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Note

^{1}H-N.m.r. and ^{13}C-n.m.r. spectroscopy of methyl ethers of D-galactopyranose

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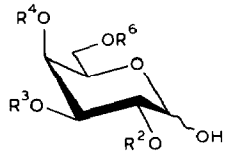
^{1}H-N.m.r. spectroscopy of methyl ethers of D-galactopyranose in aqueous solution has been studied with particular reference to the methoxyl protons[1–3]. The chemical shifts of the resonances of these protons depend on the anomeric configuration and the presence and orientation of vicinal OH or OMe groups[4]. In addition, the chemical shifts of the signals for MeO-2 and MeO-4 are independent of their orientation.

Analysis of the ^{13}C-n.m.r. chemical shift data for mono-, di-, and oligo-saccharides, and certain methyl ethers, allowed the postulation[5] of empirical rules that related changes in the chemical shifts of the ring carbon atoms with substitution. Earlier, it was proposed[6] that, for hexopyranoses, the presence of an OMe group causes an upfield shift of ~4.5 p.p.m. of the resonances of β-carbon atoms with axial OH groups. A similar effect is known for inositols[7].

Only incomplete n.m.r. data were available hitherto for methyl ethers of D-galactose. Complete ^{1}H- and ^{13}C-n.m.r. spectral assignments have now been made for solutions in D_2O of α- and β-D-galactopyranose (**1**) and its 2- (**2**), 2,3-di- (**3**) 2,4-di- (**4**), 2,3,4-tri- (**5**), 2,4,6-tri- (**6**), and 2,3,4,6-tetra-*O*-methyl (**7**) derivatives.



1 $R^2, R^3, R^4, R^6 = H$
2 $R^2 = Me, R^3, R^4, R^6 = H$
3 $R^2, R^3 = Me, R^4, R^6 = H$
4 $R^2, R^4 = Me, R^3, R^6 = H$
5 $R^2, R^3, R^4 = Me, R^6 = H$
6 $R^2, R^4, R^6 = Me, R^3 = H$
7 $R^2, R^3, R^4, R^6 = Me$

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Signals for anomeric protons in the ^{1}H-n.m.r. spectra were assigned readily and formed the basis for assigning the H-2 signals *via* the COSY experiment. The APT experiment furnished chemical shifts for the resonance of C-6. Literature data for the ring carbon atoms and the empirical rules of Bradbury and Jenkins[5] were used as a guide for the ^{13}C resonances and as a basis for ^{1}H assignments *via* HETCOR. The ^{1}H chemical shifts of the OMe resonances determined by Rathbone *et al.*[1-3] were employed to assign those of methoxyl carbons in HETCOR experiments. Signal intensities were of little help, as the percentage, at equilibrium, of the less-abundant α anomer of D-Gal is increased by *O*-methylation[8]. Tables I–IV contain the ^{1}H and ^{13}C assignments.

Figure 1a shows the effect of *O*-methylation on the chemical shifts of the resonances of the protons of D-Gal*p*. In general, there is an upfield shift of 0.4 p.p.m., but methylation of O-3 causes the signal for H-4 to be shifted downfield by 0.2–0.3 p.p.m. Similarly, methylation of O-2 results in a downfield shift of 0.2 p.p.m. in the signal for H-1α (but not for H-1β). The signal of H-6 is virtually unaffected on methylation of O-6,

