Branched-chain Sugars. XIX. On the Application of $^{13}$C NMR Spectroscopy to the Configurational Assignment of 3-C-Substituents of Aldohexopyranose Derivatives 1

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It was found that $^{13}$C NMR spectroscopy is applicable to the unequivocal configurational assignment at the quaternary carbon in seven pairs of 3-C-substituted-hexopyranose derivatives. The configuration of methyl 4,6-O-benzylidene-3-C-nitromethyl-2-O-p-tolylsulfonylex-D-glucopyranoside reported by Jordaen et al. is revised to $\alpha$-allo by a chemical method.

Determination of the configuration of a branching carbon atom in branched-chain sugars having no hydrogen atom at the branching point is difficult, no simple and reliable method being available. In our work on the subject, chemical derivations, cuprammonium complex formation, and the chemical shift of tertiary acetoxyl protons have been used. However, some exceptions in $^1$H NMR method have been found in the case of branched-chain sugars.

Recently, lanthanoid-induced changes in the chemical shifts of $^1$H NMR7 and the $^{13}$C chemical shift differences between axial and equatorial carbons8 have been used to elucidate the configuration of tertiary alcohols. Centers of several branched-chain sugars.

Among these compounds, only methyl 4,6-O-benzylidene-2-C-methyl-3-O-arabino-hexose (18),1) and one pair of 2-C-methyl-D-allo- (19) and -glucopyranoside (20).4a) was hydrogenated in the presence of well-washed Raney nickel and then subjected to N-benzoylation with benzoic anhydride to give the corresponding 3-C-(benzoylamino) methyl derivative (4). Treatment of 3 in pyridine with equimolar $p$-toluenesulfonfyl chloride also gave 4. Thus, the $\beta$-gluco configuration of 1 assigned by shift reagent method was revised to $\alpha$-allo (2) by the chemical method.

The fact that equatorially oriented branching carbons are deshielded with respect to axially oriented carbons in $^{13}$C NMR for the configurational assignment of branched-chain pyranoses has been shown by examination of three epimeric pairs of 4-C-methyl,11) two pairs of 3-C-hydroxymethyl,8) one pair of 3-C-methyl derivatives9) possessing an hydroxyl group at the quaternary carbon, and one pair of 2-deoxy-2-C-methyl derivatives.11) We have examined seven epimeric pairs of 3-C-substituted derivatives: methyl 2-O-acetyl-4,6-O-benzylidene-3-C-methyl-$\alpha$-d-allo- (5) and -glucopyranoside (6),10) their 3-O-acetyl derivatives (7 and 8),10) methyl 4,6-O-benzylidene-3-C-methyl-2-O-methyl-$\alpha$-d-allo- (9) and glucopyranoside (10),4a) methyl 4,6-O-benzylidene-3-C-methyl-2-O-methyl-$\alpha$-d-altro- (11) and -manno pyranoside (12),4a) methyl 2-O-acetyl-3-C-(benzoylamino)methyl-4,6-O-benzylidene-$\alpha$-d-allo- (13)10) and -glucopyranoside (14), methyl 3-acetylamino-2,3,6-trIDEOxy-3-C-methyl-4-O-methyl-$\alpha$-L-ribo- (15) and -arabino-hepxyneoside (16),13) 2,3,6-trideoxy-3-C-methyl-4-O-methyl-3-nitro-L-ribo- (17) and -arabino-hexose (18),13) and one pair of 2-C-methyl derivatives: methyl 4,6-O-benzylidene-2-C-methyl-3-O-methyl-$\alpha$-d-altro- (19) and -allop yranoside (20).4a) Among these compounds, only 14 was newly synthesized by acetylation of the 3-epimer of 3(10) in pyridine with acetic anhydride.

Chemical shifts of the chain carbons and 3-C-branching carbon of hexopyranoses and shift differences between axially and equatorially oriented carbons at $C_3$ in 5–18 and at $C_4$ in 19 and 20 are summarized in Table 1. The carbon shifts were distinguished.

RESULTS AND DISCUSSION

Methyl 4,6-O-benzylidene-3-C-[benzoylaminoethyl]-$\alpha$-d-allopyranoside (3) was obtained by the reaction of methyl 4,6-O-benzylidene-2-O-benzoyl-$\alpha$-d-ribo-hexopyranosid-3-olose with nitromethane, followed by hydrogenation which was accompanied by $O\rightarrow N$ benzoyl migration.10) The configuration of 3 was confirmed by comparison of the rotational change in cuprammonium solution with that of its 3-epimer synthesized from the same 3-olose by the successive reactions; spiro-epoxidation with diazomethane, epoxy-ring opening with ammonia, and then $N$-benzoylation. From the results, the assignment of 3-gluco, configuration to a 3-C-nitromethyl derivative from nitromethane and 2-O-p-tolylsulfonyl analogue of the above 3-olose was highly doubtful. From the reaction conditions the 3-C-nitromethyl derivatives were considered to be thermodynamically stable products. Consequently, 1 prepared according to the method of Jordaen et al.9) was hydrogenated in the presence of well-washed Raney nickel and then subjected to N-benzoylation with benzoic anhydride to give the corresponding 3-C-(benzoylamino) methyl derivative (4). Treatment of 3 in pyridine with equimolar $p$-toluenesulfonfyl chloride also gave 4. Thus, the $\beta$-gluco configuration of 1 assigned by shift reagent method was revised to $\alpha$-allo (2) by the chemical method.

