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Note

Application of paramagnetic shift-reagents in conformational analysis. Conformations of some isopropylidenated pyranose derivatives*

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There has been sustained interest for several years in the conformational analysis of 6-membered, saturated rings fused to a dioxolane ring to form a bicyclo-[4.3.0] system. This bicyclic feature is encountered frequently in cyclic acetal derivatives of sugars[1]. Tipson *et al.*[2] suggested that mono- and di-isopropylidene acetals of pyranoid sugar derivatives adopt conformations in which the dioxolane rings are flat and the six-membered ring has a non-chair shape. Angyal and Hoskinson[3] inferred from infrared spectroscopic analysis of hydrogen-bonded hydroxyl absorptions that the cyclohexane ring in *O*-isopropylideneinositols adopts a flattened-chair shape, and that di-*O*-isopropylideneinositols adopt a similar conformation, except for those examples having both fusions *cis*, for which a skew form of the cyclohexane ring was proposed. Early n.m.r. studies on isopropylidene acetals of 1,4,4-trideuterio-1,2-cyclohexanediol[4] and 5-*O*-substituted 2,6-anhydro-1-deoxy-1,1-bis(ethylsulfonyl)-D-talitol[5] revealed spin-coupling magnitudes[6] in accord with flattened-chair conformations. A similar conclusion was drawn from p.m.r. data on some 1,2-orthoacetate derivatives of (*a*) D-mannopyranose by Perlin[7] and (*b*) D-glucopyranose by Lemieux and Morgan[8].

Coxon and Hall[9] interpreted ambiguous n.m.r. data on 1,2-*O*-(1-aminoisopropylidene)-α-D-glucopyranose (and a number of related compounds) and on 6-*O*-acetyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose as indicative of a skew and a virtually undistorted chair conformation, respectively, but Cone and Hough[10] employed p.m.r. coupling data to assign a skew conformation to the latter compound, which contains two *cis*-fused dioxolane rings; furthermore, an X-ray crystallographic study[11] of the former compound established that the conformation in the solid state is actually a flattened chair, and it was demonstrated that the n.m.r. data are not inconsistent with this conformation in solution also. Similarly, flattened-chair conformations have been educed for 1,2-*O*-(2-butylidene)-α-D-glucopyranose and related

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acetals[12], for 3,4,6-tri-*O*-acetyl-1,2-*O*-(2-tetrahydrofuranylidene)-α-D-glucopyranose[13], for 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranoses[14], and for several mono- and di-isopropylidene acetals of D-fructopyranose and L-sorbopyranose[15]; in accord with the initial observations on inositols[2], only the *cis,cis* fused diacetal 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose appears to adopt a skew arrangement[15]. Most probably, the conformation of 4-acetamido-3-*O*-acetyl-4-deoxy-1,2-*O*-isopropylidene-α-L-xylopyranose, originally suggested[16] to be a skew form on the basis of previous interpretations[9,10], is actually a distorted $^1C_4$(L) conformation whose shape tends towards the $_4H^5$(L) form.

The potential scope and generality of p.m.r. methods of conformational analysis has not been realized for examples whose signals overlap[17] so that desired information may be concealed; however, complexation to paramagnetic ligands has been shown[18] to effect, in many instances, useful separation of the signals within the spectra of carbohydrate derivatives. Examples have been reported[19] in which the conformational equilibrium[6a] of conformationally labile molecules has been altered substantially in the presence of a full molar equivalent of a tris[β-diketonato]Eu(III) complex, and this possible effect always needs careful consideration when high concentrations of shift reagent are used. However, the conformation of an acyclic sugar derivative (D-arabinose diethyl dithioacetal) in the presence of 0.1 equivalent, or less, of Eu^{3+} has been found[20] in accord with predictions based on numerous, related examples for which no shift reagent was used[21]. For relatively low concentrations of added complexant, it seems reasonable to assume that conformational perturbations are minimal at the most, if no changes in spin-coupling values are observed in the presence of low concentrations of the shift reagent. In an earlier study based on a broad range of relative concentrations of several different lanthanide ions, the conformations of two nucleotides were estimated directly by laborious reduction of induced-shift and -linewidth data for comparison with sets of values predicted for an incrementally varied sequence of conformational models[22].

DISCUSSION

During an investigation of the configurations of branched-chain sugar derivatives by Eu(III)-shifted, p.m.r. spectroscopy[23], we observed that the incompletely separated, 100-MHz, p.m.r. spectra of 4,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (**1**), methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**2**), and 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**3**) underwent differential dispersion in the presence of 20–100 meq of tris[6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato]europium(III)[24], [Eu(fod)$_3$], allowing extraction of a complete set of first-order spin-coupling values for **1** and **2**. Although separation of all signals in the p.m.r. spectrum of **3** was accomplished only at the expense of line-broadening that obscured some of the coupling information, first-order estimation of all of the coupling constants for **3** was possible because no signal-overlaps involved strongly coupled pairs of protons.

