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CONFIGURATIONAL ASSIGNMENTS OF *C*-NITROMETHYL-*C*-HYDROXY BRANCHED-CHAIN CARBOHYDRATE DERIVATIVES BY USE OF A EUROPIUM SHIFT-REAGENT IN ^{1}H-N.M.R. SPECTROSCOPY*

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ABSTRACT

Configurational assignments for the tertiary alcoholic centers of four branched-chain 3-*C*-nitromethylglycopyranosides, namely, methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-nitromethyl-α-D-allopyranoside (**1**), benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-nitromethyl-α-D-glucopyranoside (**4**), benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-nitromethyl-α-D-allopyranoside (**5**), and methyl 4,6-*O*-benzylidene-3-*C*-nitromethyl-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (**8**), were made on the basis of the downfield chemical shifts of their identifiable protons per molar equivalent of added Eu(fod)$_3$, as compared with those of model compounds, of known configuration, having a close structural relationship. In some cases, the assignments were corroborated by the position of the acetyl resonances in the unshifted 60-MHz p.m.r. spectra of the corresponding *O*-acetyl derivatives.

INTRODUCTION

Accurate configurational assignment of the tertiary alcoholic center in a branched-chain carbohydrate derivative, produced by nucleophilic attack of a carbanionic species on the carbonyl group of a suitable glycosidulose, is possible by use of ^{13}C-n.m.r. spectroscopy[1,2]. An assignment of the configuration of the branching point based on an analysis of the chemical shifts and coupling patterns of the p.m.r. spectrum of the parent tertiary alcohol is not possible. In ^{1}H-resonance spectra, the chemical shift of the methyl protons of the corresponding tertiary acetoxyl derivative has been used[3–7] for determining molecular geometry at the branching point. These assignments were based on the premise[8,9] that protons of axial acetoxyl groups of methyl-branched carbohydrate derivatives should give signals at τ values between 7.93 and 8.04, and, similarly, that equatorial acetoxyl groups generate signals at τ values between 8.07 and 8.12. This approach may be ambiguous, especially where substituents at other positions in the molecule may exert a shielding effect[10,11].

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Lanthanide-induced changes in the chemical shifts of carbohydrate derivatives have been used[12,13] to elucidate the configuration of the tertiary alcoholic center of several branched-chain derivatives. Recently, Horton and his co-workers[14] presented a reliable method for determining these configurations with relatively simple equipment. The method circumvents most of the difficulties[15–17] inherent in a thorough study of pseudocontact shift effects, by comparing europium-induced shift gradients of identifiable protons in the ^{1}H-n.m.r. spectra of two identically substituted carbohydrate derivatives, that differ only in that one derivative bears a tertiary hydroxyl group of unknown configuration at the branching point, whereas the other derivative has a hydroxyl group of known configuration at the corresponding position.

This report describes the use of low concentrations of tris(6,6,7,7,8,8,8-heptafluoro-2 2-dimethyl-3,5-octanedionato)europium(III) [Eu(fod)$_3$] to obtain shift gradients for four 3-*C*-nitromethyl-branched carbohydrate derivatives[18] (**1**, **5**, **4**, and **8**). Comparison with shift gradients of appropriate derivatives of known configuration (**2**, **3**, **6**, **7**, **9**, and **10**) allowed assignment of branching-point configurations of the unknowns.

EXPERIMENTAL

The ^{1}H-n.m.r. spectra were recorded for samples of 50 mg, or 20 mg in the case of **3**, **4**, **5**, and **7**, in 0.4 ml of deuteriochloroform (Merck), containing 10% of tetramethylsilane as internal standard and lock signal. A saturated solution of Eu(fod)$_3$ (Norell Chemical Co. Inc., Landing, New Jersey) in deuteriochloroform was added in one-drop increments to each sample between the recording of successive spectra. No special purifications were performed on solvent or shift reagent. Relative molar concentrations of Eu(fod)$_3$ in each sample were determined by integration of the *tert*-butyl signal. Spectra were recorded under similar conditions at 60 MHz and 30°, using a Varian EM-360 n.m.r. spectrometer with an EM-3630 lock-decoupler attachment.

