13)
C-C-1	4144(3)	6962(2)	7812(2)	347(11)
C-C-2	5196(3)	6530(2)	8106(2)	419(13)
C-C-3	5321(3)	6312(2)	8906(2)	495(15)
C-C-4	4396(4)	6520(3)	9416(2)	577(18)
C-C-5	3339(3)	6940(3)	9132(2)	548(17)
C-C-6	3219(3)	7166(3)	8334(2)	458(14)

$|F_c|)^2$; $\omega = (\sigma^2(F) + a|F_0| + b|F_0|^3)^{-1}$ for $F \neq 0$, $\omega = c$ for $F = 0$. (R_w; $a = 0.00311$, $b = 0.38275$, $c = -0.21721$). The final refinement* yielded R ($\Sigma(||F_0| - |F_c||)/\Sigma|F_0|$) for 3064 independent reflections equal to 0.082, and for 2770 non-zero reflections equal to 0.065. The final atomic coordinates are given in Tables III and IV, and bond lengths and angles in Table V.

N.m.r. spectrometry. — N.m.r. spectra (^{1}H, 99.6 MHz; ^{13}C, 25.1 MHz, data points 8K) were obtained in the Fourier-transform mode in 5-mm tubes at 23°, using a JEOL FX-100 n.m.r. spectrometer. The high-field ^{1}H-n.m.r. spectrum

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***Full crystallographic details, including structure factors and anisotropic thermal parameters have been deposited with, and can 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/274/*Carbohydr. Res.*, 127 (1984) 171–179.**

TABLE IV

HYDROGEN ATOMIC COORDINATES (× 10^3) (E.S.D VALUES IN PARENTHESES) AND THERMAL PARAMETERS (× 10)

Hydrogen atom	*X*	*Y*	*Z*	*Biso*
H-1	141(3)	1183(2)	758(2)	26
H-2	−61(3)	1133(2)	731(2)	42
H-3A	−72(4)	993(3)	619(2)	64
H-3B	−57(3)	963(3)	700(2)	36
H-4	63(3)	845(3)	645(2)	54
H-5	152(3)	905(2)	760(2)	30
H-6-1	345(3)	928(3)	661(2)	27
H-6-2	360(2)	899(2)	754(1)	1
H-MeO-1	176(4)	1166(4)	892(3)	109
H-MeO-2	100(5)	1013(4)	948(3)	94
H-MeO-3	229(3)	1041(3)	884(2)	52
H-Me-2-1	37(4)	1271(4)	662(2)	90
H-Me-2-2	114(3)	1174(3)	600(2)	61
H-Me-2-3	−29(4)	1191(4)	589(2)	78
H-Me-4-1	191(5)	901(4)	541(2)	82
H-Me-4-2	85(3)	974(2)	526(2)	25
H-Me-4-3	195(3)	1029(3)	564(2)	36
H-A-2	578(2)	845(2)	747(2)	16
H-A-3	728(3)	927(3)	677(2)	34
H-A-4	743(3)	907(2)	540(1)	20
H-A-5	594(3)	825(2)	465(2)	25
H-A-6	448(3)	723(3)	534(1)	23
H-B-2	184(3)	632(3)	673(2)	37
H-B-3	135(3)	429(3)	631(2)	34
H-B-4	289(3)	327(3)	587(2)	36
H-B-5	493(3)	385(2)	593(1)	14
H-B-6	534(3)	562(3)	639(2)	31
H-C-2	594(3)	637(2)	781(2)	18
H-C-3	595(3)	594(2)	913(2)	25
H-C-4	455(3)	642(2)	996(2)	32
H-C-5	256(3)	701(3)	948(2)	28
H-C-6	240(2)	752(2)	811(1)	10

(400.5 MHz, data points 32K) of **1** was recorded in $CDCl_3$ solution (~10 mg/0.3 mL) with a JEOL FX-400 instrument. Although the 100-MHz ^{1}H-n.m.r. spectrum of **1** was poorly resolved, especially the ring-proton signals, the 400-MHz spectrum gave good dispersion for all protons. These were assigned by spin decoupling, and, except for the complex splitting-patterns for H-2 and H-4, the patterns for the other protons could be analyzed and all of the coupling constants determined (Table II). The signal assignments for carbon atoms were established by proton-selective, heteronuclear decoupling. The $^1J_{C\text{-}1,H\text{-}1}$ value was determined by a gated, ^{1}H-decoupler sequence to retain the n.O.e.; $\delta^{C}_{Me_4Si}$: 104.3 (C-1), 33.75 (C-2), 34.69 (C-3), 30.59 (C-4), 71.93 (C-5), 63.12 (C-6), 18.31 (Me-2), 15.91 (Me-4), 55.34 (MeO-), and 128–144 (trityl).

