

# P.M.R Evidence for Diaxial Long-Range Couplings in Some Pyranosid-2- and 3-Ulose Derivatives

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## Introduction

Long-range coupling constants over four bonds ( ${}^4J$ ), which are closely correlated with stereochemistry, provide valuable information on structures, conformations and configurations of organic compounds (1,2). It is generally known that the occurrence of intensive  ${}^4J$  long-range couplings in saturated cyclic systems requires a bonding system of the coupled protons in the planar W-arrangement (3,4), and indeed the protons of a 1,3-diequatorial orientation in a pyranoid carbohydrate with the chair conformation have been reported to show  ${}^4J_{e,e}$ . On the contrary, there have been several reports demonstrating occurrence of 1,3-diaxial long-range couplings in halogenocyclohexanones (5) and carbohydrates (6-8). In a previous paper (9), the author has reported a small  ${}^4J_{a,a}$  long-range coupling constant (1.0 Hz) between H-2 and H-4 in methyl 2-O-acetyl-4, 6-O-benzylidene- $\alpha$ -D-ribo-hexopyranosid-3-ulose (1).

This communication describes the existence of " ${}^4J_{a,a}$  long-range couplings" and the relative signs of the long-range couplings using a series of methyl 4,6-O-benzylidene- $\alpha$ - and  $\beta$ -D-hexopyranosid-2- and 3-ulose derivatives (1-8) (Fig. 1) which may serve as good models for p.m.r. study on ulose derivatives by virtue of their conformational rigidity due to the *trans* fused 4,6-O-benzylidene acetal ring.

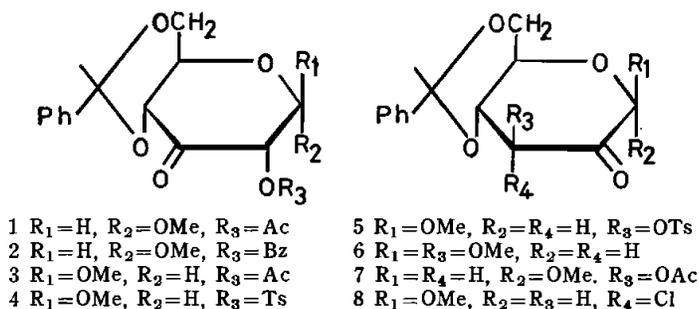


Fig. 1 Structural formular.

1) A similar study on  ${}^4J_{a,a}$  long-range couplings of hexopyranosiduloses, but with no conformational discussion, by Collins *et al.* (23) has been reported at the completion of this study.

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### Discussion

The p.m.r. spectra of compounds 1-6 were obtained from solution in chloroform-*d* and the data obtained from first-order analyses of the spectra are summarized in Table 1. These assignments were further confirmed by

Table 1. Chemical shifts ( $\tau$ ) and coupling constants (Hz) of methyl 4,6-*O*-benzylidene- $\alpha$ - and  $\beta$ -D-hexopyranosidulose derivatives in  $\text{CDCl}_3$  at 90 MHz

Compounds	1	2	3	4	5	6
benzylic	4.44(s)	4.41(s)	4.45(s)	4.44(s)		4.42(s)
H-1	4.81(d)	4.67(d)	5.38(d)	5.42(d)	5.63(s)	5.62(s)
H-2	4.62(q)	4.37(q)	4.50(q)	4.98(q)		
H-3					5.40(d)	
H-4	5.20(q)		5.63(q)	5.71(q)		
OMe	6.57(s)	6.53(s)	6.44(s)	6.53(s)	6.62(s)	6.29(s) 6.39(s)
OAc	7.80(s)		7.82(s)			
$\text{CH}_3$				7.59(s)	7.77(s)	
$J_{1,2}$	4.3	4.5	8.0	7.4	0	0
$J_{1,3}$					0	0
$J_{2,4}$	1.0	1.0	1.4	1.2		
$J_{3,4}$					9.8	
$J_{4,5}$	9.5		9.5	9.8		

s=singlet; d=doublet; q=quartet.

