290. *Proton Resonance Studies of Methoxy- and Acetoxy-derivatives of Pyranose Molecules Applied to the Conformation of Methyl* 3-O-*Carbamoyl-α- and* -β-L-*novioside.*

By S. A. Barker, J. Homer, M. C. Keith, and L. F. Thomas.

Nuclear magnetic resonance studies on a range of pyranose sugars containing methoxy- and acetoxy-substituents have enabled rules to be postulated which have been applied in conformational assignments of certain noviose derivatives.

In a study of the nuclear magnetic resonance spectra of a range of acetylated sugars, Lemieux *et al.*[1] were able to correlate the ring proton signals with molecular conformation satisfactorily, the main features being that axially oriented protons are more shielded than equatorial ones, and that the magnitude of spin coupling between protons in adjacent ring positions depends on whether they are gauche (small) or *trans* (large) to each other. This treatment can be applied in the determination of the conformation of related cyclic molecules provided that the shielding differences between the various ring protons are sufficiently large compared with the coupling constants to permit analysis of the spectrum. These conditions usually prevail at operating frequencies of 40 Mc./sec. and above, but at lower frequencies the smaller chemical shifts make analysis virtually impossible without the use of spin-decoupling techniques. Conformational studies can still be made, however, by using resonance signals which are not affected by spin coupling and hence are more easily resolved. Such signals arise from the protons of acetoxy- and methoxy-substituents. Lemieux and his co-workers [1] observed that axial acetoxy-groups are generally less shielded than equatorial ones, but the effect of ring position and neighbouring substituents, whilst recognised, was not investigated in detail. With improved resolution of the acetoxy-signals we have been able to make consistent correlations in this respect for both fully acetylated pyranose molecules and the corresponding acetylated methyl glycosides. The methoxy-resonances obtained from a variety of methylated sugars have been treated similarly, and the combined rules give a consistent indication of the configuration of, and the conformation adopted by, methyl 3-*O*-carbamoyl-α- and -β-L-novioside. Dimethylformamide was found to be the most satisfactory solvent for the wide range of compounds studied and was used exclusively in an attempt to minimize effects arising from solute–solvent interaction. The aldehyde signal of the solvent provides a convenient internal reference and the *gem*-dimethyl absorption does not obscure the relevant signals.

The chemical shifts of the 1-methoxy-protons of some methyl pyranosides (Table 1) fall into two groups around $\tau = 6{\cdot}69$ and $\tau = 6{\cdot}85$. If the more probable C1 conformation

Table 1.

Proton resonance shifts of 1-methoxy-substituents.

Me glycoside	Orientation of OMe	τ		τ in fully acetylated glycoside
α-D-Glucopyranoside	ax.	6·88		6·69
β- ,, ,, ...	eq.		6·68	6·68
α-D-Mannopyranoside	ax.	6·85		6·71
β- ,, ,, ...	eq.		6·68	6·71
α-D-Galactopyranoside	ax.	6·84		6·71
β- ,, ,, ...	eq.		6·70	6·69
α-D-Arabinopyranoside	ax./eq.?	6·76		6·68
β- ,, ,, ...	ax.	6·85		6·71

of the hexose derivatives is assumed, these values correspond, respectively, to the equatorial and the axial orientation of the group. Similarly, assumption of the 1C form for methyl

[1] Lemieux, Kullnig, Bernstein, and Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6098.