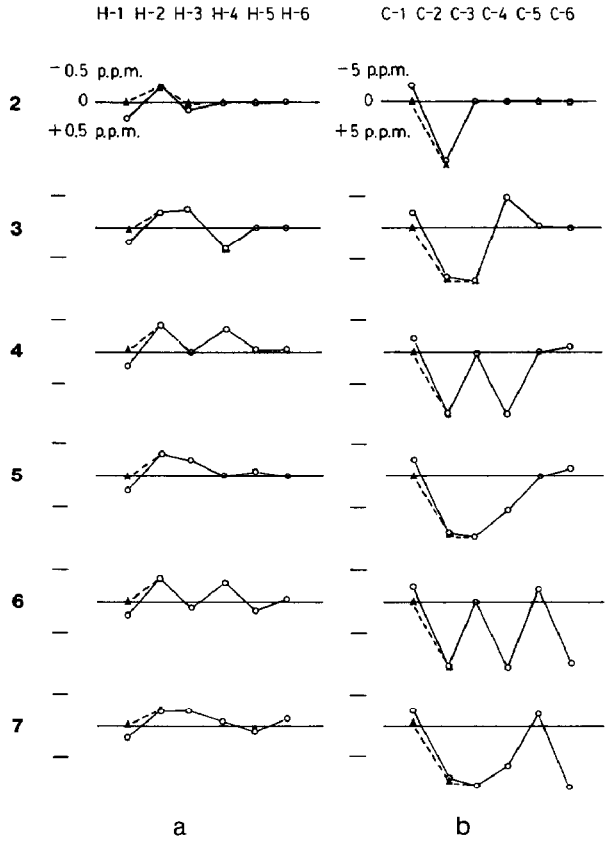

Fig. 1. Changes in the chemical shifts of the resonances of (a) H-1/6 ($\Delta\delta_H$, p.p.m.) and (b) C-1/6 ($\Delta\delta_C$) on *O*-methylation of D-Gal: α (-o-o-) and β (-▲-▲-) anomers of **2–7**. Negative values of $\Delta\delta$ represent upfield shifts (shielding effects) and positive values represent downfield shifts (deshielding effects).

TABLE I

^{1}H assignments (δ, p.p.m.) for α anomers of compounds **1** to **7**

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*	$J_{1,2}$
1	5.24	3.78	3.81	3.95	4.06	3.72					3.26
2	5.48	3.51	3.91	3.96	4.05	3.72	3.45				3.84
3	5.48	3.52	3.53	4.25	4.03	3.72	3.43	3.40			2.41
4	5.37	3.34	3.83	3.59	3.96	3.65	3.38		3.44		3.30
5	5.45	3.45	3.58	3.96	4.01	3.73	3.43	3.48	3.50		3.65
6	5.43	3.42	3.92	3.65	4.19	3.64	3.45		3.50	3.38	3.66
7	5.43	3.45	3.58	3.92	4.15	3.62	3.43	3.48	3.49	3.39	3.59

TABLE II

^{1}H assignments (δ, p.p.m.) for β anomers of compounds **1** to **7**

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*	$J_{1,2}$
1	4.56	3.46	3.62	3.90	3.68	3.72					7.71
2	4.60	3.19	3.66	3.84	3.63	3.70	3.59				7.92
3	4.61	3.21	3.34	4.18	3.62	3.76	3.57	3.42			7.73
4	4.49	3.04	3.64	3.54	3.56	3.65	3.51		3.44		7.83
5	4.58	3.14	3.40	3.91	3.56	3.73	3.57	3.50	3.50		7.82
6	4.55	3.12	3.71	3.61	3.78	3.64	3.58		3.50	3.38	7.84
7	4.57	3.13	3.39	3.86	3.72	3.62	3.56	3.49	3.49	3.38	7.75

TABLE III

^{13}C assignments (δ, p.p.m.) for α anomers of compounds **1** to **7**

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*
1	93.03	69.10	69.92	70.06	71.22	61.93				
2	90.30	78.36	69.50	69.98	71.01	61.65[a]	58.15			
3	90.15	77.31	78.48	65.51	70.93	62.00	57.87	56.46		
4	90.23	78.64	69.62	80.43	71.15	61.32	58.24		62.01	
5	90.11	77.64	79.21	75.93	71.18	61.43	57.96	57.33	61.56	
6	90.33	78.61	69.55	80.76	69.18	71.99	58.31		62.07	59.01
7	90.15	77.56	79.13	76.26	69.12	72.03	57.98	57.41	61.58	59.01

[a] Or 61.90.

TABLE IV

^{13}C assignments (δ, p.p.m.) for β anomers of compounds **1** to **7**

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*
1	97.20	72.62	73.55	69.50	75.89	61.73				
2	97.02	82.48	73.16	69.19	75.82	61.90[a]	61.00			
3	97.03	81.44	82.36	65.12	75.72	61.77	60.90	56.85		
4	96.88	82.70	73.54	79.86	75.82	61.09	61.05		62.09	
5	96.85	81.73	83.08	75.47	75.77	61.21	60.96	57.74	61.68	
6	96.89	82.66	73.48	80.19	73.88	71.76	61.13		62.15	59.15
7	96.82	81.63	83.00	75.78	73.71	71.80	60.95	57.81	61.69	59.15

[a] Or 61.65

whereas the chemical shift of the H-5 resonance is unchanged, apart from minor variations when O-4 and O-6 are substituted.

