

Branched-chain Sugars. XIX. On the Application of ^{13}C NMR Spectroscopy to the Configurational Assignment of 3-C-Substituents of Aldohexopyranose Derivatives¹⁾

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It was found that ^{13}C NMR spectroscopy is applicable to the unequivocal configurational assignment at the quarternary carbon in seven pairs of 3-C-substituted-hexopyranose derivatives. The configuration of methyl 4,6-*O*-benzylidene-3-*C*-nitromethyl-2-*O*-*p*-tolylsulfonyl- α -D-glucopyranoside reported by Jordaan *et al.* is revised to D-*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,¹⁾ and the chemical shift of tertiary acetoxyl protons³⁾ have been used. However, some exceptions in ^1H NMR method have been found in the case of branched-chain sugars.^{4–6)}

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

In the lanthanoid method, the magnitude of the shift gradient (proportional shift of the concentration to shift reagent) for each identifiable proton resonance of a tertiary alcoholic derivative is compared with that of the corresponding secondary alcohol of known stereochemistry. The uniform correspondence of the entire set of shift gradients is taken as evidence of their same relative configuration.⁷⁾ However, during the course of examination of the method for branched-chain sugars synthesized in our laboratory, we found that it is ambiguous in a few instances; the configuration of methyl 4,6-*O*-benzylidene-3-*C*-nitromethyl-2-*O*-*p*-tolylsulfonyl- α -D-glucopyranoside (**1**)⁹⁾ assigned by this method⁶⁾ has been revised to D-*allo* (**2**).

More data seemed necessary to establish the ^{13}C NMR method. In this paper, the above structure revision and consistent results in the examination of the ^{13}C NMR method for seven pairs of 3-C-substituted hexopyranose derivatives having various functional groups at the branching point are described.

Results and Discussion

Methyl 4,6-*O*-benzylidene-3-*C*-(benzoylaminomethyl)- α -D-allopyranoside (**3**) was obtained by the reaction of methyl 4,6-*O*-benzylidene-2-*O*-benzoyl- α -D-ribohexopyranoside-3-ulose 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-ulose by the successive reac-

tions; spiro-epoxidation with diazomethane, epoxy-ring opening with ammonia, and then *N*-benzoylation. From the results, the assignment of D-*gluco* configuration to a 3-*C*-nitromethyl derivative from nitromethane and 2-*O*-*p*-tolylsulfonyl analogue of the above 3-ulose 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 Jordaan *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*-(benzoylaminomethyl) derivative (**4**). Treatment of **3** in pyridine with equimolar *p*-toluenesulfonyl chloride also gave **4**. Thus, the D-*gluco* configuration of **1** assigned by shift reagent method was revised to D-*allo* (**2**) by the chemical method.

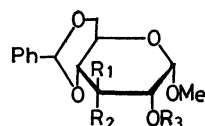
The fact that equatorially oriented branching carbons are deshielded with respect to axially oriented carbons in ^{13}C NMR for the configurational assignment of branched-chain pyranoses has been shown by examination of three epimeric pairs of 4-*C*-methyl,¹¹⁾ two pairs of 3-*C*-hydroxymethyl,⁸⁾ one pair of 3-*C*-methyl derivatives⁸⁾ possessing an hydroxyl group at the quarternary 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- α -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- α -D-allo- (**9**) and glucopyranoside (**10**),^{4a)} methyl 4,6-*O*-benzylidene-3-*C*-methyl-2-*O*-methyl- α -D-alto- (**11**) and -mannopyranoside (**12**),^{4a)} methyl 2-*O*-acetyl-3-*C*-(benzoylaminomethyl)-4,6-*O*-benzylidene- α -D-allo- (**13**)¹⁰⁾ and -glucopyranoside (**14**), methyl 3-acetyl-amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl- α -L-ribo- (**15**) and -arabino-hexopyranoside (**16**),¹⁾ 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-ribo- (**17**) and -arabino-hexose (**18**),¹⁾ and one pair of 2-*C*-methyl derivatives; methyl 4,6-*O*-benzylidene-2-*C*-methyl-3-*O*-methyl- α -D-alto- (**19**) and -allopyranoside (**20**).^{4b)} 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 C₃ in **5**—**18** and at C₂ in **19** and **20** are summarized in Table 1. The carbon shifts were distinguished

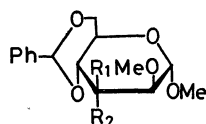
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from other carbon shifts in phenyl, methine, methoxyl, and acetyl groups on the basis of their position, multiplicity and consistency.^{7,8,11-13} The methyl signals of the same chemical shift in a pair of 3-epimers were assigned to confusing methyl carbons in acetyl groups.