β-D-arabinoside [2,3] implies an axial methoxy-group with a shift consistent with the above. The intermediate value of $\tau = 6{\cdot}76$ shown by methyl α-D-arabinoside could be explained by relatively rapid interconversion between the two possible chair forms, since this molecule lacks the stabilizing influence of a 5-hydroxymethyl group and has two axial and two equatorial groups in each conformation. The similarity of shifts for the glucose and mannose derivatives indicates that shielding is independent of the orientation of the neighbouring 2-hydroxyl group. Acetylation of the methyl pyranosides results (Table 1) in a methoxy-resonance uniformly in the region of $\tau = 6{\cdot}70$ irrespective of group orientation. The reason for this is not clear, though it must be associated with the spatial arrangement adopted by the long and flexible acetoxy-groups. Nevertheless, the result appears to afford an empirical means of determining the orientation of the glycosidic methyl group, by observing whether the methoxy-resonance is unchanged (equatorial), or shifted about 0·16 p.p.m. to lower field (axial), on acetylation of the 2-hydroxyl group. It will be seen that the τ-value of 6·68 for methyl 2,3,4-tri-*O*-acetyl-α-D-arabinopyranoside gives no indication of the conformation of this molecule, but consideration of its acetoxy-signals (see below) favours the 1C form.

The methoxy-shifts in polymethoxypyranose derivatives are given in Table 2. A detailed analysis [4] of the results in relation to the orientation, ring position, and neighbouring substituents of each group leads to the tabulated assignment. This is the only possible

TABLE 2.

Methoxy-proton shielding values in pyranose molecules.

	Methoxy-proton assignment (τ)						
	1-OMe	2-OMe		3-OMe	4-OMe		CH_2·OMe
Compound	ax	ax	eq	eq	ax	eq	eq
2,3,4,6-Tetra-*O*-methyl-D-glucose			6·65	6·75		6·70	6·85
2,3,6-Tri-*O*-methyl-D-glucose			6·64	6·76			6·88
Me 2,3-di-*O*-methyl-α-D-glucoside	6·85		6·70	6·82			
Me 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucoside	6·84			6·69		6·69	6·88
1,4-Di-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-glucose			6·68	6·72			6·79
1,2,4,6-Tetra-*O*-acetyl-3-*O*-methyl-D-glucose				6·69			
2,3,4,6-Tetra-*O*-methyl-D-mannose		6·75		6·75		6·75	6·84
2,3,4,6-Tetra-*O*-methyl-D-galactose			6·69	6·69	6·79		6·84
Me 2,4,6-tri-*O*-methyl-α-D-galactoside	6·78		6·73		6·78		6·78
Me 2,4,6-tri-*O*-methyl-3-*O*-acetyl-α-D-galactoside	6·82		6·66		6·75		6·82
Me 2,4-di-*O*-methyl-α-D-galactoside	6·85		6·68		6·74		

assignment which is entirely self-consistent, and indicates a dependence on each of these factors, but the dominant feature is that axial methoxy-groups in any ring position are more shielded than their equatorial counterparts.

The acetoxy-group signals of the fully acetylated pyranoses (Fig. 1) were in many cases, more fully resolved than in ref. 1, and they justified a correlation study. It is recognised that such a study is complicated by the uncertainty of the spatial arrangement of the extended acetoxy-groups with consequent possible variations in shielding influence of their magnetically anisotropic bonds on the protons of adjacent groups. Nevertheless, reasonably consistent assignments can be made (Table 3) on the basis that axial groups are less shielded than equatorial [1,5] and that the shielding of a particular group will be influenced by the orientation of the group in the adjacent ring position, as, for example, in an anomeric pair where the differing orientation of the 1-group may modify the shielding of the 2-group. The acetoxy-resonances of the acetylated methyl glycosides (Fig. 2) can

[2] Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 107.
[3] Barker, Bourne, Stephens, and Whiffen, *J.*, 1954, 3468.
[4] Homer, Thesis, Birmingham, 1962.
[5] Lichtenthaler and Fischer, *J. Amer. Chem. Soc.*, 1961, **83**, 2005.

be assigned in the same manner (Table 3), and a noticeable feature is the small effect on remaining signals brought about by the substitution at position 1. It is also evident that the chemical shifts of the axial groups are fairly constant ($\tau \approx 8{\cdot}0$) and independent of the nature and orientation of neighbouring substituents, but the shielding of ring equatorial

