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CHEMICAL SHIFTS OF THE METHYL GROUPS IN DI-*O*-ISOPROPYLIDENE FURANOSES, AND THEIR RELATIONSHIP TO MOLECULAR CONFORMATION AND SITE OF RING FUSION. SPIN–LATTICE RELAXATION MEASUREMENTS, AND MOTIONAL CHARACTERISTICS

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ABSTRACT

Aspects of the conformation and mobility of a series of di-*O*-isopropylidene furanose derivatives in solution have been examined by ^{1}H- and ^{13}C-n.m.r. spectroscopy. Attention has been focused particularly on the chemical shifts of the methyl substituents of the acetal rings, in an attempt to extract information about molecular conformation and site of fusion. Obtained unambiguously by a combination of chemical and spectroscopic techniques, the methyl chemical shifts were found not to reflect consistently the site of fusion to the furanose ring nor the overall molecular conformation, although they represent useful probes for ring-size determination. This inconsistency may be related to the flexibility of the fused ring systems and associated individual differences in the conformations of both the *O*-isopropylidene and sugar rings. Through measurements of ^{13}C spin–lattice relaxation times, a number of noteworthy motional characteristics related to overall molecular tumbling, hydrogen bonding, and internal mobility, were detected.

INTRODUCTION

O-Isopropylidene groups, in the form of cyclic acetals, are used extensively for the specific protection of diol functional groups in sugars. As a result, *O*-isopropylidene derivatives have been the subject of many studies[1–5] on structure and conformation. A great deal of attention has been focused[6–18] on n.m.r. parameters for the ^{1}H and ^{13}C nuclei of the sugar rings, because they clearly reflect changes in the stereochemistry of the parent sugars upon acetal ring-formation. It also has been shown[15] that ^{13}C signals of the methyl substituents are sensitive to ring size, i.e., are often distinctive for 1,3-dioxane, 1,3-dioxolane, and 1,3-dioxepane structures, respectively. However, it is not clear[10] that the position and conformation of the *O*-isopropylidene rings may be correlated with chemical shift as well, mainly because of ambiguities commonly encountered in the assignment of CH_3 signals.

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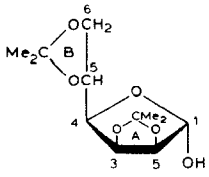
This latter problem is addressed in the present study on *O*-isopropylidene derivatives in various ways. Thus, it is shown that relatively labile acetal substituents undergo selective acid-catalysed exchange with acetone-d_6 solvent molecules, as found previously[17] for the 5,6-*O*-isopropylidene group of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose, which proved to be of particular value for the identification of overlapping methyl ^{1}H-resonances. Supporting evidence is furnished by ^{1}H-n.O.e. experiments, and the assignments of the corresponding methyl ^{13}C-signals are based largely on heteronuclear, two-dimensional experiments. Overall, data are reported here for eight di-*O*-isopropylidene furanose derivatives, namely, the 2,3:5,6-α-D-mannose (**1**), 2,3:5,6-β-D-allose (**2**), 1,2:5,6-



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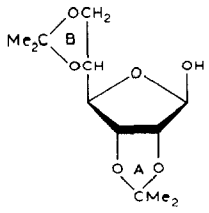

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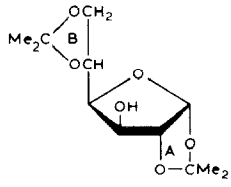

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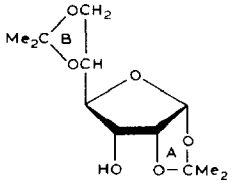

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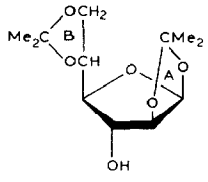

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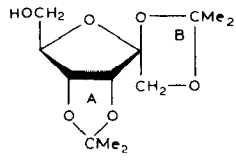

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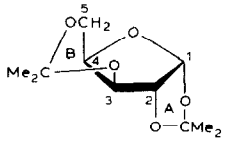

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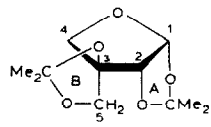

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α-D-glucose (**3**), 1,2:5,6-α-D-allose (**4**), 1,2:5,6-β-D-altrose (**5**), 1,2:3,4-β-D-psicose (**6**), 1,2:3,5-α-D-xylose (**7**), and 1,2:3,5-β-L-apiose* (**8**) isomers. Although all of these compounds contain a stable arrangement of two *cis*-fused five-membered rings, wide variations in their other structural features provide a number of contrasting environments for the *O*-isopropylidene CH_3 groups. This may be seen in

*For convenience of tabular correlations, the chain-branch carbon atom at C-3 of apiose is designated C-5 instead of by the conventional numbering.

the chemical-shift data, which are assessed in relation to the conformations of individual acetal rings. The shapes of the sugar rings to which the latter are appended also are examined, based mainly on a combination of ^1H–^1H spin coupling and n.O.e. data. In addition, some aspects of the molecular dynamics of these types of molecules are described, based on ^{13}C spin-relaxation measurements, in extending the study already reported for one of the group, namely, compound **1**.