decoupling experiments and a typical example is shown in Fig. 2. Irradiation of the H-1 signal causes the quartet of H-2 to collapse into a narrow doublet. Irradiation of H-2 signal results in collapse of the H-4 quartet to a large spacing doublet and the H-1 doublet to a sharp singlet. Irradiation of the H-4 signal also causes the H-2 quartet to a doublet. These results distinctly indicate the existence of the  $^4J$  long-range coupling between H-2 and H-4. The stable conformation of methyl 4,6-*O*-benzylidene- $\alpha$ - and  $\beta$ -D-*ribo*-hexopyranosid-3-ulose derivatives (1-4), in which conformational changes are expected by introduction of a carbonyl group to the pyranoid ring, was concluded by applying the Karplas equation (10) to the vicinal coupling constants obtained from the spectra. It is generally known (11) that the H-4, H-5, H-6, and H-6' signals of benzylidene derivatives appear as an unresolved complex band, making their  $J_{4,5}$  coupling constants difficult to analyse. However, it is of interest to note that the signal of H-4 of compounds 1,3 and 4 occurs at relatively low-field, and hence the  $J_{4,5}$  values could be readily measured. Since the chair conformation is considered to be reasonable in the benzylidene acetal ring, in which the large phenyl group adopts the equatorial orientation (11), it follows that the possible conformation for the present 3-ulose derivatives (1-4) are the chair ( $\text{C}_1^4$ ), the boats ( $\text{B}^{4'1}$ ) and ( $\text{B}_{5,2}$ ), and the skew boat ( $\text{S}_5^1$ ) (11,12). The proton-proton

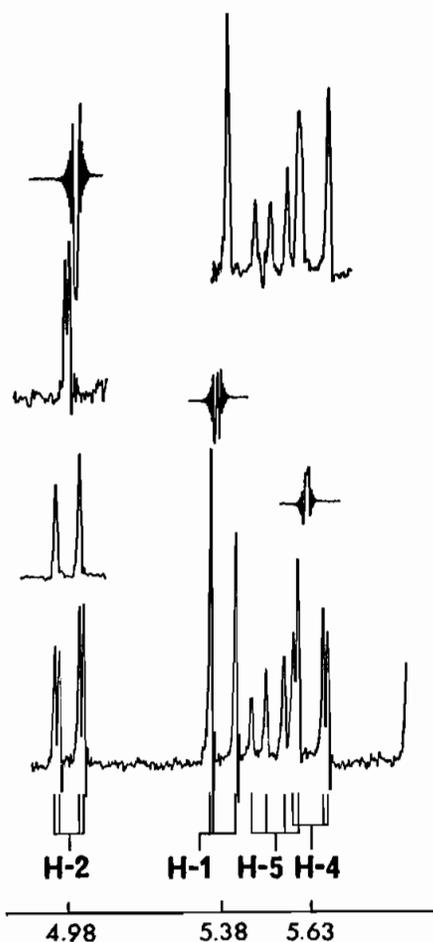


Fig. 2 Double resonance spectra of methyl 2-*O*-acetyl- 4,6-*O*-benzylidene- $\beta$ -*D*-*ribo*-hexopyranosid-3- ulose in  $\text{CDCl}_3$  ( $\tau$ ).

dihedral angles of the pyranoid ring in the above conformations are summarized in Table 2.

Table 2. Dihedral angles between substituents on the *D*-glucopyranoside ring

Conformation	$\phi_{1,2}$		$\phi_{4,5}$
	$\alpha$	$\beta$	
Chair ( $C_1^4$ )	$60^\circ$	$180^\circ$	$180^\circ$
Boat ( $B_4^{1'}$ )	$60^\circ$	$60^\circ$	$180^\circ$
Boat ( $B_{5,2}$ )	$60^\circ$	$60^\circ$	$180^\circ$
Skew ( $S_5^1$ )	$71^\circ$	$49^\circ$	$169^\circ$

The coupling constants ( $J_{1,2} = 4.3$ - $4.5$ ,  $J_{4,5} = 9.5$  Hz) for the  $\alpha$ -*D*-3-uloses 1 and 2 exhibit the 1,2-*gauche* ( $\phi = 60^\circ$ ) and the 4,5-*trans* diaxial ( $\phi = 180^\circ$ ) orientations of the protons, whereas for the  $\beta$ -*D*-3-uloses 3 and 4, the values of  $J_{1,2}$  (7.4-8.0 Hz) and  $J_{4,5}$  (9.5-9.8 Hz) indicate the existence of the 1,2-*trans* diaxial and the 4,5-*trans* diaxial arrangements of the protons, respectively. These facts support that the pyranoid ring of the  $\beta$ -*D*-3-uloses exists in the chair ( $C_1^4$ ) conformation. For the  $\alpha$ -*D*-3-uloses, only conformation precluded by the above observations is the skew boat ( $S_5^1$ ) conformation.