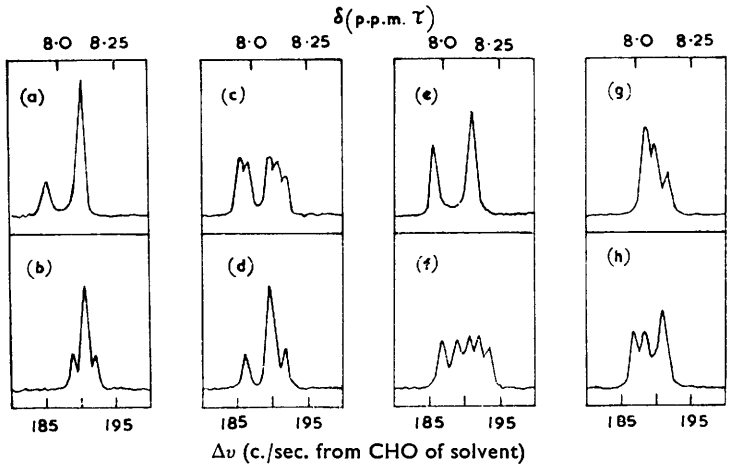


FIG. 1. Acetoxy-proton resonance spectra of the penta-acetates of (a) α- and (b) β-D-glucose, (c) α- and (d) β-D-mannose, (e) α- and (f) β-D-galactose and of the tetra-acetates of (g) α- and (h) β-L-arabinose.

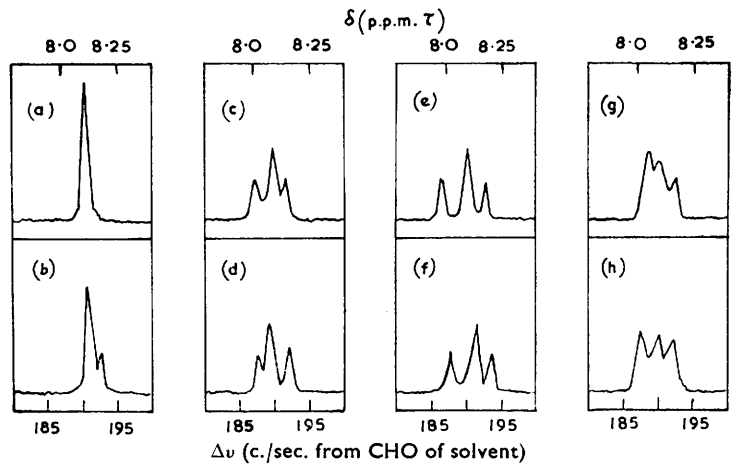


FIG. 2. Acetoxy-proton resonance spectra of the tetra-acetates of (a) methyl α- and (b) β-D-glucoside, (c) methyl α- and (d) β-D-mannoside, (e) methyl α- and (f) β-D-galactoside and of the tri-acetates of (g) methyl α- and (h) β-L-arabinoside.

groups (τ 8·04—8·21) is much more sensitive to environment. The close correspondence of the assigned shifts of the arabinose and fucose derivatives with the configurationally analogous galactoses strongly suggests that these compounds adopt the conformations indicated in the Table.

The crystalline methyl novioside ($[\alpha]_D$ −64°) isolated by Walton, Rodin, Stanmer,

Holly, and Folkers [6] was shown by them to be methyl 3-*O*-carbamoyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside but the configuration at position 1 and the conformation were not determined. L-Rhamnose has a configuration similar to that of noviose and could be named 5-methyl-L-lyxose. Hence their glycosides should have similar rotations. The crystalline methyl novioside, $[\alpha]_D$ −64°, clearly was the α-anomer (methyl α-L-rhamnoside, $[\alpha]_D$ −62·5°) and application of Hudson's rules [7] suggested that the anomeric methyl novioside would have $[\alpha]_D$ +110° or −239° (methyl β-L-rhamnoside, $[\alpha]_D$ +95°). After a lengthy series of fractional crystallizations, Folkers and his co-workers [8] subsequently isolated the anomeric methyl novioside, $[\alpha]_D$ +106°, and rightly assigned to it the β-configuration on the basis of its more positive rotation. The problem of the conformation

TABLE 3.