DISCUSSION AND RESULTS

Plots of the chemical shifts of identifiable protons at 60 MHz, expressed in Hz displacement downfield from tetramethylsilane, against the molar concentration of added Eu(fod)$_3$ for each carbohydrate derivative, **1**–**10**, are depicted in Figs. 1–3. Inspection of the plots shows that, at the relatively low concentrations of Eu(fod)$_3$ employed, the measured shifts are linear to the concentration of lanthanide ion. The shift gradients ($\Delta\delta$) recorded in Table I represent the slopes of the straight lines of the figures, and are expressed in p.p.m. per molar equivalent of Eu(fod)$_3$. Signals for individual protons were identified by first-order inspection on the basis of initial shift, intensity, multiplicity, and line-spacing. The configurational assignments were made by comparing the shift gradients of the *C*-nitromethyl derivatives, obtained[18] by reaction of sodium nitromethanide with the appropriate 3-glycosidulose, with closely related analogs of known configuration.

TABLE I

SHIFT-GRADIENTS[a] ($\Delta\delta$) FOR COMPOUNDS **1**–**10** AT 60 MHz

Signal	*Compound*									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
OH	1.17	3.01	18.18	16.67	4.39	4.44	17.54	4.81	18.08	6.67
H-1	2.48	1.39	0.76	2.25	7.02	6.00	3.80	2.96	3.95	1.67
H-2	11.70	13.43						3.15	4.52	3.10
ArCHO$_2$	[b]	[b]	1.01	0.68	[b]	[b]	2.34	1.48	2.54	[b]
ArH(Ts)								0.93	1.69	0.71
ArH(NBz)	6.03	4.62	[b]							
NH	7.09	6.25	9.34	3.38	8.77	7.33	5.83			
NAc				4.05	14.04	9.78	1.46			
CH$_2$				3.15	8.77					
OCH$_2$Ar[c]				1.13	1.75	2.44	1.67			
				0.90	0.88	2.22	2.05			

[a]Expressed in p.p.m. displacement downfield per molar equivalent of Eu(fod)$_3$ added. [b]No observable shift. [c]Chemical-shift nonequivalence exists in the benzyl group[22] in this case.

The chemical-shift gradients of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-nitromethyl-α-D-hexopyranoside[18] (**1**), of hitherto unknown configuration at the branching point, were compared (Fig. 1) with those of methyl 3-*C*-acetoxymethyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside[5] (**2**) and methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[19] (**3**), both of known configuration. Most of the $\Delta\delta$ values (Table I) of the readily identifiable proton-signals of **1** and **2** are in fair agreement, but differ markedly from those of **3**. This is especially apparent in the shift gradients of the respective hydroxyl resonances. The hydroxyl group of **2** is axial, and that of **3** is equatorial; thus, assignment of the *allo* configuration to **1** is indicated. This assignment is corroborated by the position of the unperturbed acetoxyl-proton resonance (at 60 MHz) of the *O*-acetyl derivative[18] of **1**. The three-proton singlet at τ 7.80 is in agreement with that to be expected[8] for an axial acetoxyl group.

Similar comparisons (Fig. 2) were made between a set of shift gradients of distinguishable resonance signals of the two 3-epimers of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-nitromethyl-α-D-hexopyranoside[18] (**4** and **5**), of unknown configuration at the branching point, with shift gradients of the corresponding unbranched allopyranoside[18] (**6**) and of the glucopyranoside[20] (**7**), both of known configuration. Large differences between the $\Delta\delta$ values of **4** and **6**, and a close similarity between those of **4** and **7** (Table I), allow assignment of the *gluco* configuration to **4**. Similarly, the $\Delta\delta$ values of **5** are comparable to those of **6**, but are significantly different from those of **7**, thus allowing assignment of the *allo* configuration to **5**. The 60-MHz n.m.r. spectrum of the acetyl derivatives of **4** and **5** both showed a three-proton acetyl singlet at 8.15, which, consequently, could not be used for confirmation[8] of the configurational assignments.