EXPERIMENTAL

One-dimensional ^1H- and ^{13}C-n.m.r. experiments were conducted with a Varian XL-200 spectrometer. Samples of 0.1 and 0.5M in acetone-d_6 were used for ^1H- and ^{13}C-n.m.r. experiments, respectively. ^1H-n.O.e. measurements were performed as described elsewhere[16], with carefully degassed samples by using at least 4 "freeze–pump–thaw" cycles, following which the samples were sealed.

The ^{13}C spin–lattice relaxation times were measured by the fast inversion recovery (FIRFT) technique[19], and analyzed by a three-parameter non-linear procedure. The pulse duration for a 180° flip angle was 29 μs. Other details on relaxation experiments and ^{13}C n.O.e. measurements are given elsewhere[17]. The r.m.s. error in the three-parameter fit was ±10% or better. Two-dimensional

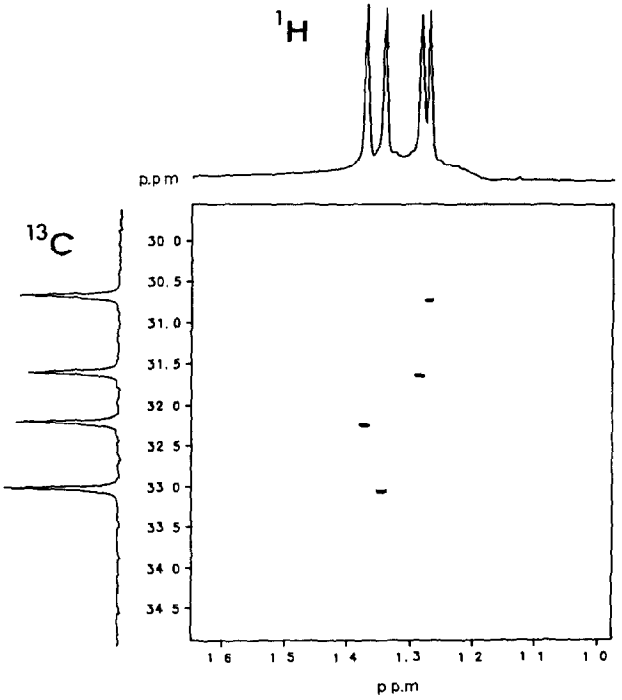


Fig. 1. ^1H–^{13}C 2D-chemical-shift correlation n.m.r. spectrum for the methyl groups of compound **1** presented as a contour plot. The assignments of the ^1H-n.m.r. chemical shifts were obtained by selective deuterium-exchange and n.O.e. experiments.

heteronuclear ^{13}C–^{1}H chemical-shift correlation experiments were performed on samples in 5-mm tubes with a Varian XL-300 spectrometer. The pulse sequence applied was (90°, ^{1}H) – ($t_{1/2}$) – (180°, ^{13}C) – ($t_{1/2}$) – (τ_1) – (90°, ^{1}H; 90°, ^{13}C) – (τ_2) – (BB, ^{1}H; FID, t_2) with τ_1 = 3.6 ms and τ_2 = 2.4 ms. The spectral width, F_1, was 200–1500 Hz and F_2 = 400–8000 Hz, depending on the experiment. The number of data points in F_2 was 1024, and 128 increments were acquired. Before the Fourier transformation, the data were multiplied with sine-bell shifted $\pi/10$ in F_2, and Lorentz–Gauss in F_1 to obtain the desired resolution in both domains. The 90° pulse was 17 μs for ^{13}C and the decoupler 90° pulse for ^{1}H, checked in each experiment, was 49–50 μs. A representative set of data, Fig. 1, shows the heteronuclear chemical-shift correlation map obtained for the methyl groups of compound **1**.

Selective acid-catalyzed exchange with acetone-d_6 solvent was effected by adding 1–2 drops of CF_3CO_2H to the sample solution contained in the n.m.r. tube. The exchange process, checked periodically from the decrease in the intensity of methyl proton signals, was complete in 1–5 h. The 5,6-*O*-isopropylidene rings exhibited the highest rates of exchange.

RESULTS AND DISCUSSION

Assignments of ^{1}H- and ^{13}C-resonances were made by a combination of one- and two-dimensional experiments and, where applicable, were compared with corresponding literature values[6–11,13–16]. As already noted, selective deuteration of *O*-isopropylidene groups through exchange with acetone-d_6, together with ^{1}H-

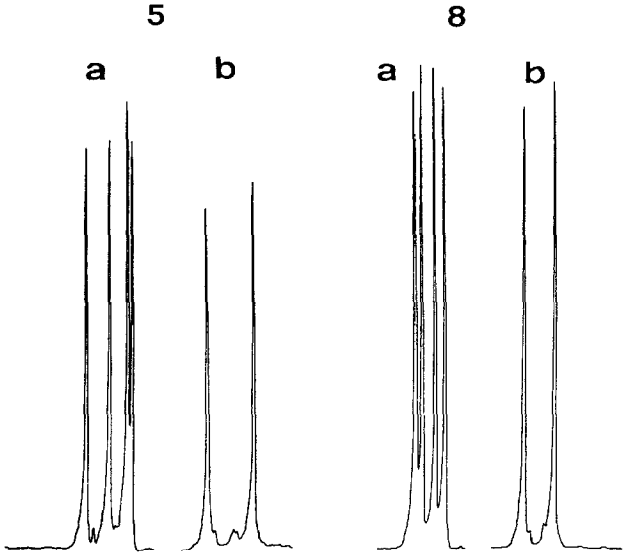


Fig. 2. Partial ^{1}H-n.m.r. spectra of compounds **5** and **8** in acetone-d_6, showing the methyl proton region; (a) nondeuterated compounds; (b) deuterated compounds.

