Conformational Studies on the 1,2;5,6-Di-O-isopropylidene-D-hexoses

L. D. HALL

University of British Columbia, Vancouver 8, British Columbia

AND

S. A. BLACK, K. N. SLESSOR,¹ AND A. S. TRACEY Simon Fraser University, Burnaby, British Columbia

Received January 28, 1971²

Nuclear magnetic resonance studies on the 1,2;5,6-di-O-isopropylidene-D-hexofuranose sugars have provided information on the conformational preferences of the five-membered rings in these molecules. They appear to have strong conformational preferences rather than existing as freely pseudorotating systems. The furanose rings of the 3-deoxy-*ribo* and *lyxo* derivatives are found to preferentially exist in an envelope conformation in which C-4 is displaced from the plane of the ring. The *arabino* and *xylo* derivatives are found to be much less distorted, with preferred conformations approaching twist forms involving displacements of C-1 and -2. Substitution of various *endo* and *exo* groups at C-3 appears to have only minor influence on the parent furanose conformation.

Les études r.m.n. sur les sucres de la série des di-O-isopropylidène-1,2;5,6-D-hexofuranoses ont fourni des renseignements sur les conformations privilégiées des cycles à cinq dans ces molécules. Plutôt que d'être en pseudo-rotation libre, ces systèmes apparaissent sous des conformations nettement préférentielles. Les cycles furanoses des dérivés déoxy-3 *ribo* et *lyxo* existent préférentiellement dans la conformation enveloppe dans laquelle le C-4 est au dehors du plan du cycle. Les dérivés *arabino* et *xylo* sont nettement moins tordus et adoptent la conformation privilégiée proche des formes "twist" impliquant les déplacements des C-1 et -2. La substitution des divers groupes *endo* et *exo* sur le C-3 semble n'avoir qu'une influence mineure sur la conformation du furanose parent.

Canadian Journal of Chemistry, 50, 1912 (1972)

Introduction

The importance of 1,2;5,6-di-O-isopropylidene-D-hexoses as synthetic intermediates as well as an interest in conformational problems inherent in molecules containing a heterocyclic five-membered ring has prompted us to investigate the stereochemistry of these compounds and their 3-deoxy, 3-O-acetyl, and 3-keto analogues. Several specifically deuterated derivatives were prepared (1) since these allowed unambiguous assignment of proton resonance positions and thus aided in computer analysis of the n.m.r. spectra.

The inclusion of the 3-deoxy derivatives in this study is particularly important since the conformational properties of these compounds may be studied with the use of Dihedral Angle Estimation by the Ratio Method (DAERM) (2). DAERM is based on the assumption that the $\cos^2 \theta$ term of the Karplus equation (3) is not significantly affected by various atomic and molecular parameters such as ring size and electronegativity. These perturbations would then have their major effect on the size of the Karplus constants. Using this approach, a consistent and complete solution of the conformations of the four furan rings (1, 4, 7, 10) has been obtained (see Fig. 1). The preferred conformations of the di-O-isopropylidene-D-hexoses were obtained from correspondence in couplings between the deoxy sugars and their parent sugar derivatives.

In the following discussion, the section of the furan ring (a) is the focal point of the conformational discussions. In DAERM, ω is the projection angle of the methylene protons along the C_2 — C_3 or C_4 — C_3 bond (b). In a perfect tetrahedral system, ω is 120°. Internal angles between carbon atoms involved in a furan ring are known (4) to be smaller than the regular tetrahedral value of 109.5°. Assuming constant pcharacter in the carbon bonding, the angle subtended by the hydrogens on a methylene function of a furan ring will necessarily be greater than the tetrahedral angle (5). Recognizing this

¹To whom correspondence should be addressed.

²Revision received February 7, 1972.



FIG. 1. 1, 1,2;5,6-Di-*O*-isopropylidene-3-deoxy- α -Dxylo-hexose. 4, 1,2;5,6-Di-*O*-isopropylidene-3-deoxy- β -Darabino-hexose. 7, 1,2;5,6-Di-*O*-isopropylidene-3-deoxy- β -D-lyxo-hexose. 10, 1,2;5,6-Di-*O*-isopropylidene-3-deoxy- α -D-ribo-hexose.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by SAVANNAHRIVNATLABBF on 06/18/13 For personal use only.



effect, an ω value of 124° has been selected for the DAERM calculations as has a ratio k_1/k_2 of 0.9. Evidence is presented to show that considerable deviations of either the ratio or ω from their assigned values has minimal effect on conformational arguments.

Results

Spectral assignments were made on the basis of the easily recognized H-1 and -2 resonances at low field with assignment of the remaining protons being made by general procedures. Assignment of configuration to the methylene protons was made from the n.m.r. data and in one instance a specifically deuterated analogue was prepared to confirm these assignments. All n.m.r. spectra were computer simulated from first order data and an iterative fit to experimental data was performed using the LAOCN III program of Bothner-By and Castellano (6). The necessity of computer-analyzed data is indicated by a comparison of the first order (Fig. 2A), fitted (Fig. 2B), and experimental (Fig. 2C) spectra for 3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-arabino-hexose (4).

From a consideration of the general appearance of the n.m.r. spectra and their molecular architecture, the di-O-isopropylidene-hexoses are dealt with as four sets of compounds. These are the families derived from 3-substitution of the 3-deoxy- α -D-ribo-, - α -D-xylo-, - β -D-lyxo-, and - β -D-arabino-hexose derivatives. The chemical shift results which have not been published elsewhere (7, 8) are listed in Table 1 and the vicinal proton coupling parameters are listed in Table 2 (see also Fig. 3).

Conformational Assignments

1,2;5,6-Di-O-isopropylidene-α-D-xylo-hexose Derivatives

Considering first 3-deoxy-1,2;5,6-di-O-isopropylidene- α -D-xylo-hexose (1), four solutions for the couplings from H-2 to -3's are obtained from DAERM. In Table 3 and all subsequent discussion, J-1 is taken to be the *cis* coupling and θ -1 the corresponding angle.