However, a favored conformation for the  $\alpha$ -*D*-3-uloses is considered to be the same chair conformation as that for the  $\beta$ -*D*-3-uloses, since the methoxyl group at C-1 is more stable in axial than in equatorial orientations because of the anomeric effect (13). Accordingly, the protons of H-2 and H-4 in compounds 1-4 must be in axial orientations and therefore the  $^4J$  long-range couplings observed in the compounds are unequivocally the 1,3-diaxial long-range couplings. On the other hand, no  $^4J_{en}$  long-range couplings between H-1 and H-3 were observed for methyl 3-*O*-acetyl-4,6-*O*-benzylidene- $\alpha$ -*D*-*arabino*-hexopyranosid-2-ulose (7) and methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy- $\beta$ -*D*-*ribo*-hexopyranosid-2-ulose (8). It is noteworthy that this compound is prepared *via* oxidation of methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy- $\beta$ -*D*-*allopyranoside* (14) by dimethyl sulfoxide-acetic anhydride and during the oxidation the axial chloro-deoxy

group remains intact in spite of its adjacency to the carbonyl group at C-2. This completely eliminates the possibility that the epimerization (15) at asymmetric centers adjacent to a carbonyl group could take place through transition-state phase followed by interchange of an adjacent axial substituted group to the thermodynamically more favored equatorial one. This result seems to indicate the absence of the 1,3-diaxial interaction consequent upon an equatorial orientation of the methoxyl group at C-1.

These results are analogous to those obtained with halogenocyclohexanone and halogenodecalone (5), in which  $^4J$  long-range couplings are observed when the protons of  $\alpha$ ,  $\alpha'$ -type exist in axial-axial orientations rather than in axial-equatorial orientations. This finding may be explained by  $\sigma$  and  $\pi$  contributions (3,5), *i.e.*, this type of the long-range coupling is accentuated when the protons involved are in diaxial orientations which are most favorable for the transmission of spin state information *via* overlapping of  $\sigma$ - $\pi$  orbital.

It was demonstrated (3) that the relative signs of nuclear spin coupling constants provide informations on the spin-states of a nucleus to a neighboring nucleus. Accordingly, the determination of the relative signs may be useful for studying the theories of molecular electronic structure. In order to determine the signs of the  $^4J_{n,n}$  long-range coupling constants of the 3-uloses, INDOR (internuclear double resonance) techniques (16,17) were applied.

The spectra of compound **3** are presented in Fig. 3. Four different INDOR spectra were obtained. Each of the INDOR spectra contains positive and negative peaks and the spacings  $\Delta\nu_{1,3}$  and  $\Delta\nu_{5,6}$ ,  $\Delta\nu_{1,2}$ ,  $\Delta\nu_{3,4}$ ,  $\Delta\nu_{7,8}$  and  $\Delta\nu_{9,10}$ , and  $\Delta\nu_{7,9}$  and  $\Delta\nu_{8,10}$  equal to  $J_{1,2}$  and  $J_{2,4}$ , and  $J_{2,8}$ , respectively. Monitoring of line 1 causes the appearance of three pairs of negative-positive peaks (Spectrum 1) whereas monitoring of line 2 leads to the occurrence of two pairs of positive-negative peaks at high-field with respect to those of spectrum 1 (Spectrum 2). These results indicate that the spin system of H-2 and H-4 is an AB system. Therefore, the relative sign could not be determined unfortunately.

The long-range coupling between H-1 and H-3 similar to those observed for the 3-uloses **1-4** is expected for methyl 4,6-*O*-benzylidene- $\beta$ -D-*arabino*-hexopyranosid-2-ulose derivatives (**5** and **6**), since H-2 and H-4 in the 3-uloses **1-4** and H-1 and H-3 in the 2-uloses **5** and **6** are similarly arranged in a system H-C-C-C-H on the chair conformation. Indeed, Collins *et al*, (8) reported