The configuration at the branching point of the addition product[18], **8**, of nitromethane to methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranosid-3-ulose was established by comparison (Fig. 3) of its shift gradients (Table I) with those of the corresponding alloside[19] **9** and the glucoside[21] **10**. It is evident that the shift gradients of **8** resemble those of **10**, and that they differ considerably from those of **9**. As would be expected from the proton closest to the point of complexation

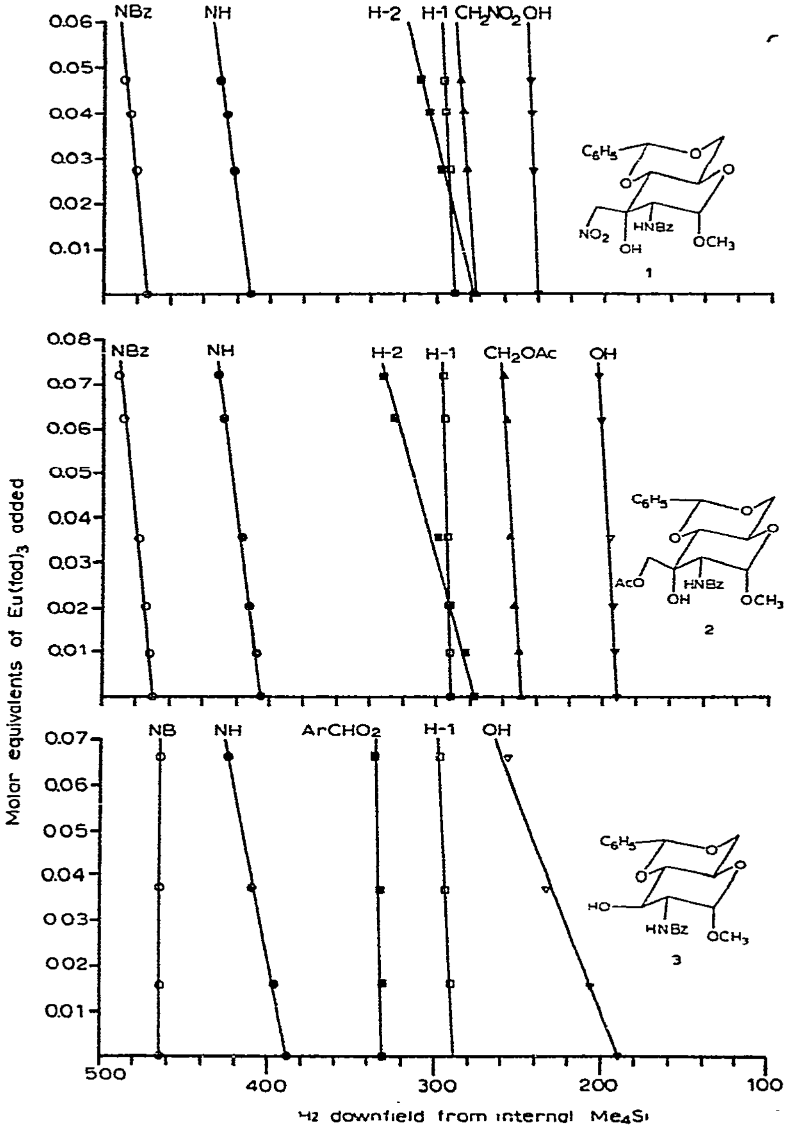

Fig. 1. Plots of chemical-shift values measured for solutions of the three similarly substituted compounds **1**, **2**, and **3** at different concentrations of $Eu(fod)_3$.