Cases i and iii are both solutions for which few steric interactions within the molecule would be expected whereas cases *ii* and *iv* do not seem to be reasonable solutions since they represent conformations in which there is a large torsional twist on the C_2 — C_3 bond. This places the "tail" (C-5, -6, and their substituents) in a position where large steric interactions with the 1.2-Oisopropylidene group would be expected. The rather large values for the calculated Karplus constants also indicate that solutions *ii* and *iv* are not valid. DAERM analysis of the $J_{3_1,4}-J_{3_2,4}$ couplings indicates that cases vi and viii can be eliminated since the Karplus constants are unacceptably large. As only very severe distortions of the furan ring could possibly make *ii* and iv compatible with any but cases vi and viii, cases *ii* and *iv* now must be eliminated and only *i* and iii, and v and vii remain as acceptable solutions.

The remaining problem is to decide which set



FIG. 2. The n.m.r. spectra for 3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-*arabino*-hexose (4). A, Computer drawn spectrum on first order data. B, Computer drawn spectrum on computer fitted data. C, 100 MHz experimental spectrum.

of solutions is valid, *i.e.*, i/v or iii/vii. The former (i/v) indicates a conformation in which the "tail" involves less steric interactions but requires a rather severe distortion towards the envelope ²V form. The latter solution (iii/vii) appears less distorted although there are eclipsing interactions between the furan ring substituents.

To establish unequivocally the conformation of 1, deuteration at the H₃₁ position was carried out and the resulting disappearance of the large coupling (6.30 Hz) rather than the smaller (1.35 Hz) clearly indicates the conformation *iii/vii* is correct (see Fig. 4). This follows from the definition of J-1 and θ -1 as the *cis* coupling and dihedral angle respectively.

If the torsional twists of two adjacent bonds within a five-membered ring are defined, the geometry of the complete ring, within the limits of bond distortion, must be uniquely defined. Assignment of torsional angles between C-2, -3, and -4 thus indicates the position of C-1 and the ring oxygen. On this basis, the conformation of compound 1 has been assigned. 3-Deoxy-1,2;5,6di-O- α -D-xylo-hexose (1) prefers a conformation $V_0 \rightleftharpoons^{-1} T_0 \rightleftharpoons^{-1} V$, where the conformational symbols are those defined by Hall *et al.* (9). The degree of distortion from planarity is slight in this molecule and inspection of a molecular model indicates that the H₁—H₂ dihedral angle is probably not more than 10° and may well be closer to 0°.

Since the value of $\omega = 124^{\circ}$ has been estimated, the effect of varying ω over a 20° range was investigated. Evidence is presented in Table

HALL ET AL.: CONFORMATIONAL STUDIES ON FURANOSES

TABLE 1. Proton chemical shifts*

1,2;5,6-Di-O-isopropylidene	No.	Ηι	H ₂	H3	H₄	H ₅	Η _{6ι}	H_{6_2}
-a-D-gulose	2	4.23	5.35	5.73	6.09	5.49	6.32	6.37
-α-D-galactose	3	4.13	5.45	5.90	6.13	5.64	5.93	6.16
-β-D-altrose	5	4.11	5.46	5.60	6.18	5.74	5.90	6.08
-β-D-mannose	6	4.30	5.33	5.71	6.14	5.43	5.88	6.03
-β-D-idose	8	4.03	5.50	5.81	5.88	5.55	5.85	6.07
-β-D-talose	9	4.20	5.43	6.13	6.24	5.81	5.95	6.04
-α-D-allose	11	4.21	5.40	5.98	6.17	5.71	5.95	6.01
-α-D-glucose	12†	4.17	5.51	5.84	5.96	5.69	5.97	6.11
3-O-Acetyl-a-D-gulose	13	4.20	5.19	4.92	5.93	5.39	5.91	6.45
3-O-Acetyl-a-D-galactose	14	4.11	5.42	5.10	6.15	5.55	5.97	6.17
3-O-Acetyl-β-D-altrose	15	4.13	5.44	4.68	6.02	5.68	5.91	6.05
3-O-Acetyl-β-D-mannose	16	4.29	5.24	4.83	5.98	5.50	5.92	6.03
3-O-Acetyl-B-D-idose	17	4.04	5.50	4.82	←	—5.70 to	6.35—	\longrightarrow
3-O-Acetyl- β -D-talose	18	4.17	5.21	5.21	←	—5.80 to	6.13—	 →
3-O-Acetyl-a-D-allose	19	4.22	5.16	5.16	_	5.75	5.96	6.14
3-O-Acetyl-a-D-glucose	20	4.16	5.54	4.77	+	—–5.75 to	6.05—	
α-D-xylo-hexos-3-ulose	21	3.94	5.49		5.85	5.66	5.90	6.03
β-D-arabino-hexos-3-ulose	22	3.99	5.53		5.82	5.65 ←	<u> </u>	.0 - <u>→</u>
β -D-lyxo-hexos-3-ulose	23	3.88	5.61	_	←	5.56 to	6.03—	<u> </u> →
α-D-ribo-hexos-3-ulose	24	3.88	5.62	_	6.0	5.68	5.94	6.04
α-D-ribo-hexos-3-ulose-hydrate	25	4.18	5.72	_	6.08	5.57	5.86	5.91

*CDCl₃ solution with TMS as internal standard (10.0 τ).

†Measured in acetone- d_6 solution.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by SAVANNAHRIVNATLABBF on 06/18/13 For personal use only.



FIG. 3. Observed couplings in Hz for the furanose ring hydrogens of the 3-deoxy and 1,2;5,6-di-O-isopropylidene-D-hexoses (read from right to left C-1, C-2, C-3, and C-4).

4 which indicates that conformational assignments are not appreciably changed by varying ω through reasonable limits. Similarly, variation of the value k_1/k_2 , as has been indicated before

(2), results only in small changes in dihedral angle. Molecular models conveniently show that small changes in ω and the ratio result in little difference in the conformational assignment.