These trends are mirrored in the ^{13}C spectra (Fig. 1b). *O*-Methylation results in a downfield shift (8–10 p.p.m.) in the resonance for *C*-OMe on which is superimposed an upfield shift of ~4.5 p.p.m. for the resonance of C-4 (axial OH or OMe) if O-3 is methylated (*cf.* Voelter *et al.*[6]). *O*-Methylation at the 2-position results in an upfield shift of 2.7–2.9 p.p.m. of the C-1α signal but has no effect on that of C-1β. In contrast to the ^{1}H spectra, the ^{13}C spectra are sensitive to *O*-methylation at the 6-position, a downfield shift of 10 p.p.m. for the C-6 resonance being the result; there is minor shielding of C-5. The effects of *O*-methylation at C-2 upon the resonances of H-1 and C-1, and at C-3 upon those of H-4 and C-4, are summarised in Figs. 2 and 3, respectively; O-5 has some influence on the magnitudes of the changes in shifts.

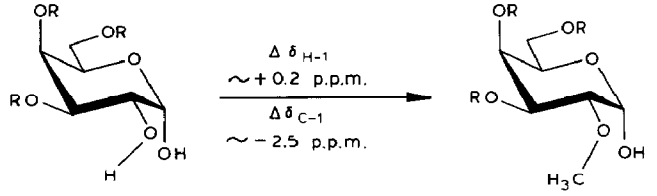

Fig. 2. Effect of methylation of O-2 on the chemical shifts of the resonances of H-1 and C-1 of α-D-Gal*p* (R = H or Me); there are no changes for the β anomer.

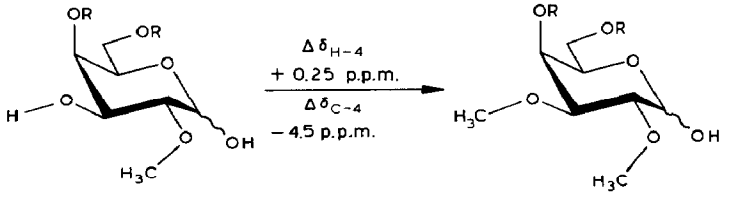

Fig. 3. Effect of methylation of O-3 on the chemical shifts of the resonances of H-4 and C-4 of α- and β-D-Gal*p* (R = H or Me).

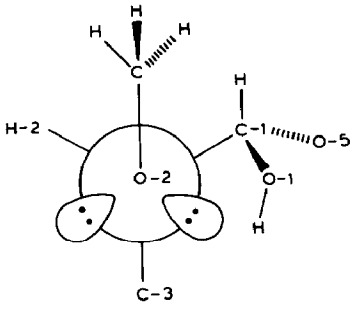

Fig. 4. Newman projection along the O-2–C-2 bond of the α anomers of **2–7**.

The general consequence of *O*-methylation on the chemical shift of the resonance of the α carbon can be explained[9] by the changes in the paramagnetic and diamagnetic terms that give rise to the shielding tensor (σ). Cheney and Grant[10] showed that replacement of H by Me in saturated hydrocarbons leads to a contraction of the carbon 2*p* orbitals, which increases (0.7 p.p.m.) the diamagnetic (shielding) and decreases (10.6 p.p.m.) the paramagnetic (deshielding) terms of the chemical shift expression. Similar results are seen for aliphatic alcohols *cf.* CH_3CH_2OH (δ 57) with $CH_3CH_2OCH_3$ (δ 67.9) and CH_3OH (δ 49) with CH_3OCH_3 (δ 57.6). On the other hand, the upfield shift of 0.4 p.p.m. of the ^1H resonances upon *O*-methylation is due to the neighbouring anisotropy effect[11,12], *cf.* CH_3OH (δ 3.4) and CH_3OCH_3 (δ 3.2).