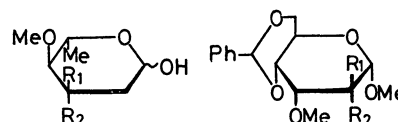
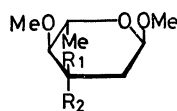
Of the carbon shifts given, C₁, C₆, quarternary carbon atoms and branching carbon atoms were identified



	R ₁	R ₂	R ₃
1	OH	CH ₂ NO ₂	Ts
2	CH ₂ NO ₂	OH	Ts
3	CH ₂ NHBz	OH	H
4	CH ₂ NHBz	OH	Ts
5	Me	OH	Ac
6	OH	Me	Ac
7	Me	OAc	Ac
8	OAc	Me	Ac
9	Me	OH	Me
10	OH	Me	Me
13	CH ₂ NHBz	OH	Ac
14	OH	CH ₂ NHBz	Ac



	R ₁	R ₂		R ₁	R ₂
11	Me	OH	15	NHAc	Me
12	OH	Me	16	Me	NHAc



	R ₁	R ₂		R ₁	R ₂
17	NO ₂	Me	19	OH	Me
18	Me	NO ₂	20	Me	OH

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 C₂ in **9**–**12**, C₄ in **15** and **17**, and C₃ 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 C₃ in **15**–**18** are attributed to the deshielding effects of the groups attached to them; the chemical shifts of C₂ and C₅ in **15**–**18** are reasonable for the deoxy carbon atoms of 2,6-dideoxy-4-*O*-methylhexoses.¹³ Data of **17** and **18** support the ¹H NMR spectra which show that **17** exists almost completely in the β -form, whereas **18** exists in an α,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 benzoylaminoethyl group or a nitro group at quar-

TABLE 1. ¹³C CHEMICAL SHIFTS OF CHAIN CARBON ATOMS AND BRANCHING CARBON ATOMS OF BRANCHED-CHAIN SUGARS AND THE CHEMICAL SHIFT DIFFERENCES BETWEEN AXIALLY AND EQUATORIALLY ORIENTED CARBON ATOMS (ppm from Me₄Si in CDCl₃)

Hexoses (configuration)	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆	C ₃ -CH ₃ (C ₃ -CH ₂ NHBz)	$\Delta(\epsilon-a)$
5 (D- <i>allo</i>)	98.1	72.3	71.6	81.8	59.2	68.9	20.7	3.7
6 (D- <i>gluco</i>)	97.7	74.8	72.5	83.5	61.3	69.0	17.0	
7 (D- <i>allo</i>)	97.9	72.9	79.9	82.7	58.9	69.1	19.3	3.2
8 (D- <i>gluco</i>)	98.4	70.2	83.3	78.1	61.4	69.1	16.1	
9 (D- <i>allo</i>)	97.8	80.3 ^a	72.1	81.8 ^a	58.9	68.8	20.6	3.9
10 (D- <i>gluco</i>)	97.9	83.0 ^a	73.8	83.3 ^a	61.0	69.0	16.7	
11 (D- <i>altro</i>)	99.0	79.6	71.1	82.8	59.7	68.9	21.0	2.5
12 (D- <i>manno</i>)	98.9	82.0	70.7	84.9	62.4	69.0	18.5	
13 (D- <i>allo</i>)	98.2	70.0	72.6	80.0	59.0	68.9	(43.1)	1.9
14 (D- <i>gluco</i>)	97.7	73.0	75.1	84.5	61.5	69.0	(41.2)	
15 (L- <i>ribo</i>)	99.7	38.5	56.7	87.9	69.7	18.4	24.7	4.6
16 (L- <i>arabino</i>)	99.7	40.5	56.4	82.9	70.3	19.0	20.1	
17 (L- <i>ribo</i>)	91.8	42.7	89.3	85.8	70.1	18.7	25.4	8.8
18 (L- <i>arabino</i>)	{92.4 90.5}	{44.2 40.9}	{90.3 89.8}	{84.4 84.7}	{71.2 66.1}	{18.4 ^a 18.4 ^a }	{16.6 18.6 ^a }	
19 (D- <i>altro</i>)	104.8	73.4	77.9	82.2	58.1	69.2	22.5	-1.5
20 (D- <i>allo</i>)	104.7	69.0	78.7	83.7	58.1	69.4	24.0	

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 $\Delta(e-a)$ values in the ¹³C 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 $J_{3,4}=2.0$ Hz value for **20**, more data being needed for 2-C-branching sugars.