$^4J_{1,3}$  long-range couplings (0.8 Hz) in alkyl (isopropyl- or *ter*-butyl-) 3,4-*O*-isopropylidene- $\alpha$ -L-*erythro*-pentopyranosid-2-uloses. However, it was found that compounds **5** and **6** showed no  $^4J_{n,n}$  long-range coupling between H-1 and H-3. This finding is of interest in relation to their stereochemistry, since it is considered that  $^4J_{n,n}$  long-range coupling is observed when the coupled protons are in axial-axial orientations. On the basis of the above arguments, a possible conformation for the 2-uloses **5** and **6** is suggested to be a slightly strained

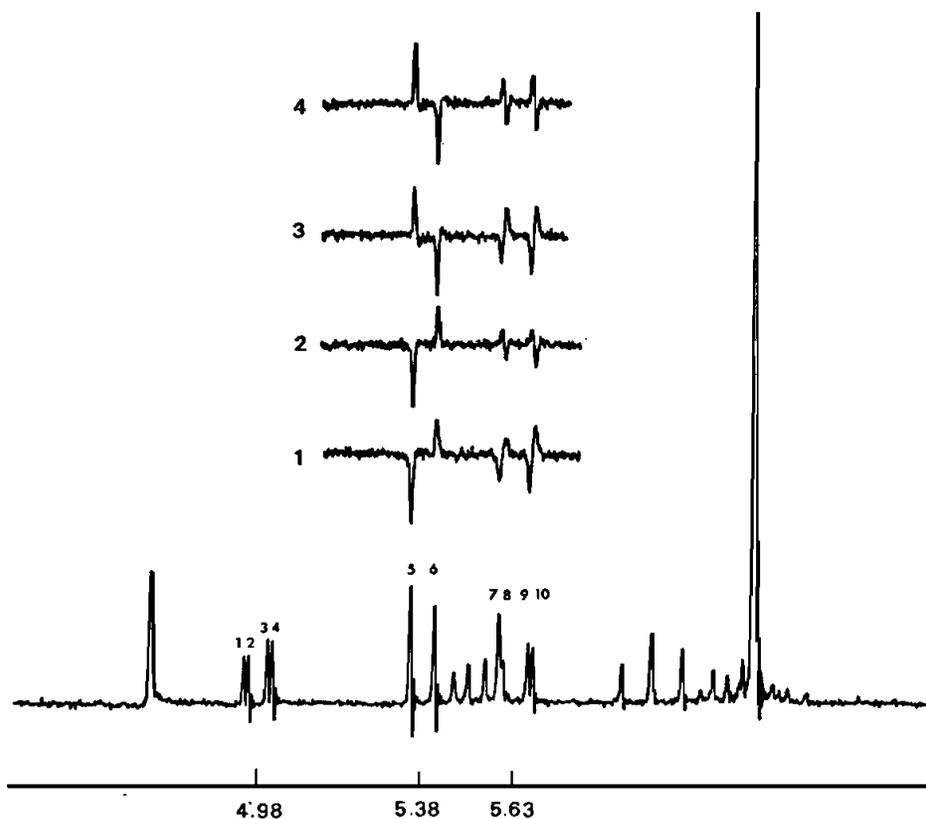


Fig. 3 INDOR spectra of methyl 2-*O*-acetyl-4,6-*O*-benzylidene- $\beta$ -D-ribohexopyranosid-3-*ulose* (3) in  $\text{CDCl}_3$  ( $\tau$ ).

chair conformation, in which H-1 and H-3 are, accordingly, slightly distorted from the normal diaxial orientations.

### Experimental

Melting points were determined on a Yanagimoto hot stage microscope and are uncorrected. Optical rotations were measured with a Yanagimoto OR-20 polarimeter and IR spectra were recorded with a Hitachi EPI-G3 by the potassium bromide disk method. P.m.r. spectra were measured on a Hitachi-Perkin-Elmer 90 MHz spectrometer using tetramethylsilane as an internal reference at the normal operating temperature of the instrument. The solutions used were either saturated, or contained *ca.* 30 mg of compound in 0.4 ml chloroform-*d* and chemical shifts were measured at the 800-Hz sweep-width and coupling constants directly obtained from the spectra recorded at the 400-Hz or 200-Hz sweep-widths. INDOR spectra were measured on a Varian HA-100D spectrometer with a Varian Wave Tek oscilator.

The sugar derivatives investigated in this study were either prepared by standard procedures in the literature or by the methods to be published elsewhere.

Methyl 2-*O*-acetyl-4,6-*O*-benzylidene- $\alpha$ -D-*ribo*-hexopyranosid-3-ulose (1) was prepared by the method of Kondo and Takao (9).