1915

	The second se		
and the second	•		
		All and a second s	
· · · ·			
			 • • • • • • • • • • • • • • • • • • •
1943/1949			
			the second s
		and the second	
1.8.7.7.4.8			
			the second s
			and a second
	· · ·		

TABLE 2. Proton coupling constants*

1,2;5,6-Di-O-isopropylidene	No.	J _{1,2}	$J_{2,3_1} J_{2,3_2}$	$J_{3_{1,3_{2}}}$	$J_{3_{1,4}}$ $J_{3_{2,4}}$	J _{4,5}	$J_{5,6_1}$	J _{5,62}	J _{61,62}	$J_{\rm H_3OH}^{\dagger}^{\dagger}$
-3-Deoxy-a-D-xylo-hexose	1	3.78	6.30 1.35	-14.20	8.45 4.13	8.14	6.71	6.91	-8.27	
-a-D-gulose	2	4.06	6.05		6.17	8.80	6.64	7.30	-8.66	6.3
-a-D-galactose	3	3.85	1.13		4.15	7.48	6.70	7.15	-8.67	4.0
-3-Deoxy-β-D-arabino-hexose	4	3.76	0.82 6.24	-14.74	2.63 8.45	9.65	6.13	5.61	-9.08	
$-\beta$ -D-altrose	5	3.90	0.60		1.94	9.51	6.25	5.49	8.94	4.0
$-\beta$ -D-mannose	6	4.17	5.83		5.52	8.36	6.41	5.69	-8.76	5.2
-3-Deoxy-β-D-lyxo-hexose	7‡	3.52	0.55 4.76	-13.11	4.52 10.62	5.51	6.56	6.81	-8.28	
$-\beta$ -D-idose	8	3.70	<0.5		2.92	5.31	6.89	6.93	-8.37	4.1
$-\beta$ -D-talose	9	3.80	5.05		8.77	4.97	6.50	7.61	-8.26	9.0
-3-Deoxy-α-D-ribo-hexose	10	3.68	4.79 0.41	-13.41	9.98 3.94	-		_		
-α-D-allose	11	3.73	5.01		8.66	4.55	6.61	6.68	-8.57	7.3
-a-D-glucose	12§	3.61	0.48		3.07	7.27	6.46	5.95	-8.60	4.3
3-O-Acetyl-α-D-gulose	13	4.11	5.58		6.66	9.04	6.55	7.19	-8.30	
3-O-Acetyl-α-D-galactose	14	3.8	~0.7		2.56	7.84	6.66	6.92	-8.66	
3-O-Acetyl- β -D-altrose	15	3.78	0.70		1.16	9.67	6.14	4.80	-9.03	
3-O-Acetyl- β -D-mannose	16	4.02	5.75	۰.	5.92	8.48	6.50	5.22	-8.42	
3-O-Acetyl-β-D-idose	17	3.8	0.6		2.3	—	—			
3-O-Acetyl-β-D-talose	18	3.8				_				
3-O-Acetyl-α-D-allose	19	3.7			_	—	6.5	5.8	8.6	
3-O-Acetyl-α-D-glucose	20	3.7	~0.5		~2.0					
x-D-xylo-hexos-3-ulose	21	4.4	N.C.		N.C.	6.08	6.39	6.91	-8.50	
β-D-arabino-hexos-3-ulose	22	4.3	N.C.		N.C.	~6.0				
β -D-lyxo-hexos-3-ulose	23	4.40	N.C.		N.C.	1.85	7.62	6.95	-8.41	
α-D-ribo-hexos-3-ulose	24	4.4	N.C.		N.C.	_				
α-D-ribo-hexos-3-ulose-hydrate	25	3.80	N.C.		N.C.	6.66	6.58	6.04	8.90	

*All spectra run in CDCl₃ at 100 MHz; J's in Hz; iterative computer analyzed couplings to second decimal. N.C. indicates no coupling present. †J_{H30H} not computer analyzed. ‡Measurements obtained from 220 MHz spectrum. §Acetone-d₆ solution.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by SAVANNAHRIVNATLABBF on 06/18/13 For personal use only.

TABLE 3.	DAERM	analysis*	of cour	olings	in 1
IADLE J.	DADINE	anary 313	OI COUL	JIIIES	111 1

Protons coupled	Case	Obsd. J-1	Obsd. J-2	Calcd. θ -1	Calcd. θ -2	Calcd. k_1	Calcd. k_2
H_2, H_{3_1}, H_{3_2}	i	1.35	6.30	58	182	5.93	6.59
	ii	1.35	6.30	72	52	17.27	19.19
	iii	6.30	1.35	6	118	6.65	7.39
	iv	6.30	1.35	52	72	17.27	19.19
H_{3_1}, H_{3_2}, H_4	υ	4.13	8.45	43	167	8.27	9.19
	vi	4.13	8.45	67	57	29.21	32.46
	vii	8.45	4.13	8	132	8.90	9.89
	viii	8.45	4.13	57	67	29.21	32.46

 $\omega = 124^{\circ}; k_1/k_2 = 0.9.$





FIG. 4. DAERM analysis of 3-deoxy-1,2;5,6-di-O-isopropylidene- α -D-xylo-hexose (1).

1,2;5,6-Di-O-isopropylidene- α -D-gulose (2) and - α -D-galactose (3) are assigned the same conformational preferences as the 3-deoxy analogue (1) on the basis of the close correspondence in n.m.r. coupling parameters for these three compounds. A large coupling of about 8 Hz for the $J_{4,5}$ couplings observed for this family indicates a rotational preference for the



Calculated Karplus constants: C_2 — C_3 $k_1 = 6.79; k_2 = 7.55$ C_3 — C_4 $k_1 = 8.73; k_2 = 9.70$

FIG. 5. Conformation of 3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-arabino-hexose (4).

"tail". Obviously this preference is not regulated by hydrogen bond formation to the "tail" since the deoxy xylo-hexose (1) and galactose (2) derivatives cannot form such a bond.

1,2;5,6-Di-O-isopropylidene-β-D-arabinohexose Family

The DAERM solutions for 3-deoxy-1,2;5,6di-O-isopropylidene- β -D-arabino-hexose (4) are shown in Fig. 5 and suggest the conformational preferences ${}^{0}T_{1} \rightleftharpoons V_{1} \rightleftharpoons {}^{2}T_{1}$. The distortion from planarity, as in the xylo-hexose case, is only slight. Again the 1,2 dihedral angle is probably less than 10–12°.