*4,6-Dideoxy-1,2-*O*-isopropylidene-α-*D-xylo*-hexopyranose* (**1**). — Spin-coupling values, measured as the spacings between lines of multiplets in the 100-MHz, p.m.r. spectrum (Fig. 1) of **1** in the presence of 24 meq of Eu(fod)$_3$ in carbon tetrachloride solution, were: $J_{1,2} = J_{2,3}$ 5.1, $J_{3,4}$ 6.0, $J_{3,4'}$ 6.7, $J_{4,4'}$ 13.8, $J_{4,5}$ 4.6, $J_{4',5}$ 9.6, and $J_{5,6}$ 6.0 Hz. These couplings are inconsistent with a conformation having the fully staggered arrangement that characterizes chair conformations of non-fused pyranoses. The values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ are all intermediate in magnitude between those expected[6] for gauche (2–3 Hz) and for antiparallel (8–9 Hz) vicinal pairs of protons, which suggests that flattening of the 6-membered ring has occurred by torsion about the C-1–C-2 bond to narrow the H-1–H-2 dihedral angle and amplify $J_{1,2}$; twisting of the H-2–H-3 arrangement away from the antiparallel, diaxial relationship would accompany this flattening, and the depressed value of $J_{2,3}$ relative to a normal $J_{\text{antiparallel}}$ is in accord with this formulation. The observation of a large (9.6 Hz) coupling between H-5 and one proton on C-4 indicates that H-5 is close to the axial disposition, so that a conformation distorted away from the $^4C_1$(D) towards the $^4H_5$(D) form is indicated for **1** in the presence of 24 meq of Eu(fod)$_3$. As the resonances of H-1 and H-4, which are also identifiable in the spectrum of compound **1** prior to the introduction of the shift reagent, are not visibly altered in shape by the presence of 24 milliequivalents of Eu(fod)$_3$, this conformational assignment may be extended to uncomplexed **1** as well.

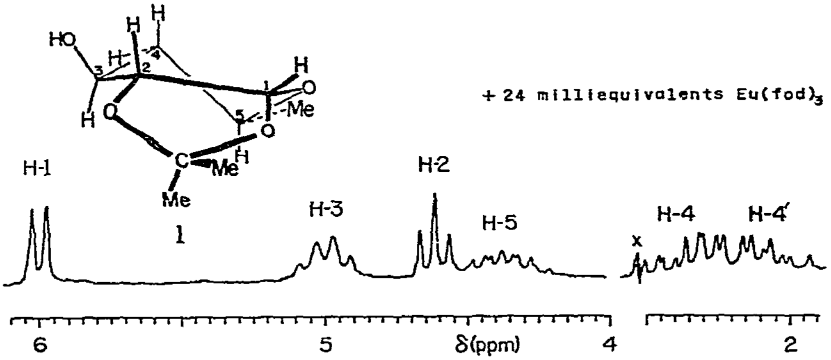
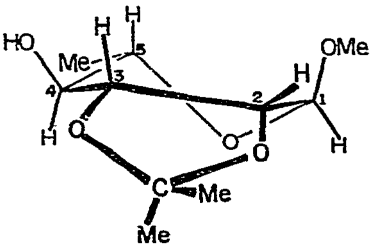


Fig. 1. Partial, 100-MHz, p.m.r. spectrum of 4,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (**1**) in the presence of 24 milliequivalents of Eu(fod)$_3$; the solvent is carbon tetrachloride.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*L*-mannopyranoside* (**2**). — First-order spin-coupling parameters ($J_{1,2}$ ~0, $J_{2,3} = J_{3,4}$ 5.8, $J_{4,5}$ 3.9, $J_{5,6}$ 6.1 Hz) measured from the p.m.r. spectrum of **2** in the presence of 60 meq of Eu(fod)$_3$ in carbon tetrachloride are inconsistent with a chair conformation; the small values observed for $J_{1,2}$ (~0 Hz) and $J_{4,5}$ (3.9 Hz) accord with twisting of the C-2–C-3 bond of **2** in order to bring C-1 and C-4 closer to the same plane, which increases the dihedral angle relating H-1 and H-2 from 60° to ~90° and decreases the dihedral angle relating H-4 and H-5 from 180° to some smaller value. The magnitude of the coupling (5.8 Hz) between the protons on the dioxolane ring is similar to that (5.1 Hz) measured for the analogous pair of protons in **1**. Accordingly, **2** in the presence of 60 meq of Eu(fod)$_3$ and, by extrapolation, **2** may be assigned the approximate conformation illustrated, which is intermediate between the $^1C_4$(L) and $^5H_0$(L) conformations.