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene- $\alpha$ -D-*ribo*-hexopyranosid-3-ulose (2) had m.p. 214-216°C (lit. (18), m.p. 211-213°C) and methyl 4,6-*O*-benzylidene-3-*O*-methyl- $\beta$ -D-*arabino*-hexopyranosid-2-ulose (6) had m.p. 171-173°C (lit. (19), 172°C).

Methyl 2-*O*-acetyl-4,6-*O*-benzylidene- $\beta$ -D-*ribo*-hexopyranosid-3-ulose (3) was prepared by the method previously reported (20).

Preparation of methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl- $\beta$ -D-*ribo*-hexopyranosid-3-ulose (4) and methyl 4,6-*O*-benzylidene-3-*O*-*p*-tolylsulfonyl- $\beta$ -D-*arabino*-hexopyranosid-2-ulose (5) will be described elsewhere (21).

*Methyl 2-O-Acetyl-4,6-O-benzylidene- $\alpha$ -D-arabino-hexopyranosid-2-ulose (2).*

A solution of methyl 3-*O*-acetyl-4,6-*O*-benzylidene- $\alpha$ -D-glucopyranoside (22) (300 mg) in dimethyl sulfoxide (15 ml) and acetic anhydride (3 ml) was stirred for 4 days at room temperature. The solution was poured into a chilled mixture of chloroform and saturated sodium bicarbonate solution. The chloroform layer was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to give a white residue which, on recrystallization from ethanol, gave the title compound (273 mg), m.p. 103-104°C,  $[\alpha]_D^{14} + 36.0^\circ$  ( $c=0.6$ ,  $\text{CHCl}_3$ ). The i.r. data:  $\nu_{\text{max}}$  1768 ( $\text{C}=\text{O}$ ),  $1752\text{cm}^{-1}$  ( $\text{C}=\text{O}$ , ester). The p.m.r. data (in  $\text{CDCl}_3$ ):  $\tau$  4.23 (1H doublet, H-3,  $J_{3,4}=11.0$  Hz), (1H singlet, benzylic H), 5.20 (1H singlet, H-1), 6.47 (3H singlet, OMe), 7.80 (3H singlet, OAc).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{18}\text{O}_7$ : C, 59.62; H, 5.63. Found: C, 59.54; H, 5.91.

*Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy- $\beta$ -D-ribo-hexopyranosid-2-ulose (8).*

A solution of methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy- $\beta$ -D-allopyranoside (300 mg) in dry dimethyl sulfoxide (30 ml) with acetic anhydride (2 ml) was stirred for 3 days at room temperature. The solution was diluted with chloroform and then extracted with chloroform. The extract was washed with aqueous saturated sodium bicarbonate solution and water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The crystalline residue was recrystallized from ethanol to give fine needles (226 mg), m.p. 219°C  $[\alpha]_D^{20} - 118.0^\circ$  ( $c=0.5$ ,  $\text{CHCl}_3$ ). The i.r. data:  $\nu_{\text{max}}$  1755 ( $\text{C}=\text{O}$ ),  $796\text{cm}^{-1}$  (Cl). The p.m.r. data (in  $\text{CDCl}_3$ ):  $\tau$  4.44 (1H singlet, benzylic H), 5.54 (1H singlet, H-1), 5.69 (1H doublet, H-3,  $J_{3,4}=4.0$  Hz), 6.35 (3H singlet,  $\text{OCH}_3$ ).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{15}\text{O}_5\text{Cl}\cdot\text{H}_2\text{O}$ : C, 53.09; H, 5.41; Cl, 11.19. Found: C, 52.87; H, 5.72; Cl, 11.16.

### Summary

Diaxial long-range couplings over four bonds ( $^4J_{a,n}$ ), which are extremely rare with carbohydrates, were observed in the system  $\text{H}-\text{C}-\text{C}-\text{C}-\text{H}$  in a series of methyl 4,6-*O*-benzylidene- $\alpha$ - and  $\beta$ -D-*ribo*-hexopyranosid-3-ulose

derivatives. The conformation of a series of the compounds has been studied from the coupling constants directly obtained from first-order analyses of the spectra by p.m.r. spectroscopy. Determination of the relative signs of the  ${}^4J_{n,n}$  long-range coupling constants has been attempted by means of INDOR (internuclear double resonance) techniques.

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