The coupling results, displayed in Table 2, strongly suggest that the conformational preferences of 1,2;5,6-di-O-isopropylidene- β -D-altrose (5) and - β -D-mannose (6) are not different from the 3-deoxy analogue (4). It is again clear that the "tail" prefers an orientation independent of possible hydrogen bonding interactions.

1,2;5,6-Di-O-isopropylidene-β-D-lyxo-hexose Derivatives

DAERM analysis of the 2,3 and 3,4 couplings of 3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-

1917

CANADIAN JOURNAL OF CHEMISTRY. VOL. 50, 1972

 ω°	k ₁ /k ₂	J _{2,31}	J _{2,32}	$\theta_{2,3_1}$	$\theta_{2,3_2}$	k_1	
130	0.9	6.30	1.35	13	117	6.9	7.7
124	0.7	6.30	1.35	10	114	6.8	9.7
124	0.8	6.30	1.35	8	116	6.7	8.4
124	0.9	6.30	1.35	6	118	6.6	7.4
124	1.0	6.30	1.35	4	120	6.6	6.6
120	0.9	6.30	1.35	2	118	6.6	7.3
110	0.9	6.30	1.35	8	118	6.7	7.4
		J _{31,4}	J _{32,4}	$\theta_{3_{1,4}}$	$\theta_{3_{2,4}}$		
130	0.9	8.45	4.13	2	132	8.7	9.7
124	0.7	8.45	4.13	2	126	8.7	12.5
124	0.8	8.45	4.13	5	129	8.8	11.0
124	0.9	8.45	4.13	8	132	8.9	9.9
124	1.0	8.45	4.13	10	134	9.0	9.0
120	0.9	8.45	4.13	11	131	9.1	10.1
110	0.9	8.45	4.13	19	129	9.8	10.9

TABLE 4. Variation of ω and k_1/k_2 in dihedral angle estimation*

*DAERM analysis of couplings into the methylene function of 3-deoxy-1,2;5,6-di-O-isopropylidene-α-D-xylo-hexose (1).

TABLE 5. DAERM analysis* of couplings in 3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-lyxo-hexose (7)

Protons coupled	Case	Obsd. J-1	Obsd. J-2	Calcd. θ -1	Calcd. θ -2	Calcd. k_1	Calcd. k_2
H_2, H_{3_1}, H_{3_2}	i	0.55	4.76	65	189	4.65	5.17
	ii	0.55	4.76	75	49	11.87	13.19
	iii	4.76	0.55	12	112	5.26	5.85
	iv	4.76	0.55	49	75	11.87	13.19
H ₃₁ , H ₃₂ , H ₄	v	4.52	10.62	46	170	10.09	11.21
	vi	4.52	10.62	68	56	34.61	38.46
	vii	10.62	4.52	5	129	10.98	12.20
	viii	10.62	4.52	56	68	34.61	38.46

 $*\omega = 124^{\circ}; k_1/k_2 = 0.9.$



FIG. 6. DAERM analysis of 3-deoxy-1,2;5,6-di-O-iso-propylidene- β -D-lyxo-hexose (7).

lyxo-hexose (7) are found in Table 5. Case ii can be rejected as a reasonable solution on the basis of the extreme distortion of the furan ring necessary to satisfy the angles. Cases vi and viii can be rejected because of their unacceptably large Karplus constants. Rejection of cases vi and viii leaves case i as an unacceptable solution as no reasonable conformation is possible from the solution of case *i* with *vii*. Similarly, case *vii* is not compatible with *iii* or *iv* as a *trans* coupling from H₂ to an H₃ proton must have a corresponding cis coupling from that H₃ proton to H₄. There remain two reasonable solutions, iii/v, or iv/v (Fig. 6). Conformation iii/v is taken as the correct conformation because iv/v requires a severe twisting in the furan ring and also the Karplus constants calculated for *iii/v* agree well with those calculated for the xylo (1) and arabino (4) derivatives at these positions. Thus,

HALL ET AL.: CONFORMATIONAL STUDIES ON FURANOSES



O Carbon • Oxygen O Chlorine FIG. 7. Conformation of 3-chloro-3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-idose in the crystalline state.

having defined the torsional angles about C-2, -3, and -4, the conformation of 7 must be ${}^{4}T_{3} \rightleftharpoons {}^{4}V \rightleftharpoons {}^{4}T_{0}$. As in the previous cases the correspondence in couplings (Table 2) strongly suggests that replacement of hydrogen by hydroxyl at position 3 has little effect on the conformational preference.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by SAVANNAHRIVNATLABBF on 06/18/13 For personal use only.

The i.r. studies (1) indicate that a strong hydrogen bond between the "tail" and 3-OH of the idose derivative (8) is possible. The 4.1 Hz coupling into the hydroxyl group is consistent with formation of such a bond and in fact, such a bond would effectively lock the conformation into that proposed. The 9.0 Hz coupling into the hydroxyl group of 1,2;5,6-di-O-isopropylidene- β -D-talose (9) is consistent with hydrogen bond formation to the 2-oxygen of the 1,2-O-isopropylidene ring. All members of the β -D-lyxohexose family are thus expected to have the ${}^{4}T_{3} \rightleftharpoons {}^{4}V \rightleftharpoons {}^{4}T_{0}$ conformational preference. A recently completed crystal structure (10) of 3-chloro-3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-idose (Fig. 7) clearly shows C-4 to be out of the plane. A computer drawn representation of the atomic coordinates clearly indicates the ⁴V conformation in the crystalline state.

1,2;5,6-Di-O-isopropylidene-α-D-ribo-hexose Derivatives

The DAERM calculations on the n.m.r. results obtained from this compound indicate that 3-deoxy-*ribo*-hexose (10) has the ${}^{3}T_{4} \rightleftharpoons V_{4} \rightleftharpoons {}^{0}T_{4}$ conformational preference. The similarity of the couplings reported in Table 2 indicates that the *endo* (11) and *exo* (12) hydroxylated derivatives of 3-deoxy-*ribo*-hexose (10) have



FIG. 8. Conformation of 3-deoxy-1,2;5,6-di-O-isopropylidene- α -D-*ribo*-hexose (10).

a conformational preference identical to the parent compound. The 7.3 Hz coupling into the hydroxyl group of 1,2;5,6-di-O-isopropylidene- α -D-allose (11) is in agreement with an *anti* arrangement of H_3 and hydroxyl proton (11). This orientation of the hydroxyl group and the suggested conformation are completely consistent with the proposed hydrogen bond formation between the C-3 hydroxyl and the C-2 oxygen of the 1,3-dioxolane ring (1). In the allose compound the coupling constant $J_{4,5}$ of 4.55 Hz may reflect freedom of rotation of the "tail" whereas in glucose the coupling constant, $J_{4.5}$ of 7.3 Hz, indicates a more preferred conformer. All observations are in complete agreement with the assignment of ${}^{3}T_{4} \rightleftharpoons V_{4} \rightleftharpoons {}^{0}T_{4}$ for the conformational preferences of these ribohexose derivatives (Fig. 8).