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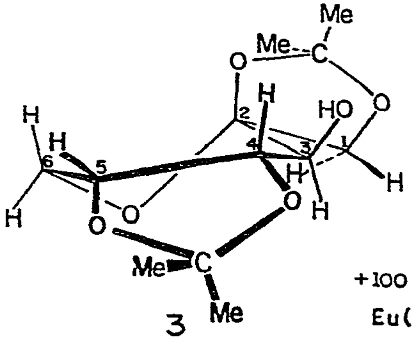
1,2:4,5-Di-O-isopropylidene-β-D-fructopyranose (**3**). — First-order coupling values ($J_{1,1'}$ 9.0, $J_{3,4}$ 6.5, $J_{4,5}$ 5.5, $J_{5,6}$ 2.5, $J_{5,6'}$ <1, $J_{6,6'}$ 13.2 Hz) were determined as spacings within multiplets in the 100-MHz p.m.r. spectrum (Fig. 2) of a 10% solution of **3** in chloroform-*d* to which 100 meq of Eu(fod)$_3$ had been added as a saturated solution in carbon tetrachloride. As with **1** and **2**, the coupling data ($J_{3,4}$ 6.5, $J_{4,5}$ 5.5 Hz) do not support a fully staggered conformation for the 6-membered ring in compound **3**, but rather suggest flattening of the C-4–C-5 bond to



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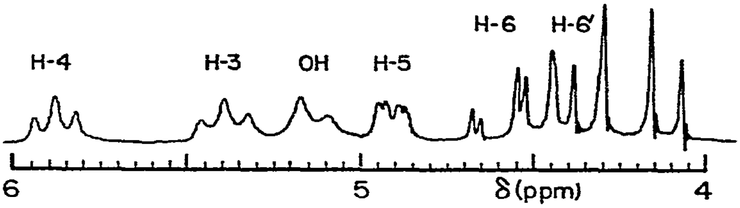

Fig. 2. Partial, 100-MHz, p.m.r. spectrum of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (3) in the presence of 100 milliequivalents of Eu(fod)$_3$; the solvent is chloroform-*d* containing ~20% of carbon tetrachloride.

(*a*) draw the H-4–C–C–H-5 angle towards 0° (amplifying $J_{4,5}$ from ~3 Hz), (*b*) narrow the H-3–C–C–H-4 angle from 180° to ~140° (decreasing $J_{3,4}$ from the large value characteristic[6] of the antiparallel arrangement of protons), and (*c*) rotate H-5 towards an eclipsed arrangement with the *cis*-related proton on C-6; the latter proton experiences a stronger coupling interaction with H-5 ($J_{5,6}$ 2.5, $J_{5,6'}$ <1 Hz) and is, therefore, identified as the C-6 proton resonance (H-6) observed at lower field. The data thus indicate for **3** in the presence of 100 meq of Eu(fod)$_3$ (and, by extension, for **3**) a conformation intermediate between the $^2C_5$(D) and $^2H_0$(D) forms. The same general conformation has been demonstrated[25] for **3** in the solid state by X-ray crystallography, and for the acetate of **3** in solution, by n.m.r. spectroscopy[15].

Interestingly, the hydroxyl proton resonance of **3** occurred as a broad singlet in the unperturbed 100-MHz spectrum, but the addition of a trace of Eu(fod)$_3$ caused this signal to be converted into a doublet having $J_{3,OH}$ 7.4 Hz; this effect may possibly be a consequence of some change in the exchange rate of the hydroxyl proton arising from complexation to the cation.

EXPERIMENTAL

P.m.r. spectra of solutions of **1** and **2** (in carbon tetrachloride) and of **3** (in chloroform-*d*) containing ~5% of tetramethylsilane as an internal calibrant and lock

TABLE I

UNPERTURBED[a] CHEMICAL SHIFTS (δ) AND SHIFT-GRADIENTS[b] (Δδ) MEASURED FOR COMPOUNDS 1–3 AT 100 MHz

Signal	**1**		**2**		**3**	
	$\delta^{c,d}$	$\Delta\delta^{b}$	$\delta^{c,d}$	$\Delta\delta^{b}$	$\delta^{c,e}$	$\Delta\delta^{b}$
H-1	5.49	(20)	4.77	(2.7)	3.96	(1.2)
H-1′					4.25	(1.3)
H-2	3.80	(34)	4.04	(4)		
H-3	3.80	(48)	3.97	(10)	3.67	(17)
H-4	1.95	(16)	3.19	(11)	4.12	(17)
H-4′	1.25	(35)				
H-5	4.06	(15)	3.55	(5.5)	4.19	(6.8)
H-6	1.17	(12)	1.30	(1.6)	4.12	(4.5)
H-6′					3.96	(4.2)
OH	3.45	(170)	3.60	(24)	2.47	(25)
OMe			3.32	(1.5)		
OCMe	1.36	(4)	1.21	(2.3)	1.36	(4.2)
	1.50	(6.5)	1.45	(2.4)	1.45	(0.5)
					1.49	(3.8)
					1.51	(1.2)

[a] Chemical-shift values for ~10% solutions of compounds **1–3**, extrapolated to zero concentration of added Eu(fod)$_3$. [b] Expressed in p.p.m. displacement downfield per equivalent of Eu(fod)$_3$ added; maximum relative concentrations of Eu(fod)$_3$ were 0.04 eq (**1**), 0.14 (**2**), and 0.17 (**3**). [c] In p.p.m. downfield from tetramethylsilane. [d] In carbon tetrachloride. [e] In chloroform-*d*.

signal were measured with a Varian HA-100 spectrometer in the frequency-swept mode. A saturated solution of Eu(fod)$_3$ was added incrementally between spectral acquisitions. Specific procedures are described in ref. 23. Values of chemical shifts and shift gradients thus determined are recorded in Table I.

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