Acetoxy-proton shielding values in pyranose molecules.

	Acetoxy-proton assignment (τ) *							
	1-OAc		2-OAc		3-OAc	4-OAc		CH_2·OAc
	ax	eq	ax	eq	eq	ax	eq	eq
α-D-Glucose penta-acetate	7·94			8·10	8·10		8·10	8·10
Me 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside				8·10	8·10		8·10	8·10
β-D-Glucose penta-acetate		8·05		8·15	8·11		8·11	8·11
Me 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside				8·17	8·11		8·11	8·11
α-D-Mannose penta-acetate	7·95		7·98		8·16		8·08	8·11
Me 2,3,4,6-tetra-*O*-acetyl-α-D-mannoside			8·00		8·13		8·08	8·08
β-D-Mannose penta-acetate		8·08	7·97		8·14		8·08	8·08
Me 2,3,4,6-tetra-*O*-acetyl-β-D-mannoside			8·02		8·16		8·07	8·07
α-D-Galactose penta-acetate	7·96			8·12	8·12	7·96		8·12
Me 2,3,4,6-tetra-*O*-acetyl-α-D-galactoside				8·10	8·18	7·98		8·10
β-D-Galactose penta-acetate		8·05		8·15	8·20	7·98		8·11
Me 2,3,4,6-tetra-*O*-acetyl-β-D-galactoside				8·13	8·21	8·01		8·13
α-L-Arabinose tetra-acetate (C1)		8·04		8·08	8·14	8·04		
Me 2,3,4-tri-*O*-acetyl α-D-arabinoside (1C)				8·09	8·17	8·04		
β-L-Arabinose tetra-acetate (C1)	7·98			8·13	8·13	8·02		
Me 2,3,4-tri-*O*-acetyl-β-D-arabinoside (1C)				8·09	8·16	8·01		
Me 2,3,4-tri-*O*-acetyl-α-L-fucoside (1C)				8·08	8·18	7·97		

* It is possible to make an alternative assignment amongst the 2-, 3-, 4-equatorial, and CH_2·OAc positions which is self-consistent with respect to environment, but which implies a major shielding influence arising from the orientation of groups two ring positions removed.

TABLE 4.

Proton shielding values in the methyl noviosides.

	Proton shifts of subst. (τ)				
Novioside	1-OMe	4-OMe	2-OAc	3-OAc	5,5-Me_2
Me 3-*O*-carbamoyl α-L-	6·68	6·81			8·91
Me 2-*O*-acetyl-3-*O*-carbamoyl-α-L-	6·68	6·80	8·07		8·86
Me 2,3-di-*O*-acetyl-α-L-	6·66	6·78	8·08	8·02	8·83
Me 3-*O*-carbamoyl-β-L-	6·70	6·76			8·87, 8·97
Me 2-*O*-acetyl-3-*O*-carbamoyl-β-L-	6·68	6·78	8·09		8·85, 8·94
Me 2,3-di-*O*-acetyl-β-L-	6·69	6·78	8·07	8·17	8·85, 8·95

adopted by the anomers, however, still remained. The possibilities are shown in the formulæ. The α-anomer has an equal number of equatorial and axial substituents in either chair form, and hence, according to Reeves,[2] there is an equal probability of either conformation being adopted. However, the nuclear magnetic resonance spectra of this compound and its 2-*O*-acetyl derivative (Table 4; Fig. 3) exhibit methoxy-resonances in the region of $\tau = 6{\cdot}68$ and 6·80. From the earlier observations it is probable that the

[6] Walton, Rodin, Stanmer, Holly, and Folkers, *J. Amer. Chem. Soc.*, 1958, **80**, 5168.
[7] Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 994; *Adv. Carbohydrate Chem.*, 1948, **3**, 1.
[8] Walton, Rodin, Holly, Richter, Shunk, and Folkers, *J. Amer. Chem. Soc.*, 1960, **82**, 1489.