Acetyl and Keto Derivatives

The 3-O-acetyl- and 3-keto-derivatives of the 1,2;5,6-di-O-isopropylidene-D-hexoses yield much more complex spectra than those obtained from the parent compounds. Complete analysis was not achieved in several cases. The results that were obtained are given in Table 1 (chemical shifts) and Table 2 (coupling constants).

Comparisons of the coupling data in Table 2 and the values presented in Fig. 3 appear to indicate that there is little change in conformation of the furan ring on acetylation of the C-3 hydroxyl group. It should be noted, however, that on acetylation of 1,2;5,6-di-O-isopropylidene- α -D-galactose (3), the position 3 to 4 coupling drops from 4.15 to 2.56 Hz. At the same time the position 2 to 3 coupling goes from 1.13 to 0.7 Hz. Comparison of these couplings with those obtained from the *arabino*-hexose family (4, 5, 6) indicates that the molecule shifts

1919

CANADIAN JOURNAL OF CHEMISTRY. VOL. 50, 1972

TABLE 6. Long-range couplings*								
1,2;5,6-Di-O-isopropylidene	No.	J _{1,3}	J _{2,4}					
β-D-altrose	5	_	~0.4					
α-D-glucose	12	_	~ 0 .					
3-Q-acetyl- β -D-altrose	15	0.64	0.41					
$3-O$ -acetyl- β -D-idose	17		~ 0 .					
α-D-xylo-hexos-3-ulose	21	N.C.	0.8					
β-D-arabino-hexos-3-ulose	22	N.C.	0.9					
β -D-lyxo-hexos-3-ulose	23	N.C.	1.15	1				
3-O-acetyl- β -D-idose α -D-xylo-hexos-3-ulose β -D-arabino-hexos-3-ulose β -D-lyxo-hexos-3-ulose	17 21 22 23	— N.C. N.C. N.C.	~0. 0.8 0.9 1.15					

*Measured in CDCl₃, values in Hz; N.C., no coupling observed; (--) indicates a coupling not measured.

its conformational preference after acetylation, from the $V_0 \rightleftharpoons^1 T_0 \rightleftharpoons^1 V$ of the parent to ${}^1 T_0 \rightleftharpoons^1 V \rightleftharpoons^1 T_2$ of the derivative. Similar results are obtained for the benzoylated derivative, but not for 3-fluoro-3-deoxy-1,2;5,6-di-*O*-isopropylidene- α -D-galactose (12).

Little information can be gained from the sparse results on the 3-keto compounds. A significant increase in the coupling $J_{1,2}$ to about 4.4 Hz in these compounds (21-24) can be attributed to the effect of carbonyl group electronegativity $(J_2^{\rm V})$ as described by Cohen and Schaefer (13). The ketones (21-24) exhibited rather large long-range couplings from H₂-H₄ across the carbonyl function. Long-range couplings were found to be a general phenomenon in the 1,2;5,6-di-O-isopropylidene-D-hexose system. Both H_1-H_3 cis and H_1-H_3 trans couplings were observed with the latter being generally larger. Double resonance experiments were used to confirm some of the assignments and in one case, the H_1-H_3 trans coupling in 3-deoxy-3,4-dideutero-1,2;5,6-di-O-isopropylidene- α -D-galactose (Fig. 4) of -0.55 Hz was determined. Sign determination was simplified by deuterium decoupling. trans H_2-H_4 couplings were not observed, although H2-H4 cis couplings were quite common. Since both trans and cis H₂-H₄ long-range couplings were observed for the 3-keto-derivatives it seems likely that the preceding results are simply a reflection of the difference in ring conformations for the two ring systems. Table 6 lists some of the long range couplings which were observed.

"Tail" Conformational and Rotational Preference

In order to better evaluate the possible influence of hydrogen bonding on the orientation of the "tail" the temperature dependence of



FIG. 9. Plot of log K^{T_1}/K^{T_2} vs. $1/T_1 - T_2$ for 1,2;5,6di-O-isopropylidene- α -D-glucose (12) in the temperature range -14.1 to +19.5°; slope = 693.

hydrogen bond formation was investigated for several di-O-isopropylidene derivatives. The i.r. spectra of 1,2;5,6-di-O-isopropylidene- β -Dmannose (1) (6) and $-\beta$ -D-idose (8) revealed no observable shift in equilibrium upon varying the temperature from -30 to $+50^{\circ}$. The spectrum of 1,2;5,6-di-O-isopropylidene- α -D-glucose (12) indicated a continuous change with temperature. A ΔH of -3.1 ± 0.2 kcal/mol was calculated (Fig. 9) for this process, a value typical of H—O...H systems (14). The presence of free hydroxyl in the *gluco* derivative (12) and in the ribo-hexofuranos-3-ulose gem diol (25) and the presence of a second possible hydrogen bond in the *manno* derivative (6) indicate the presence of alternate forces which may provide some rotameric preference to the "tail". That such forces are present is indicated by many of the $J_{4,5}$ couplings, the magnitude of which cannot possibly represent freely rotating systems.