TABLE I

^{1}H-N.O.E. VALUES OF RING PROTONS FOR COMPOUNDS **1–8** UPON IRRADIATION OF METHYL SUBSTITUENTS

Compound	*Irradiated CH_3*[b]	*Proton observed*								
		H-1	*H-1'*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	*H-6*	*H-6'*
1	CH_3(1)									
	CH_3(2)[c]									
	CH_3(3)[c]						0.055			
	CH_3(4)			0.078	0.100					
2	CH_3(1)					0.040				
	CH_3(2)[c]					0.037				
	CH_3(3)[c,d]						0.036			
	CH_3(4)			0.080	0.091					
3	CH_3(1)					0.057				
	CH_3(2)[c]					0.057				0.052
	CH_3(3)[c]									
	CH_3(4)	0.54		0.040						
4	CH_3(1)									
	CH_3(2)[c]									
	CH_3(3)[c]						0.061			
	CH_3(4)	0.041		0.080						
5	CH_3(1)									
	CH_3(2)[c]									
	CH_3(3)[c]						0.042			0.050
	CH_3(4)		0.052							
6	CH_3(1)[c]		0.044		0.060					
	CH_3(2)									
	CH_3(3)[c]	0.051								
	CH_3(4)				0.066	0.044				
7	CH_3(1)[c]				0.112		0.039			
	CH_3(2)									
	CH_3(3)			0.061						
	CH_3(4)[c]							−0.065		
8	CH_3(1)									
	CH_3(2)[c]			0.039			0.030			
	CH_3(3)[c]									
	CH_3(4)	0.030		0.054						

[a]For all experiments, 0.1M degassed solutions in acetone-d_6 were used. [b]Numbering of the methyl groups from (1) to (4) in decreasing order of δ^1H values in the spectra; for a specific assignment of each signal, see Table II. [c]Methyl protons which were exchanged in the presence of acetone-d_6. [d]Overlapping resonances.

n.O.e. measurements, facilitated the identification of CH_3 signals. For example, Fig. 2 shows that the ^{1}H-signals arising from the 5,6- and 3,5-*O*-isopropylidene groups of **5** and **8**, respectively (Fig. 2a), are not observable in the spectra (Fig. 2b) of **5**-d_6 and **8**-d_6, respectively, following exchange. In addition, by observing enhancements in the intensities of ring-proton signals upon irradiation of the protons of each resolved methyl group (Table I), a distinction was made between *endo* and *exo* methyl protons, because these ^{1}H-n.O.e. values reflected the proximity of the latter to individual ring protons. The chemical shifts of the methyl protons

TABLE II

ASSIGNMENTS OF ^1H AND ^{13}C RESONANCES FOR THE METHYL GROUPS OF COMPOUNDS **1–8**, BASED ON ^2H-EXCHANGE, N.O.E., AND 2D-N.M.R. EXPERIMENTS

		CH_3(exo-A)[a]	CH_3(endo-A)[b]	CH_3(exo-B)[c]	CH_3(endo-B)[d]
1	δ^1H	1.26	1.36	1.33	1.27
	$\delta^{13}C$	24.66	26.19	26.99	25.59
2	δ^1H	1.27	1.38	1.36	1.27
	$\delta^{13}C$	24.97[e]	26.74	27.17	25.57[e]
3	δ^1H	1.25	1.40	1.33	1.26
	$\delta^{13}C$	26.40	27.16	27.05	25.59
4	δ^1H	1.28	1.46	1.34	1.29
	$\delta^{13}C$	26.78	26.91	26.56	25.74
5	δ^1H	1.24	1.42	1.33	1.26
	$\delta^{13}C$	25.70	27.21	27.08	25.92
6	δ^1H	1.28	1.37	1.40	1.33
	$\delta^{13}C$	25.19	26.74	26.74	26.74
7	δ^1H	1.26	1.39	1.24	1.42
	$\delta^{13}C$	26.43	27.04	29.28	19.14
8	δ^1H	1.27	1.39	1.37	1.31
	$\delta^{13}C$	26.35	27.19	26.87	26.56

[a]A-methyl *cis* to the ring protons. [b]A-methyl *trans* to the ring protons. [c]B-methyl *trans* to the C-*i*,H-*i* bond [*i* = 1 (**6**), 5 (**1–5, 8**)]. [d]B-methyl *cis* to the C-*i*,H-*i* bond. [e]These assignments may be interchangeable as their corresponding ^1H resonances overlap (Table I).

were then correlated (for instance, as in Fig. 1) with the chemical shifts of the methyl ^{13}C-nuclei to obtain assignments for the latter; both sets of data are listed in Table II. N.m.r. parameters for the ring protons of compounds **1–8** are given in Table III, whereas Table IV presents the corresponding ^{13}C chemical-shift data.