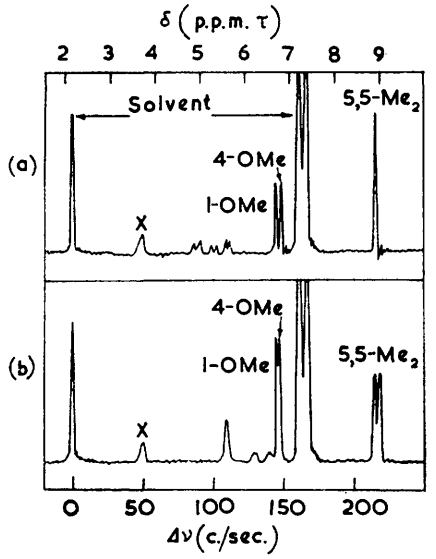
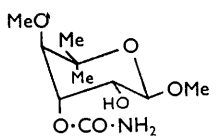
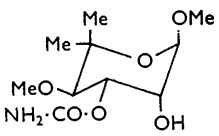


FIG. 3. Proton resonance spectra of (a) α- and (b) β-anomer of methyl 3-*O*-carbamoyl-L-novioside. X = 3-O·CO·NH_2.

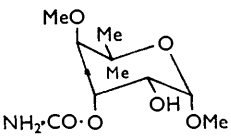
former signal is derived from the 1-methoxy-group. The immediate environment here invites direct comparison with the glucose and galactose derivatives, and the absolute shielding value, combined with the fact that acetylation at position 2 produces no displacement, suggests that this methoxy-group is equatorially disposed. Further, the signal



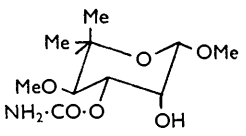
α, C1



α, 1C

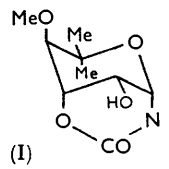


β, C1



β, 1C

at τ 8·07 is typical of an equatorial acetoxy-group unless a direct comparison is invalidated by the presence of the 3-carbamoyl group. That this is not so is shown by the spectrum of the 2,3-di-*O*-acetyl derivative, where the acetoxy-resonance remains virtually unchanged and the additional (C-3) signal appears to low field at τ = 8·02, indicative of axial orientation. The implied axial orientation of the 3-*O*-carbamoyl group is supported by the chemical evidence of Hinman, Caron, and Hoeksema,[9] who isolated the cyclic compound (I), together with 3-*O*-carbamoylnoviose, when methyl 3-*O*-carbamoyl-α-novioside was hydrolysed with sulphuric acid. The structure shown, with the cyclic carbamate ring linked axially to the sugar skeleton at positions 1 and 3, is the only possible conformation for such a compound and suggests that the carbamoyl group is in an axial orientation before cyclization. The C1 conformation for this anomer is thus strongly favoured.



(I)

For the β-anomer, the 1C form is favoured on the grounds that this has a preponderance of bulky substituents equatorially oriented,[2] and this is borne out by the nuclear magnetic resonance evidence. The chemical shift of the 1-methoxy-signal and the absence of displacement upon acetylation at position 2 suggest an equatorial disposition of this group. The acetoxy-resonance of the 2-*O*-acetate at τ 8·09 is rather more shielded than might be expected for an axial group, but the assignment of this orientation is supported by the fact that acetylation at position 3 produces an additional signal at higher field

[9] Hinman, Caron, and Hoeksema, *J. Amer. Chem. Soc.*, 1957, **79**, 3789.

($\tau = 8{\cdot}17$) indicative of an equatorial group at this latter position with a reasonable axial–equatorial separation between the two signals.