The protons in *γ-gauche* (1,4) positions shield[13] the corresponding carbon atoms. With oxygen as part of the connecting sequence of atoms, the effect at C-4 of O-3 methylation is shown in Fig. 3. Kochetkov *et al.*[14] proposed that this effect stems from a spatial interaction of the protons attached to the carbon atoms in the 1,4-*gauche* conformation. Figures 2 and 3 accommodate the present results. Additionally, in the conformer shown (Fig. 4, looking along the O-2–C-2 bond), hydrogen bonding between O-1 and O-2 may (*cf.* Usui *et al.*[15]) contribute to the enhanced shielding of C-1α experienced in the methylation of O-2; the rotamer displayed has the *γ-gauche* relationship between protons. Hydrogen bonding between HO-4 and O-3 leads to a satisfactory rotamer (Fig. 5), but as O-4 methylation has no effect on $\Delta\delta_{C\text{-}4}$ or $\Delta\delta_{H\text{-}4}$ produced by O-3 methylation, the explanation must lie in the *γ-gauche* inter-proton relationship.

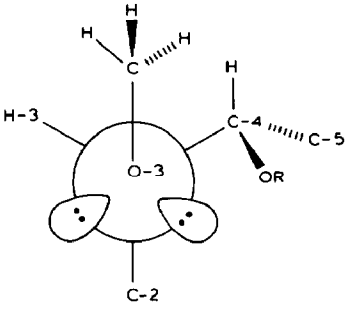

Fig. 5. Newman projection along the O-3–C-3 bond of **3** (R = H) or **5** and **7** (R = Me).

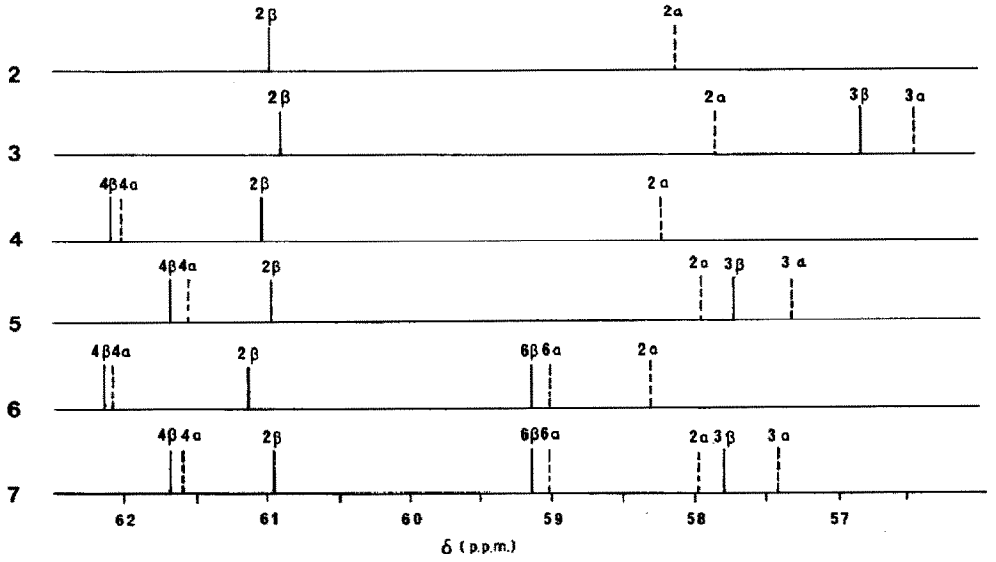

Fig. 6. Chemical shifts of the methoxyl carbon atoms for **2**–**7**.

From Fig. 6, it is clear that the signals for OCH_3 fall into two regions, namely, upfield and downfield of 59.5 p.p.m. The downfield signals reflect the lack of steric interactions with protons in 1,4 *gauche* positions, whereas the upfield signals reflect such effects. MeO-3α and MeO-3β would be expected to interact with the corresponding protons on C-4, causing both C-4 and the carbon of MeO-3 to be more shielded.

The crystal structures of α- and β-D-Gal[16] and of 2,4-di-*O*-Me-D-Gal hydrate have been reported[17]. The present n.m.r. study indicates that 2,4-di-*O*-Me-D-Gal adopts different conformers in solution from that of the solid hydrate.

EXPERIMENTAL

Compounds **2** and **3** were obtained as described[18] and **4**–**7** were isolated from a hydrolysate (100°, 16 h, 0.5M H_2SO_4) of methylated gum exudate from *Encephalartos longifolius* by column chromatography on cellulose[19]. Deuterium exchange was effected by thrice freeze-drying solutions in D_2O. Samples (11–32 mg) were examined at 25° as solutions in D_2O (internal Me_2CO, δ_H 2.21, δ_C 31.0), using a Varian VXR-200 spectrometer.

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