Chemical shifts of methyl groups, and conformation. — The methyl groups fall into two categories: "A", which are those of *O*-isopropylidene substituents fused to the furanose ring, and "B", those of exocyclic substituents or (as in **7** and **8**) of substituents involving both a ring and an exocyclic oxygen atom. For all compounds, the ^1H and ^{13}C nuclei of "A-*endo*"* methyl groups absorb at lower field than do "A-*exo*"* methyl groups, which is in accord with the observation[16,20] that methyl groups *cis* to substituents on C-4 and C-5 of a dioxolane ring, give rise to downfield ^{13}C-signals. Within category "A" it appears, in general, that chemical shifts do not consistently reflect the site of fusion to the furanose ring and the overall conformation of the bicyclic system involved. It is likely, as proposed earlier, that this inconsistency is related to the flexibility in the dioxolane ring. As to the "B" methyl groups, it is apparent from Table II that those oriented *exo* in compounds **1–5** absorb at lower field than their *endo* counterparts. Nuclei of the "B" methyl groups in **6** and **8** are characterized by nearly the same ^{13}C chemical shifts,

*In this representation, A-*exo* methyl groups are those that are *cis* with respect to the ring protons, whereas A-*endo* methyl groups are *trans* to these protons. For "B" methyl groups, the *exo* and *endo* designations refer to *trans* or *cis* orientations, respectively, with respect to C-*i*,H-*i*.

TABLE III

^{1}H-N.M R. CHEMICAL SHIFTS (A, δ) AND ^{1}H–^{1}H COUPLING CONSTANTS (B, Hz) FOR COMPOUNDS **1–8**[a]

Parameter for	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
A, Proton								
H-1	5.2	5.5	5.8	5.7 (5.7)[b]	5.9	4.2	5.9	5.9
H-1′						3.9		
H-2	4.5	4.6	4.5	4.6 (4.5)	4.5		4.4	4.4
H-3	4.8	4.8	4.1	[c]	4.3	4.6	4.3	
H-4	4.1	3.9	4.0	(3.8)	3.8	4.8	3.9	4.3
H-4′								3.9
H-5	4.3	4.2	4.3	4.3 (4.2)	4.2	4.1	4.1	3.9
H-5′							3.9	3.8
H-6	4.0	4.0	4.0	[c]	4.0	3.5		
H-6′	3.9	3.8	3.9	[c]	3.8	3.5		
OH	5.3	5.3	4.4	(2.5)	4.7	3.7		
B, Spacing								
H-1,H-1′						9.5		
H-4,H-4′								9.4
H-5,H-5′							13.4	9.6
H-6,H-6′	8.4	8.5	8.4	[c]	8.5	12.4		
H-1,H-2	[d]	[d]	3.7	3.9	3.8		3.8	3.7
H-2,H-3	5.9	5.9	[d]	5.1	[d]		0.5	
H-3,H-4	3.4	2.1	2.8	8.5	[d]	5.9	2.5	
H-4,H-5	6.6	9.3	7.2	4.6	9.5	0.9	0.6	
H-4,H-5′							2.4	
H-5,H-6	6.3	6.2	6.2	6.6	6.2	6.5		
H-5,H-6′	5.8	5.2	5.9	5.9	5.2	6.5		
H-*i*,OH	3.7	4.4	4.9	(8.3)	3.9	3.6		
H-*i*′,OH						12.5		
H-2,H-4					0.5			
H-2,H-5′								0.9

[a]Methyl chemical shifts are given in Table II; acetone-d_6 was the solvent, unless otherwise indicated. [b]Values in parentheses obtained with $CDCl_3$ as the solvent. [c]Signal not resolved. [d]Spacings ≤0.1 Hz.

TABLE IV

^{13}C-N.M.R CHEMICAL SHIFTS (δ) FOR COMPOUNDS **1–8**[a,b]

Carbon atom	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
C-1	101.95	103.67	106.03	105.76	106.92	70.34	106.06	106.96
C-2	86.77	83.19	86.34	80.33	90.40	114.26	85.65	85.04
C-3	80.63	87.16	74.90	73.17	76.06	86.20	74.04	88.94
C-4	80.78	88.45	82.29	80.16	87.93	82.93	72.44	65.53
C-5	73.98	76.84	73.55	76.45	76.70	86.97	60.66	73.86
C-6	67.14	67.86	67.56	65.53	67.99	63.70		
C-A	112.56	112.49	111.91	112.74	112.36	112.76[c]	111.80	112.62[c]
C-B	109.00	110.20	109.21	109.06	109.94	111.89[c]	97.77	111.24[c]

[a]Methyl chemical shifts are given in Table II. [b]Solvent, acetone-d_6. [c]Assignments may be interchanged.

despite the marked differences in the sites of attachment of their *O*-isopropylidene rings. This suggests an augmented flexibility of these 1,2- and 3,5-substituents, leading to an averaging of the methyl chemical shifts.

Compound **7** exhibits the most widely separated methyl signals ($\Delta\delta_H = 0.15$, $\Delta\delta_c = 10$ p.p.m., Table II), which are those of the only 1,3-dioxane (3,5-*O*-isopropylidene) ring represented within the group. Observed earlier, this pattern is attributable[15,20] to an axial methyl (upfield ^{13}C and/or downfield ^1H) and an equatorial methyl (downfield ^{13}C and/or upfield ^1H), respectively, located on a chair conformation of the 1,3-dioxane ring (see later).