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Chemical shifts of the chain carbons and 3-C-branching carbon of hexopyranoses and shift differences between axially and equatorially oriented carbons at $C_3$ in 5–18 and at $C_4$ in 19 and 20 are summarized in Table 1. The carbon shifts were distinguished.
from other carbon shifts in phenyl, methine, methoxyl, and acetyl groups on the basis of their position, multiplicity and consistency.7,8,11-13) The methyl signals of the same chemical shift in a pair of 3-epimers were assigned to confusing methyl carbons in acetyl groups.

Of the carbon shifts given, C₃, C₅, quaternary carbon atoms and branching carbon atoms were identified from their chemical shifts and single frequency off-resonance decoupled spectra, the other carbons being assigned from their chemical shifts. The effect of acetylation of the tertiary hydroxyl group14) was observed on the chemical shifts of C₃ and branching carbons in 7 and 8, as compared with those in 5 and 6. The deshielding effect12) by O-methylation is also prominent in the chemical shifts of C₅ in 9—12, C₄ in 15 and 17, and C₅ in 19 and 20, but very small in the cases of 16 and 18. The lower field shifts from the usual position of branching carbons in 13 and 14, and of C₅ in 15—18 are attributed to the deshielding effects of the groups attached to them; the chemical shifts of C₄ and C₅ in 15—18 are reasonable for the deoxy carbon atoms of 2,6-dideoxy-4-O-methylhexoses.P) Data of 17 and 18 support the 'H NMR spectra which show that 17 exists almost completely in the B-form, whereas 18 exists in an a,β-mixture of nearly equal amounts.

The resonance due to the equatorial carbon atoms of 3-C-branching chains is always at a field lower than that of the axial carbons for the seven pairs of 3-C-substituted sugars examined (Table 1). Consistent results were also obtained for the sugars containing a benzoylaminomethyl group or a nitro group at quar-

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<th>Hexoses (configuration)</th>
<th>C₁</th>
<th>C₂</th>
<th>C₃</th>
<th>C₄</th>
<th>C₅</th>
<th>C₆</th>
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<td>71.6</td>
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<td>8 (D-glucu)</td>
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<td>61.5</td>
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a) Assignments may be reversed although those given here are preferred.
ternary carbon. It was established for seven pairs of 3-C-substituted sugars that the \( \Delta (\alpha-a) \) values in the \( ^{13}C \) NMR spectra permit the configurational assignment at the 3-C position. Inconsistent results for the 2-C-methyl derivatives 19 and 20 seem to be related to their conformations. At present only a somewhat flattened configuration can be deduced from the \( J_{\alpha,\beta}=2.0 \) Hz value for 20, more data being needed for 2-C-branching sugars.

**Experimental**

\( ^{13}C \) NMR spectra of branched-chain sugars, 5, 6, 9–12, 19, and 20 were obtained at 30 °C on a JEOL JNM FX-100 spectrometer in pulse Fourier transform/proton noise decoupled mode at 25.13 MHz in deuterochloroform. The corresponding spectra of 7, 8, and 13–18 were similarly recorded 32 °C on a Varian XL-100-15-FT spectrometer. Each spectrum was obtained after 1000 transients with a spectral width of 5000 Hz, a computer data memory size for the free induction decay of 8 K, an acquisition time of 0.8 s, a pulse delay of 0.8 s, and pulse angle of 45°. \( 'H \) NMR spectra were measured on a JEOL PS-100 spectrometer in pulse Fourier transform/proton noise decoupled mode at 25.13 MHz in deuteriochloroform. The corresponding spectra of 7, 8, and 13–18 were similarly recorded 32 °C on a Varian XL-100-15-FT spectrometer. Each spectrum was obtained after 1000 transients with a spectral width of 5000 Hz, a computer data memory size for the free induction decay of 8 K, an acquisition time of 0.8 s, a pulse delay of 0.8 s, and pulse angle of 45°.

\( ^{13}C \) NMR spectra permit the configurational assignment at the 3-C position. Inconsistent results for the 2-C-branching sugars.

**References**