DAERM (2) calculations were performed on the position 5 to 6 couplings in order to evaluate the twist in the dioxolane ring of the "tail". The results are seen in Table 7 and indicate that the "tail" is distorted from planarity and that this distortion is $21-25^{\circ}$ for all the compounds investigated. The X-ray crystal structure of 3-

1920

1,2;5,6-Di-O-isopropylidene	No.	Obsd. J-1	Obsd. J-2	Calcd. <i>θ</i> -1	Calcd. θ -2	Calcd. k_1	Calcd. k_2
-3-deoxy- α -D-xylo-hexose	1	6.91	6.72	24	148	8.7	9.6
-a-D-gulose	2	7.20	6.50	23	147	8.8	9.7
-α-D-galactose	3	7.15	6.70	23	147	8.8	9.8
-3-deoxy-β-D-arabino-hexose	4	5.70	5.71	25	149	7.3	8.1
-β-D-altrose	5	6.25	5.50	22	146	7.6	8.4
-β-D-mannose	6	6.41	5.70	22	146	7.8	8.7
-β-D-idose	8	6.93	6.89	25	149	8.8	9.8
- β -D-talose	9	7.61	6.50	21	145	9.1	10.1
-α-D-allose	11	6.68	6.61	25	149	8.5	9.4
-α-D-glucose	12	6.50	5.95	23	147	8.0	8.9

TABLE 7. DAERM* calculations on the 5,6-O-isopropylidene group analysis of $J_{5,6_1}$, $J_{5,6_2}$ couplings

 $\omega = 124^{\circ}, k_1/k_2 = 0.9.$

chloro-3-deoxy-1,2;5,6-di-O-isopropylidene- β -D-idose (Fig. 7) shows a twist of 25° in the $O_5-C_5-C_6-O_6$ dihedral angle. Calculations on X-ray data from 3-deoxy-3,4-C-(dichloromethylene)-1,2;5,6-di-O-isopropylidene- α -Dgalactofuranose (15), shows a twist of 24.9° for the "tail". Both these results are in excellent agreement with the n.m.r. conclusions.

Inspection of Table 7 reveals a surprising variation in the Karplus constants, particularly since ring size and substitution patterns in the "tail" are identical for all ten compounds. Recognizing that the n.m.r. spectra of D and L isomers are identical then these derivatives may be compared as five sets of C-5 isomers (D- C_5) D-C₄ vs. L-C₅ D-C₄). The sets are gluco/ido; allo/talo; altro/galacto; manno/gulo; and 3deoxy-arabino/3-deoxy-xylo, and in each case the first member of each set has the lower Karplus constant. Inspection of the DAERM results for couplings from H_4 to the H_{31} , H_{32} protons in the 3-deoxy derivatives shows an identical pattern, indicating a proximity effect due to a preferential orientation of the "tail". The effect of solvent on Karplus constants, suggested in a previous paper (2), may well be a more general example of such proximity effects.

The magnitude of the coupling, $J_{4,5}$, for the *xylo*- and *arabino*-hexose derivatives (13–16), indicates that the rotameric preference of the "tail" is probably not significantly affected by the presence of the acetoxy group at C-3. It should be noted, though, that a change of rotameric preference from *anti* to eclipsed or vice versa would not have an appreciable effect on the n.m.r. couplings observed. H₄ to H₅ couplings for the 3-uloses (21, 22, 25) of 6–7 Hz

indicate a reasonable degree of conformational purity of an eclipsed or *anti* nature. The $J_{4,5}$ (1.85 Hz) coupling in the *lyxo* ketone (23) is the only coupling observed for this position definitive enough to indicate a preferred rotamer other than the eclipsed or *anti* configurations previously discussed.

Discussion

The n.m.r. parameters obtained from spectra of flexible molecules represent a weighted average of the parameters of all individual conformers present. This allows two interpretations of a conformation assigned to a potentially flexible molecule from n.m.r. data. Either the molecule has a strong preference for the pseudorotational segment predicted or two or more conformations exist whose coupling parameters time-average to give the observed values resulting in a time-averaged conformational assignment.

In the case of the *ribo* and *lyxo* derivatives it is difficult to see how the presence of a significant percentage of conformations other than those predicted could provide *trans* H_2-H_3 couplings of about 0.5 Hz and at the same time retain large *trans* couplings H_3-H_4 of about 10 Hz.

This question is not so easily resolved in the case of the xylo and arabino derivatives. The presence of the large *cis* position 3 to 4 couplings (8.5 Hz) indicates a high percentage of a single conformer since alternate conformers could only reduce this value. It should be noted that if this value is already partially reduced from some higher value the conformational assignment would not be altered. Low temperature n.m.r. studies on the 3-deoxy-xylo and arabino

derivatives ($\sim -60^{\circ}$) showed no significant deviations from the spectra obtained at room temperature. It seems unlikely, then, that the spectra of any of these compounds represent any significant degree of conformational averaging.

In this work the dihedral angle between H_1 and H_2 has been assigned a value of $10-12^\circ$ or less based on the assigned conformational preference. Previous studies (16) have assigned values of from $40-50^{\circ}$ on the basis of coupling constants. The smaller value of $0-12^{\circ}$ is in excellent agreement with X-ray crystal structures exhibiting this structural feature. The crystal structure of the chloroidose derivative, previously mentioned, indicated a torsional angle of about 4° for the $O_1 - C_1 - C_2 - O_2$ dihedral angle. Without gross deformation of the tetrahedral geometry about carbons one and/or two, the H_1 — H_2 dihedral angle must be of this order. The chloro derivative exhibits a typical coupling, $J_{1,2}$ of 3.6 Hz in deuterochloroform solution. Other X-ray structure determinations confirm this work with $O_1 - C_1 - C_2 - O_2$ dihedral angles of 4.6 (15) and 9.0° (17).

It is difficult to ascertain whether the differences in ring conformation for the two systems (*cis* or *trans* ring substitution) are important chemically since the overriding effect is undoubtedly that of *cis* or *trans* substitution. On the other hand it does appear that the "tail" can have a significant effect on the chemistry of these compounds. This is indicated in that the times required for enol acetate formation from the parent ketones (7) are faster for the D-C₅, D-C₄ configuration than for the D-C₅, L-C₄ configuration.