Having, then, obtained definitive ^1H- and ^{13}C-assignments for each of the four methyl groups of all of the acetals, one may conclude that there is no inherent relationship between methyl chemical shifts and the positions of attachment of the 1,3-dioxolane rings. Undoubtedly, this lack of uniformity is related to flexibility in the latter and the associated individual differences in their conformations, as well as those of the sugar rings themselves, as discussed in the following section.

Conformations of di-O-isopropylidene derivatives. — As found[6] in the original n.m.r. studies on compounds of this class, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) exhibits (Table III) small H-1,H-2 amd H-3,H-4 couplings, whereas there is no coupling (dihedral angle of ~90°) between H-2 and H-3. This has been taken as evidence that the furanose ring of **3** favors the $^3T_2$ conformation. By the same token, the absence of vicinal coupling between H-1 and H-2 of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**1**) and -β-D-allofuranose (**2**) (Table III), is consistent with $^2T_3$ and $^3T_2$ conformations, respectively, for these compounds. Consequently, it appears that C-2 and C-3 in **1** tend to lie, respectively, above and below the plane formed by C-1, O-1, and C-4, whereas in **2** and **3** their positions relative to the plane of the ring tend to be reversed. The latter geometry also is compatible with the *α-allo* configuration when the furanose ring bears a 1,2-*O*-isopropylidene substituent (isomer **4**), from the fact that the large value of $^3J_{3,4}$ (8.5 Hz) is indicative of an *anti* disposition of H-3 and H-4. For 1,2:5,6-di-*O*-isopropylidene-β-D-altrofuranose (**5**) the lack of observable spin interactions between H-2 and H-3, as well as between H-3 and H-4, are commensurate with dihedral angles of ~90° in both instances, and hence the E_3 conformation appears to preponderate. Further evidence for this is the long-range coupling, $^4J_{2,4} = 0.5$ Hz, consistent with a "W" array of atoms H-2, C-2, C-3, C-4, and H-4 in the E_3 conformation of **5**.

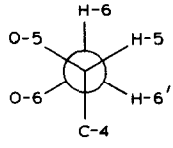
An example of a ketofuranose is provided by 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose[21] (**6**). Here the weak coupling (0.9 Hz) between H-4 and H-5, and much stronger coupling (5.9 Hz) between H-3 and H-4, corresponding to a 4,5-dihedral angle approaching 90° and a small 3,4-dihedral angle, suggest that the furanose ring of **6** exists largely in the $^2T_3$ conformation. Based on the n.O.e. evidence that the *endo* B-methyl group is close to H-3 (Table I), a feasible conformation for the 1,2-*O*-isopropylidene ring is one in which C-1 and O-1 lie, respectively, below and above the plane of C-2, O-2, and the quaternary carbon atom.

Noteworthy also is the exceptionally large value for coupling between OH-6 and H-6′ (12.50 Hz, Table III). Coupling of this magnitude has been observed[22] for an *anti* geometry of H–C–O–H maintained with an H-bonded system. If, by analogy, OH-6 is H-bonded (as also suggested later by ^{13}C-T_1 data), a molecular model of **6** in which the furanose ring is $^2T_3$ (as proposed here), implies that bonding with O-2 is feasible when OH-6 is *anti* with respect to H-6′, and *gauche* to H-6 (3.6 Hz), and the latter two protons are symmetrically disposed with respect to H-5 ($^3J_{5,6} = {}^3J_{5,6'}$, Table III).

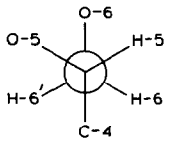
The furanose ring of 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**7**) appears to be slightly distorted, relative to the furanose ring in the α-D-*gluco* isomer (**3**), by the presence of the 3,5-bridging substituent. The larger difference between $^3J_{1,2}$ and $^3J_{3,4}$ of **7** as compared with the corresponding values for **3** (Table III), namely, 1.3 Hz *vs.* 0.9 Hz, implies that there is less tendency for **7** to adopt a symmetrical $^2T_3$ conformation but, rather, a preference for the E_3 conformation, in which the H-3,H-4 dihedral angle would be relatively larger. On constructing a molecular model of **7** based on these observations, it is found that the 3,5-*O*-isopropylidene ring can assume a (slightly distorted) chair conformation whereby the *exo*-B methyl group (Table II) is relatively close to H-3 and H-5. Consequently, this overall geometry proposed for **7** finds additional support in the fact that irradiation of the protons of that methyl group [CH_3(1), Table I] induce prominent enhancement of both the H-3 and H-5 resonances.

Although 1,2:3,5-di-*O*-isopropylidene-β-L-apiofuranose (**8**) affords few ^1H–^1H coupling constants, the four-bond coupling of 0.9 Hz between H-2 and H-5′ (Table III) indicates a "W" arrangement for atoms H-2, C-2, C-3, C-5, and H-5′. For this to occur, the most probable overall conformation of the bicyclic system of **8** is one in which the furanose ring and the 3,5-*O*-isopropylidene ring are $^2T_3$ and $^0T_5$, respectively.