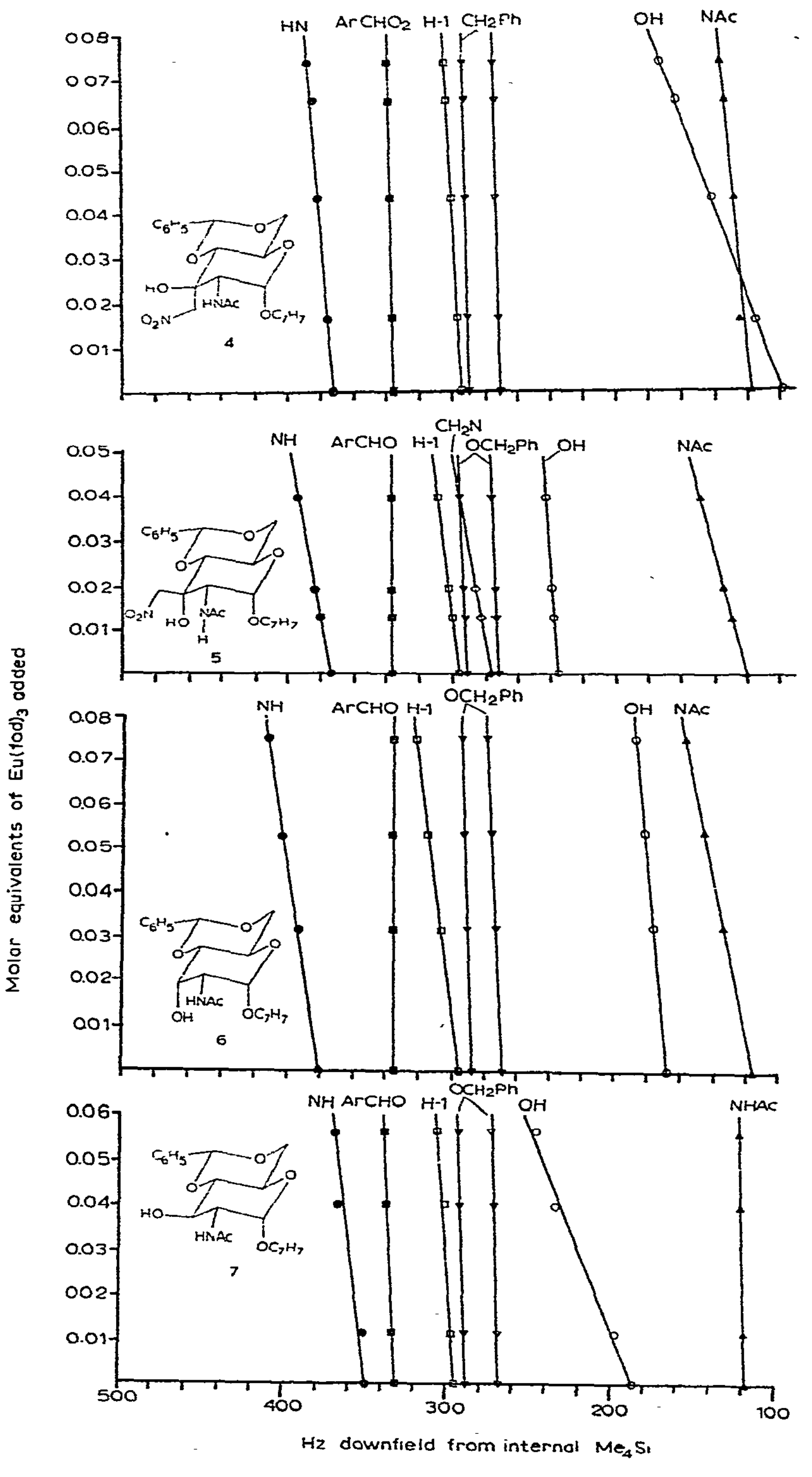

Fig. 2. Plots of chemical-shift values measured for solutions of the four similarly substituted compounds **4**, **5**, **6**, and **7** at different concentrations of Eu(fod)$_3$.

of the lanthanide, differences in shift gradients are most pronounced for the hydroxyl protons. Assignment of the *gluco* configuration to **8** is therefore indicated. An acetoxyl-resonance signal at τ 8.00 in the n.m.r. spectrum of the acetyl derivative[18] of **8** would suggest an axial orientation of the hydroxyl group of **8**. However, the