This effect is readily explained if it is assumed that the preferred rotamer of the "tail" is one in which the C-5 oxygen preferably sits on the same side of the molecule as the C-1 and ring oxygens, that is, O_5 prefers to sit gauche to the ring oxygen. The large H_4-H_5 couplings mean, then, that the C-4 and -5 protons are near eclipsed in the D-C₅, D-C₄ case and near anti in the D-C₅, L-C₄ case. The small 1.85 Hz coupling observed for the lyxo ketone (23) indicates a situation in which the gauche interaction puts the C₄--C₅ protons in a near 90° relationship. Thus both gauche rotamers are suggested from n.m.r. evidence. A gauche interaction of this type would leave the C-4 position more open to attack by base in the D-C₅, D-C₄ case and provide more steric interaction to the approach of base in the alternate case.

The i.r. spectra of ref. 1 are completely in accord with the above explanation. The gulose and idose derivatives at first sight seem anomalous with complete hydrogen bonding to the "tail" being indicated by the i.r. spectra. This hydrogen bonding is, of course, not possible if the gauche O_5 -ring oxygen configuration is present. Optical rotatory dispersion studies of the gulose derivative in various solvents indicate a major change in conformation on going from a solvent such as chloroform to water. The positive curve of the former case $[\alpha]_D^{20} + 10^\circ$ (c, 0.4 CHCl₃) being replaced by a strongly negative curve in the second case $[\alpha]_D^{20} - 34^\circ$ (c, 0.4 H₂O) (18). Interestingly enough the n.m.r. spectrum changes very little in D₂O indicating that the "tail", now no longer forming a hydrogen bond to the C-3 oxygen, has simply rotated to the conformation preferred in the absence of such a bond (i.e., from an eclipsed to an anti configuration of the C-4 and -5 protons). Optical rotatory dispersion studies of the idose derivative (8) showed a similar effect. Although the curve did not change sign when the solvent was changed to water, it went from a moderately positive curve to a very strongly positive curve, an effect in accord with the above explanation.

Conclusions

The studies on the conformations of the 1,2;5,6-di-O-isopropylidene-D-hexoses demonstrate clearly that the furan ring conformation is determined by the substitution pattern of the 1,2-O-isopropylidene unit and the "tail". If these units are substituted on the furan ring in a cis fashion, the furan ring tends to be flattened with one or two of the atoms C-1, -2, and the ring oxygen slightly displaced from the mean plane. Thus the xylo and arabino derivatives have conformational preferences most readily described as $V_0 \rightleftharpoons^1 T_0 \rightleftharpoons^1 V$ and ${}^0T_1 \rightleftharpoons V_1 \rightleftharpoons^2 T_1$, respectively. If, however, the units are substituted on the furan ring in a *trans* fashion, the ring is considerably distorted with one or two of the atoms C-3, -4, or the ring oxygen displaced in the preferred conformers. Thus the ribo and lyxo derivatives have as conformation preferences the ${}^{3}T_{4} \rightleftharpoons V_{4} \rightleftharpoons {}^{0}T_{4}$ and ${}^{4}T_{3} \rightleftharpoons {}^{4}V \rightleftharpoons {}^{4}T_{0}$ conformations respectively. Two X-ray crystal structures of compounds exhibiting this

trans arrangement (10, 17) show C-4 to be the atom displaced. This work indicates an $H_1 - H_2$ dihedral angle less than 10 to 12°, a result also in accord with X-ray analysis of related molecules.

Substitution of endo or exo groups at the C-3 position does not strongly influence the conformational preference of the furan ring. These derivatives generally show the same conformational preference exhibited by their parent deoxy analogues, although the cis substituted (xylo and arabino) derivatives seem more susceptible to influence from a substituent at C-3.

DAERM calculations on the "tail" $(C_5 - C_6)$ and substituents) have also been informative. The "tails" of the compounds investigated were twisted in the same manner and to the same extent ($\sim 24^{\circ}$). The sense and extent of this twist have been confirmed by two crystal structures (15, 10). The H_4 - H_5 coupling parameters also indicate that the "tails" of these compounds have definite preferred rotamers. The n.m.r. results can be explained in terms of rotamers in which the ring oxygen and C-5 oxygen are preferably gauche to one another. This explanation correlates well with rates of enol acetate formation (7), with hydrogen bond formation, and with optical rotatory dispersion studies (18). This work lends strong support to the recently proposed "gauche effect" (19) and is in complete agreement with it.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by SAVANNAHRIVNATLABBF on 06/18/13 For personal use only.

Experimental

Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

All compounds except 3-deoxy-1,2;5,6-di-O-isopropylidene-D-lyxo-hexose (7) gave spectra from a Varian HA-100 MHz spectrometer which were analyzable. Compound 7 was run on the Varian HR-220 MHz spectrometer of the National Research Council of Canada in Toronto, Ontario, All spectra were measured in deuterochloroform solution with TMS as an internal reference.

All spectra were analyzed using the LAOCN III n.m.r. program of Bothner-By and Castellano (6). Hydrogen bonding studies were performed in matched, jacketed cells of 1 cm path length on a Beckman IR 12. The absorbance traces were resolved on a Dupont 310 Curve Resolver to obtain the fraction of bonded and non-bonded material present.

Preparation of compounds 1, 4, 13, and 16 has been described in ref. 7, 7 and 10, in ref. 8, and 2, 3, 5, 6, 8, 9, 11, 12, 21-25 in ref. 1 and refs. therein.

cis-3,4-Dideutero-3-deoxy-1,2;5,6-di-O-isopropylidene- α -D-xylo-hexose

3-Deoxy-1,2;5,6-di-O-isopropylidene-a-D-erythro-hex-3enose (2 g), prepared by the method of Weygand and Wolz (20) was dissolved in 95% ethanol (75 ml) and reduced over palladium black with deuterium at atmospheric pressure. After uptake of deuterium had ceased, t.l.c. (ethyl ether : toluene, 2:1) indicated the reaction complete. The reaction mixture was filtered and evaporated to a sirup which crystallized spontaneously. Recrystallization from petroleum ether (65-110°) yielded long needles (1.8g), m.p. $79-80^{\circ}$, $[\alpha]_{D}^{22} - 27^{\circ}$ (c, 0.82 CHCl₃), lit. (7, 20) m.p. 81°, $[\alpha]_{\rm D} - 38.1^{\circ}$ (c, 4.11 ethanol).