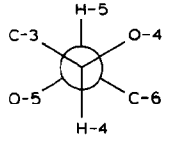
The extreme limits of puckering by the 5,6-*O*-isopropylidene rings of **1–5** are represented by projection formulas **a** and **b**. Because spin–spin couplings between H-5 and H-6 and -6′ of each compound are intermediate in value (5.2–6.6 Hz,



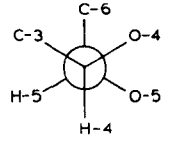
a



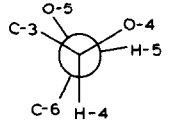
b



c



d



e

Table III), contributions from both *gauche* and *anti* interactions are implied throughout. It is noteworthy, however, that two-bond coupling was not detected[16,23] between ^{13}C-6 and H-5, of **1** and **4**. As this is more consistent with **a** (in which H-5 is *trans* to O-6) than with **b** (in which they are *gauche*), it appears that the conformation of the 5,6-*O*-isopropylidene ring in all five compounds is represented mainly by **a**. As shown later, this may be reflected in ^{13}C-T_1 data.

There is far less uniformity in the manner in which these exocyclic rings in compounds **1–5** are oriented with respect to the furanose rings, as seen from the variations in the magnitude of coupling between H-4 and H-5 (Table III). The large $^3J_{4,5}$ values of 9.3 and 9.5 Hz for compounds **2** and **5**, respectively, are commensurate with a high preponderance of the *anti* orientation, as in rotamer **c**, whereas the smaller values of 6.6 and 7.2 Hz for **1** and **3**, respectively, indicate substantial contributions from *gauche* rotamers (**d** and/or **e**). In contrast, the latter rotamers appear to be almost wholly representative of the relative disposition of the exocyclic and furanose rings of compound **4**, because of the markedly decreased $^3J_{4,5}$ value of 4.6 Hz observed. This striking conformational difference between **4** and **2**, the other D-*allo* isomer represented, has been cited[5,24] as a possible source of the lesser stability of **4** relative to **2** under acid-catalyzed equilibrating conditions, inasmuch as in **d** and **e** the 5,6-*O*-isopropylidene structure is rotated inwards ("endo") with respect to the furanose ring. It also is worth noting that OH-3 exhibits much stronger coupling with its vicinal proton (H-3) (namely, 8.3 Hz, Table III) than is observed with the other four compounds in the group (namely, 3.7–4.9, although the fact that $CDCl_3$ was the solvent in this instance, may be a factor.

^{13}C-Chemical shifts. — In addition to the characteristics of ^{13}C-chemical shifts of the methyl groups, already described, some other features of the ^{13}C-data in Table IV bear comment. For example, there are widespread differences in shielding attributable to interactions between vicinal substituents on the furanose rings, analogous to those observed[25] for furanosides and cyclopentanols. Within compounds of these latter classes, the *cis* configuration of vicinal substituents is associated with an increase in the shielding of ^{13}C-nuclei, relative to ^{13}C-nuclei engaged in the *trans* arrangement. Similarly, comparing isomers **1–5** (Table V), a greater trend towards upfield shifts is found for **1, 3,** and **4**, which incorporate a larger number of *cis* interactions than in **2** and **5**. This is evident from a summation[26] of the ^{13}C-chemical shifts ($\Sigma\delta$, Table V) for each group of six sugar-carbon atoms (isomeric differences among the other carbon atoms are relatively minor), which indicate that the ^{13}C nuclei in **1, 3,** and **4** are substantially more shielded, overall, than those in **2** and **5**. In the light of evidence[25,26] that ^{13}C-chemical shifts and conformational stability are interrelated, the large difference in $\Sigma\delta$ (25.77 p.p.m.) between the two *allo* isomers, amounting to an average upfield shift of ~5 p.p.m. for each carbon atom in **4** relative to those in **2**, is commensurate with the fact that **4** is far less stable than **2**, as already noted.

Although the resonances of the methyl groups of the *O*-isopropylidene substituents have all been assigned (Table II), the quaternary carbon signals (Table

TABLE V

EFFECT OF *trans* AND *cis* VICINAL INTERACTIONS WITHIN THE FURANOSE RINGS OF COMPOUNDS **1–5** ON THE CHEMICAL SHIFTS OF CARBON ATOMS 1 TO 5

Compound	**1**	**2**	**3**	**4**	**5**
Configurations[a] of 1/2, 2/3, 3/4 substituents	t,c,c,	t,c,t	c,t,c	c,c,t	c,t,t
$\Sigma\delta^{13}C$[b]	424.11	439.31	423.11	415.87	438.01

[a]Relative configurations of O-1, O-2, O-3, and C-5; t = *trans*, c = *cis*. [b]Sums of ^{13}C chemical shifts of C-1 to C-5 (Table IV) as a measure[24–26] of overall shielding differences on carbon.

IV) could not be identified unequivocally from the same spectra. However, these carbon atoms show a high degree of consistency in chemical shift, inasmuch as there is one signal at δ 112 ±0.4 for each compound (tentatively, row C-A), whereas the second signal (row C-B) is upfield, usually by ~2 p.p.m. Compound **7** provides a striking exception in that its second quaternary carbon atom resonates at δ 97.77, that is, 14 p.p.m. upfield. As ^{13}C-nuclei in six-membered rings generally[25,26] are more strongly shielded than those in the corresponding five-membered rings, and as seen[15] in comparing 1,3-dioxanes and -dioxolanes, this upfield signal may reasonably be ascribed to the quaternary carbon atom of the only six-membered *O*-isopropylidene ring represented, that is, the 3,5-acetal substituent (ring B) of **7***. Consequently, the signal at δ 111.80 is assigned to the A-ring and, by inference, most of the other resonances are designated C-A or C-B, as in Table IV. (Although, in principle, ^{13}C–^{13}C connectivity[27] should constitute a means for checking these assignments, it entails substantial experimental difficulties, as verified by double-quantum coherence experiments now in progress on these and other carbohydrate systems).