Experimental

¹³C 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 25.15 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°. ¹H NMR spectra were measured on a JEOL PS-100 spectrometer with a CW mode. All measurements were carried out in a CDCl₃ solution containing a drop of TMS as an internal standard. Optical rotations were measured in 0.2-dm tubes in a Carl Zeiss LEP-A1 polarimeter. IR spectra were recorded with a Hitachi Model EPI-G2 spectrometer.

Chemical shifts and coupling constants in ¹H NMR were recorded in δ (ppm) and Hz, respectively, and IR frequencies in cm⁻¹.

Methyl 3-C-(benzoylaminomethyl)-4,6-O-benzylidene-2-O-p-tolylsulfonyl- α -D-allopyranoside (4). a): Methyl 4,6-O-benzylidene-3-C-nitromethyl-2-O-p-tolylsulfonyl- α -D-allopyranoside [300 mg, mp 143–145 °C, $[\alpha]_D^{25} +39.5^\circ$ (*c* 1.01, CHCl₃)] prepared by the method of Jordaan *et al.* [lit,⁹ mp 143–144 °C, $[\alpha]_D^{25} +41.6^\circ$ (*c* 1, CHCl₃)] was hydrogenated in ethanol in the presence of well-washed Raney nickel at room temperature, and then filtered. The filtrate was evaporated under reduced pressure. The residue was *N*-benzoylated with benzoic anhydride (150 mg) in ethanol to give **4** (121 mg) in 35% yields. Mp 184–185 °C (from ethanol), $[\alpha]_D^{25} +13.3^\circ$ (*c* 1.8, CHCl₃), IR: 3450 (NH), 3340 (OH), 1636 (NHBz), NMR: 8.00–7.24 (Ph:m), 7.10 (NH), 5.57 (PhCH), 4.74 (H₁: d, $J_{1,2}=4.0$), 4.61 (H₂: d), 4.36 (H₆: q, $J_{5,6}=4.0$), 4.28–3.95 (CH₂: m), 3.95 (H_{6'}: t, $J_{5,6'}=J_{6,6'}=9.0$), 3.38 (H₅: m), 3.35 (OMe), 2.43 (PhCH₃).

Found: C, 61.01; H, 5.35; N, 2.41; S, 5.58%. Calcd for C₂₉H₃₁NO₉S: C, 61.15; H, 5.49; N, 2.46; S, 5.63%.

b): Tosylation of methyl 3-C-(benzoylaminomethyl)-4,6-O-benzylidene- α -D-allopyranoside¹⁰ in pyridine with 1.2 equi-

molar *p*-toluenesulfonyl chloride gave **4** in 82% yield.

Methyl 2-O-Acetyl-3-C-(benzoylaminomethyl)-4,6-O-benzylidene- α -D-glucopyranoside (14). Acetylation of methyl 3-C-(benzoylaminomethyl)-4,6-O-benzylidene- α -D-glucopyranoside¹⁰ in pyridine with acetic anhydride in the usual manner gave the corresponding 2-acetate as a sirup in 93% yield; it was purified by silica-gel column chromatography. $[\alpha]_D^{25} +15.8^\circ$ (*c* 1.2, CHCl₃), NMR: 7.00–7.60 (Ph: m), 5.53 (PhCH), 4.98 (H₁: d, $J_{1,2}=3.5$ Hz), 4.90 (H₂: d), 4.70–3.60 (H₄, H₅, H₆, H_{6'}, CH₂: m), 3.40 (OMe), 2.20 (Ac).

Found: C, 63.23; H, 5.25; N, 3.06%. Calcd for C₂₄-H₂₃NO₈: C, 63.57; H, 5.11; N, 3.09%.

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