3-O-Acetyl-1,2;5,6-di-O-isopropylidene-α-D-glucose (20)

1,2;5,6-di-O-isopropylidene- α -D-glucose (12) (1 g) was dissolved in a mixture of pyridine (5 ml) and acetic anhydride (2 ml). The solution was kept overnight at room temperature. Repeated co-evaporation of the solution with toluene gave a slightly orange sirup free of acetylating reagents. The sirup was dissolved in chloroform (75 ml) treated with charcoal, filtered, and evaporated. The residue crystallized readily and was recrystallized from petroleum ether (65-110°) to yield 950 mg of product melting at 59–60°; $[\alpha]_D^{22}$ -38.4 (c, 1.07 CHCl₃), lit. (21) m.p. 62°, $[\alpha]_D^{24}$ -38.5 (c, 1.3 CHCl₃).

3-O-Acetyl-1,2;5,6-di-O-isopropylidene-a-D-allose (19)

Prepared from 11 in the same way as 20; m.p. 74-75° $[\alpha]_D^{22}$ +100.6° (c, 0.73 CHCl₃), lit. (22) m.p. 75.5-76.5°, $[\alpha]_{\rm D}^{20}$ + 107.6 (c, 1.0 CHCl₃).

3-O-Acetyl-1,2;5,6-di-O-isopropylidene-β-D-idose (17)

Prepared from 8 in the same way as 20; m.p. 75.5-76.5°, $[\alpha]_{D}^{22}$ + 16.6 (c, 0.67 CHCl₃), lit. (23) for the -L-isomer, m.p. 77-78°, $[\alpha]_{D}^{15} - 12^{\circ}$ (c, 0.75 CHCl₃).

Anal. Calcd. for C14H22O7: C, 55.63; H, 7.28. Found: C, 55.82; H, 7.30.

3-O-Acetyl-1,2;5,6-di-O-isopropylidene-β-D-talose (18)

Prepared from 9 in the same way as 20 except that 18 did

not crystallize, $[\alpha]_D^{22} - 7.4^\circ$ (c, 0.38 CHCl₃). Anal. Calcd. for C₁₄H₂₂O₇: C, 55.63; H, 7.28. Found: C, 55.84; H, 7.32.

3-O-Acetyl-1,2;5,6-di-O-isopropylidene-α-D-galactose (14) Prepared from 3 in the same way as 20 except that 14 did not crystallize, $[\alpha]_{D}^{22} - 7.5^{\circ}$ (c, 1.47 CHCl₃).

Anal. Calcd. for C14H22O7: C, 55.63; H, 7.28. Found: C, 55.50; H, 7.15.

3-O-Acetyl-1,2;5,6-di-O-isopropylidene-β-D-altrose (15)

Prepared from 5 in the same way as 20. The m.p. 92-93°, $[\alpha]_D^{22} + 14.4^\circ$ (c, 0.68 CHCl₃).

Anal. Calcd. for C14H22O7: C, 55.63; H, 7.28. Found: C, 55.48; H, 7.37.

We are pleased to acknowledge the financial support of the National Research Council of Canada in the form of operating grants to L.D.H. and K.N.S.

- 1. K. N. SLESSOR and A. S. TRACEY. Can. J. Chem. 47, 3989 (1969).
- 2. K. N. SLESSOR and A. S. TRACEY. Can. J. Chem. 49, 2874 (1971).
- 3. M. KARPLUS. J. Chem. Phys. 30, 11 (1959).
- J. B. HENDRICKSON. J. Am. Chem. Soc. 83, 4537 4. (1961).

CANADIAN JOURNAL OF CHEMISTRY. VOL. 50, 1972

- E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL, and G. A. MORRISON. Conformational analysis. Interscience Publishers, Inc. New York, N.Y. 1965. p. 448.
- A. A. BOTHNER-BY and S. M. CASTELLANO. Computer programs for chemistry. Vol. 1. *Editor* D. F. DeTar. W. A. Benjamin Inc. New York, N.Y. 1968. p. 10.
- 7. K. N. SLESSOR and A. S. TRACEY. Can. J. Chem. 48, 2900 (1970).
- 8. C. R. HAYLOCK, L. D. MELTON, K. N. SLESSOR, and A. S. TRACEY. Carbohydr. Res. 16, 375 (1971).
- 9. L. D. HALL, P. R. STEINER, and C. PEDERSEN. Can. J. Chem. 48, 1155 (1970).
- 10. F. W. B. EINSTEIN and K. N. SLESSOR. Can. J. Chem. 50, 93 (1972).
- 11. R. R. FRASER, M. KAUFMAN, P. MORAND, and G. GOVIL. Can. J. Chem. 47, 403 (1969).
- 12. J. S. BRIMACOMBE, A. B. FOSTER, R. HEMS, J. H. WEST-WOOD, and L. D. HALL. Can. J. Chem. 48, 3946 (1970).
- 13. A. D. COHEN and T. SCHAEFER. Molec. Phys. 10, 209 (1966).

- 14. L. P. KUHN and R. A. WIRES. J. Am. Chem. Soc. 86, 2161 (1964).
- 15. J. S. BRIMACOMBE, P. A. GENT, and T. A. HAMOR. J. Chem. Soc. B, 1566 (1968).
- 16. R. J. ABRAHAM, L. D. HALL, L. HOUGH, and K. A. MCLAUCHLAN. J. Chem. Soc. 3699 (1962).
- 17. J. S. BRIMACOMBE, J. G. H. BRYAN, and T. A. HAMOR. J. Chem. Soc. B, 514 (1970).
- C. R. HAYLOCK. Optical rotary dispersion of the 1,2;5,6-di-O-isopropylidene-D-hexofuranoses. B.Sc. Thesis. Simon Fraser University, Burnaby, B.C. 1969.
- 19. S. WOLFE, A. RAUK, L. M. TEL, and I. G. CSIZMADIA. J. Chem. Soc. (B), 136 (1971).
- 20. F. WEYGAND and H. WOLZ. Chem. Ber. 85, 256 (1952).
- 21. I. E. MUSKAT. J. Am. Chem. Soc. 56, 2449 (1934).
- 22. M. HAGA, M. TAKANO, and S. TEJIMA. Carbohydr. Res. 14, 237 (1970).
- 23. N. BAGGETT and R. W. JEANLOZ. J. Org. Chem. 28, 1845 (1963).