^{13}C Spin–lattice relaxation times. — Table VI contains the T_1 values for all protonated carbon atoms of compounds **1–8** in acetone-d_6 solution. As all of the n.O.e. values were found to approach the asymptotic value of 2.988 ±0.15, dipole–dipole interactions constituted the preponderant relaxation mechanism.

Overall molecular motion is reflected in the T_1 values of the furanose rings. For each of compounds **1, 3, 4, 5,** and **8,** the values for C-1 to C-4 are the same, within experimental error (~11% in T_1^{dd} values), which implies that the overall motion of these molecules is isotropic. The other compounds (**2, 6,** and **7**) appear to reorient anisotropically because of the larger variations within their sets of T_1 values. It is noteworthy that **7** and **8** relax faster than the other compounds by a factor of 1.5–2.0. As there are only small differences in mass, this contrast is attributed to the fact that only **7** and **8** do not have a free hydroxyl group and hence, unlike **1–6**, are unable to form aggregates by hydrogen bonding. Accordingly, the smaller T_1 values for the latter group of compounds represent averages

*It may be noted that C-5, which also is in this ring, resonates 5–7 p.p.m. upfield of primary carbon atoms (C-6) in the five-membered, 5,6-*O*-isopropylidene rings, of **1–5**.

TABLE VI

^{13}C-N M R SPIN-LATTICE RELAXATION TIMES (IN SEC) FOR COMPOUNDS **1–8**[a]

Carbon atom	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
C-1	2.58	2.45	2.94	3.36	3.28	2.41	5.11	5.66
C-2	2.78	2.94	2.62	3.25	3.22		4.87	5.76
C-3	2.88	3.16	2.75	2.89	2.87	3.89	4.75	
C-4	2.73	2.82	2.82	3.23	3.14	3.77	4.17	2.76
C-5	2.98	2.98	2.97	3.23	3.28	3.35	2.52	3.69
C-6	1.90	2.14	2.00	2.06	2.21	2.07		
CH_3(exo-A)	1.38	1.46	1.37	1.45	1.88	2.01	1.96	2.72
CH_3(endo-A)	1.70	1.73	1.63	1.72	1.78		2.24	2.80
CH_3(exo-B)	1.74	1.85	1.82	1.89	1.53	1.88[b]	2.44	2.82
CH_3(endo-B)	1.86	1.88	1.87	1.90	1.90		2.51	2.41

[a]Solution (0.5M) in acetone-d_6. [b]Overlapping resonances.

that reflect strong solute–solute and/or solute–solvent interactions. For compound **6**, it is likely that there is restricted rotation about the C-5–C-6 bond, because the T_1 value of C-6 (moderated by *two* protons) is close to the T_1 values of the ring carbon atoms, which is not observed for the primary carbon atoms in the other compounds. Although this may be due to intermolecular association, it also is consistent with the suggestion (earlier) that OH-6 of **6** engages in intramolecular H-bonding.

Among molecules of approximately the same size and shape that are characterized by isotropic motion, the occurrence of molecular aggregates, or its absence, is evident from the diffusion coefficient, D_R, for overall molecular reorientation, which may be obtained from Eq. *1*:

$$\frac{1}{T_1} = \frac{N\gamma_c^2\gamma_H^2H^2}{r_{C\text{-}H}^6}(6D_R)^{-1} \qquad (1).$$

Hence, D_R values calculated from the average T_1 values of the ring carbon atoms (Table VII) indicate clearly that the rate of overall rotational diffusion for **8** is twice that of the isotropic tumblers that are capable of H-bonding. As to the quantitative significance of these differences, however, it may be noted that the contribution of a monomer and an associated species to the T_1 value observed depend on the lifetime of the associated species relative to D_R^{-1}. For instance, if the lifetime is longer than D_R^{-1}, then T_1 is a measure of the diffusion coefficient of the associated species, whereas if the lifetime is much shorter than D_R^{-1} then the experimental T_1 value corresponds to that of the monomer. Intermediate lifetimes relative to D_R^{-1} result in both monomeric and associated species contributing to the observed T_1 value. As T_1 measurements alone cannot partition these relative contributions, it is not feasible here to provide a description of the type of associated species formed by the various compounds in the series.

TABLE VII

DIFFUSION CONSTANTS[a] (IN SEC^{-1}) AND ENERGY BARRIERS[b] (IN KCAL/MOL) FOR COMPOUNDS HAVING ISOTROPIC MOTION

Compound	T_1	$D_R \times 10^9$	$D_i(exo\text{-}A) \times 10^{10}$	$D_i(endo\text{-}A) \times 10^{10}$	$V_i(exo\text{-}A)$	$V_i(endo\text{-}A)$
1	2.74	9.8	4.1	6.6	3.4	3.1
3	2.78	10.0	4.0	6.5	3.4	3.1
4	3.18	11.1	3.7	5.5	3.4	3.2
5	3.13	11.2	7.0	6.2	3.0	3.1
8	5.65	20.2	7.6	8.2	3.0	3.0

[a]Estimated error ±15%. [b]Estimated error ±5%.