TABLE V

BOND LENGTHS AND ANGLES (E S D VALUES IN PARENTHESES)

Bond length (Å)			
C-1–C-2	1.518(6)	C-2–C-3	1.536)6)
C-3–C-4	1.548(5)	C-4–C-5	1 534(5)
C-5–O-5	1.446(4)	O-5–C-1	1.413(5)
C-1–O(MeO)	1.413(5)	O(MeO)–C(MeO)	1.428(7)
C-2–C-Mc-2	1.521(6)	C-4–C-Me-4	1.515(6)
C-5–C-6	1.527(4)	C-6–O-6	1.421(4)
O-6–C-7	1.452(3)	C-7–CA-1	1.538(4)
C-7–CB-1	1.531(4)	C-7–CC-1	1.547(4)
	Phenyl ring C–C (mean) 1.388(5)		
Bond angles (degrees)			
C-1–C-2–C-3	109.7(3)	C-2–C-3–C-4	115.7(3)
C-3–C-4–C-5	106.5(3)	C-4–C-5–O-5	110.2(3)
C-5–O-5–C-1	113.7(3)	O-5–C-1–C-2	112.8(3)
C-1–O(MeO)–C(MeO)	114.5(4)	O-5–C-1–O(MeO)	111.2(3)
C-2–C-1–O(MeO)	108.5(3)	C-1–C-2–C-Me-2	111.6(3)
C-3–C-2–C-Me-2	113.6(3)	C-3–C-4–C-Me-4	115.6(3)
C-5–C-4–C-Me-4	113.7(3)	C-4–C-5–C-6	116.2(3)
O-5–C-5–C-6	103.2(2)	C-5–C-6–O-6	106.6(2)
C-6–O-6–C-7	113.7(2)	O-6–C-7–CA-1	109.0(2)
O-6–C-7–C-B-1	106.2(2)	O-6–C-7–CC-1	109.1(2)
CA-1–C-7–CB-1	112.1(2)	CB-1–C-7–CC-1	105.2(2)
CC-1–C-7–CA-1	114.8(2)		
	Phenyl ring C–C–C (mean) 120.0(3)		

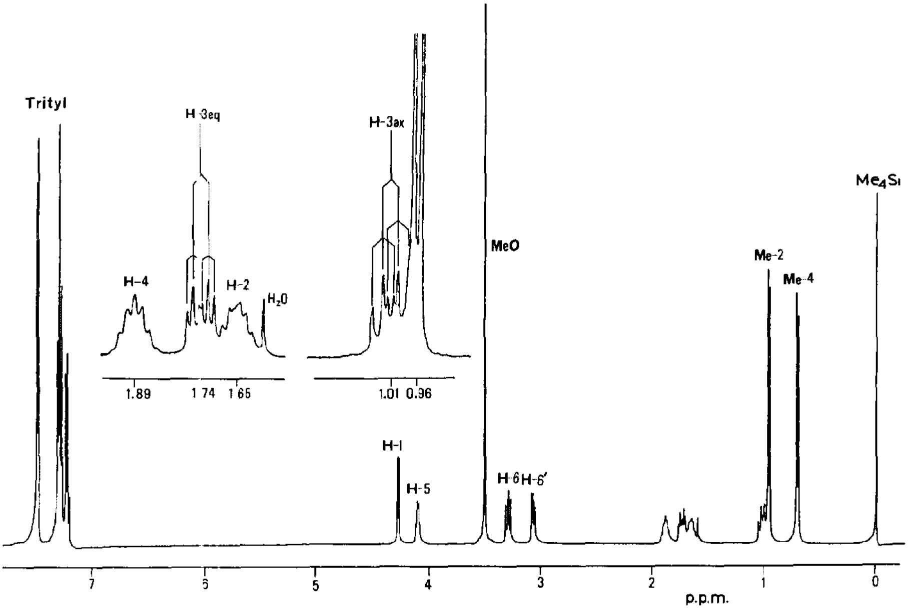

Fig. 2. The 400 MHz-^{1}H-n.m.r. spectrum of compound 1 in $CDCl_3$, and the spin-coupling patterns of H-3ax and H-3eq.

ACKNOWLEDGMENT

We are grateful to Dr. Yukishige Kitano at Torey Research Center for the X-ray crystallography of compound **1**.

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