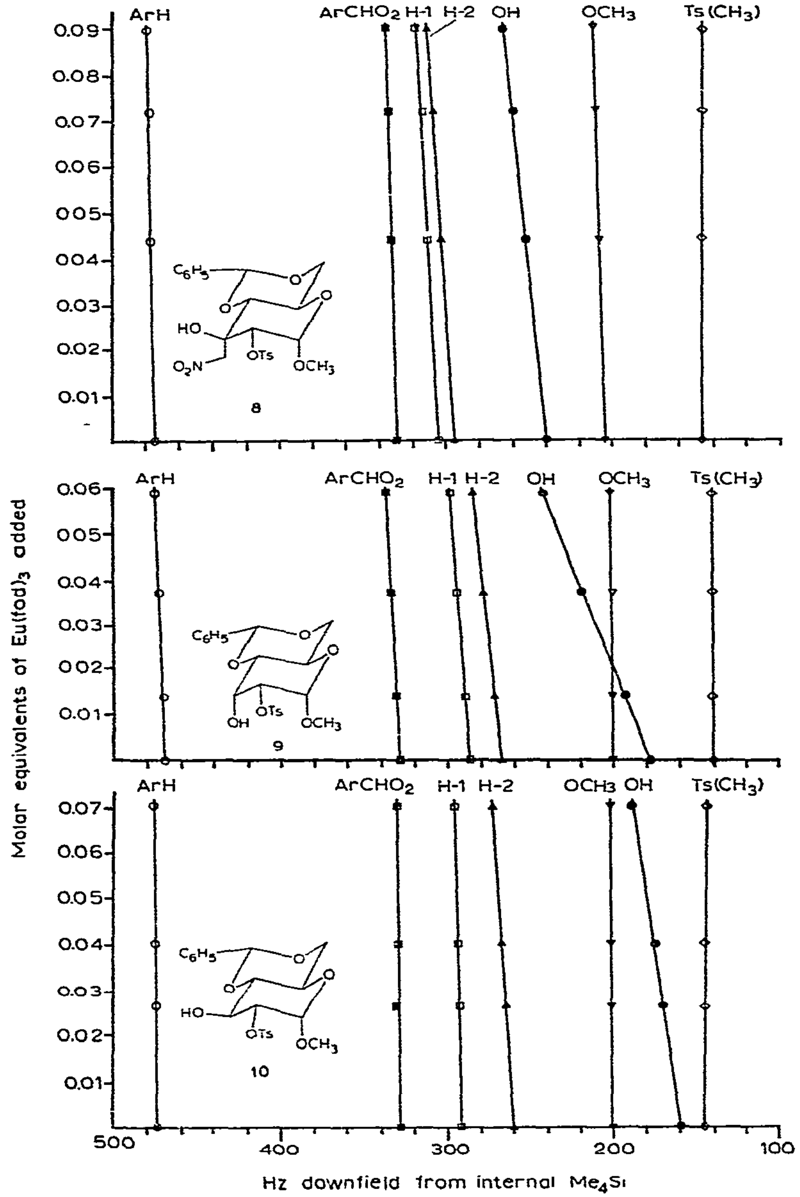

Fig. 3. Plots of chemical-shift values measured for solutions of the three similarly substituted compounds **8**, **9**, and **10** at different concentrations of Eu(fod)$_3$.

configurational assignments based on comparison of shift gradients of structurally closely related compounds seem more acceptable, particularly in view of the fact that the acetyl-resonance signals of the acetoxyl derivatives of **1** (τ 7.80) and **4** (τ 8.15) also appeared outside the narrow limits (albeit in the correct direction) laid down[8] for axially oriented acetoxyl groups (τ 7.93–8.04), and equatorial acetoxyl groups (τ 8.07–8.12). Shielding effects caused by different 2-substituents, such as the tosyl group of **8**, may indeed influence[10,11] the resonance signals of neighboring *O*-acetyl groups.

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