The T_1 values for C-5 and C-6 of compounds **1–5**, and the values for C-1 of **6** and C-5 of **7** and **8**, reflect the motional behavior of the B-type of *O*-isopropylidene rings. As may be seen in Table VI, the relaxation time of C-5 in each of isotropic molecules **1, 3, 4,** and **5** is similar to the T_1 values of the furanose ring-carbon atoms of each, within experimental error. This similarity indicates restricted rotation about the C-4–C-5 bond, which may be regarded as a very slow oscillation. However, the fact that the T_1 values for C-6 are larger than predicted by Eq. *1*, assuming that these carbon atoms relax only *via* overall molecular tumbling, suggests that the 5,6-*O*-isopropylidene rings undergo a puckering motion, which thereby influences the relaxation of C-6. The same type of motion is probably reflected as well in the T_1 values for C-6 of **2**, C-1 of **6**, C-5 of **7**, despite the anisotropic reorientation displayed by these compounds. Hence, the five-membered B-type acetal rings appear to be sufficiently flexible to accomodate pseudorotation between such conformations as **a** and **b**, evaluated earlier in terms of spin–spin coupling between H-5, -6, and -6′.

The pairs of geminal *C*-methyl groups are found in a wide range of structural situations. That the internal rotation of these groups is hindered is verified by the n.O.e. evidence that the spin-rotation mechanism makes a negligible contribution to the relaxation of these symmetric tops. Furthermore, the maximum values of the n.O.e. factors suggest an explicit relationship between the dipolar T_1 values and the barrier to rotation, which reflects the magnitude of steric interference experienced by the methyl tops. The internal methyl rotation superposed on isotropic overall motion is described[28] by Eq. *2*,

$$\frac{1}{T_1, CH_3} = \frac{3\gamma_H^2\gamma_c^2H^2}{4r_{C\text{-}H}^6}(D_R^{-1})\left[\frac{A}{6} + \frac{B}{6+p} + \frac{C}{6+4p}\right], p = D_i/D_R \qquad (2)$$

where A, B, and C are geometrical constants, and D_i is the diffusion coefficient for reorientation about the carbon-CH_3 bond.

The pair of methyl groups of 5,6-*O*-isopropylidene rings is not amenable to a

rigorous quantitative treatment in terms of internal motion about the C-CH_3 bonds, because of multiple internal motions within the rings themselves. However, this limitation does not apply to the geminal methyl groups of the fused 1,2- 2,3-, or 3,4-*O*-isopropylidene rings (A-type), because they are far more rigid, judging from the analysis of the coupling-constant data. Diffusion coefficients calculated for the *exo* and *endo* methyl groups for isotropic tumblers are depicted in Table VII, along with the barriers to rotation, V_t, calculated using $D_t = D_o e^{-V_t/RT}$, where D_o is given by $D_o = 3/2\ \sqrt{(KT/I)}$ and I is the moment of inertia of the methyl group. These barriers are recorded for C-C-H angles of 112°, as steric interactions increase[29] this angle from the normal 109.47°. It is apparent from Table VII that the barriers to rotation of the *endo*- and *exo*-methyl groups are similar in compounds **1, 3,** and **4**, and that *endo*-methyl groups rotate faster than the *exo*-methyl groups. This trend may be accounted for by an increase in the barrier for the latter groups, because of their interaction selectively with the 1,3-quasidiaxial protons across the *O*-isopropylidene ring. By contrast, there is a reversal in the order of the barriers to internal rotation in **5**, whereas the *endo*- and *exo*-methyl groups of **8** have about the same rotational barrier. The conformations already proposed for the furanose rings of these two compounds are such that the *endo*-methyl group is brought into close proximity to the C-3, H-3 bond in **5**, and the C-4, H-4 bond in **8**. Consequently, these steric interactions may be expected to bring the energy barriers for the *endo*-methyl groups more into line with those for the *exo*-methyl groups.

The dynamics of molecules undergoing anisotropic motion may be described by Woessner's equations[28,30]. The normal procedure based on this formalism assumes that the principal axes of the diffusion tensor coincide with the principal axes of the moment of inertia. Although this assumption is reasonable for simple molecules, or molecules comprised of only carbon and hydrogen atoms, it is not valid[31–33] for hydrogen-bonded and/or strongly solvated systems. In molecules containing polar groups, the orientations of the two tensors may no longer coincide. A solution to this problem could be *a priori* knowledge of the orientation of the rotational-diffusion tensor, which is feasible in favorable cases where the diffusion tensor is symmetric[33–35]. For molecules of low symmetry, the three Euler angles defining the orientation of the diffusion tensor, in addition to the three diffusion coefficients, should be determined. Therefore, six linearly independent equations, and hence six unique C-H vectors, as well as the corresponding ^{13}C T_1 values, are needed for the determination of the six parameters.

Anisotropic molecules **2, 6,** and **7** contain 5 to 6 oxygen atoms which constitute strong solvating centers. Moreover, these systems are characterized by full asymmetry, which cannot justify a preferential axis of rotation as can be inferred, superficially, from the similarity of the T_1 values for three carbon atoms of the furanose ring (Table VI). In light of the foregoing discussion, and since only four ^{13}C T_1 values are available, Woessner's treatment seems to be inapplicable at this stage.

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