The 4-methoxy-group resonances also support these assignments, the values of $\tau = 6{\cdot}81$ and 6·76 for the α- and the β-anomer being consistent with the group's being axial and equatorial, respectively.

Finally, the different signals arising from the *gem*-dimethyl groups on C-5 are not inconsistent with the proposed conformations. Normally, such an arrangement in a rigid, otherwise unsubstituted tetrahydropyran ring would be expected to give two absorptions arising from the different magnetic environment of the axially and the equatorially disposed methyl group. Introduction of a substituent in the adjacent ring position would produce different effects depending on its orientation relative to the two groups. If the substituent is gauche to both groups it would have the same shielding influence on each, and the axial–equatorial distinction should be maintained. If, on the other hand, it is gauche to one group and *trans* to the other, the shielding effect would be different on each, and the axial–equatorial separation would be changed. The coincidence of the methyl signals ($\tau = 8{\cdot}91$) in the α-anomer suggests that the 4-methoxy-group has the latter effect, as is the case in the C1 form. In contrast, the separate peaks at $\tau = 8{\cdot}87$ and 8·97 for the β-anomer are consistent with a 4-group that is symmetrically placed with respect to the methyl groups as in the 1C form.

Whilst the proposed conformation for the β-anomer is consistent with current ideas of conformational analysis, the C1 form for the α-anomer is perhaps surprising in that the bulky 3-*O*-carbamoyl group is axially oriented; a possible explanation is that this structure is stabilized by hydrogen bonding involving this group.

Experimental

Preparation of Noviose Derivatives and Reference Compounds.—The following noviose derivatives were prepared by the methods of Hinman, Caron, and Hoeksema:[9] methyl 3-*O*-carbamoyl-α-novioside, m. p. 191—192°, $[\alpha]_D^{20}$ −24° ± 1° (*c* 1 in MeOH), 2-*O*-acetyl-3-*O*-carbamoyl-α-novioside, m. p. 56—57°, $[\alpha]_D^{20}$ −13° ± 1° (*c* 1 in EtOH), α-novioside, m. p. 68—70°, $[\alpha]_D^{19}$ −62° ± 2° (*c* 1 in EtOH), and 2,3-di-*O*-acetyl-α-novioside, m. p. 61—63°, $[\alpha]_D^{19}$ −21° ± 2° (*c* 1·0 in EtOH), 3-*O*-carbamoyl-α-noviose, an oil, $[\alpha]_D^{19}$ +43° ± 2° (*c* 1·0 in EtOH). With acetic anhydride–pyridine methyl 3-*O*-carbamoyl-β-novioside, m. p. 117—118°, $[\alpha]_D^{19}$ +124° ± 4° (*c* 1·0 in EtOH), yielded its 2-acetate, m. p. 74—76°, $[\alpha]_D$ +87° ± 2° (*c* 1·0 in EtOH), recrystallized from n-hexane. Methyl β-novioside was isolated from methyl 3-*O*-carbamoyl-β-novioside in the same manner as the α-anomer and obtained as a chromatographically homogeneous oil, $[\alpha]_D^{18}$ +92° ± 2° (*c* 0·5 in EtOH), which with acetic anhydride–pyridine gave the 2,3-diacetate, $[\alpha]_D$ +85° ± 2° (*c* 1·0 in EtOH). All other compounds were recrystallized authentic specimens of high purity, as gauged from their reported physical constants.

Nuclear Magnetic Resonance Spectra.—The spectra were obtained at 33° for 1·5—2M-solutions in dimethylformamide by using a Mullard SL44 mark I spectrometer at 32 Mc./sec. Signals were measured relative to the CHO peak of the solvent by the side-band technique. Chemical shifts were converted to the τ-scale by taking $\tau_{ref} = 2{\cdot}15$, and are accurate to 0·02 p.p.m.

The authors thank Professor M. Stacey, F.R.S., for his interest. Two of them (J. H. and M. C. K.) are grateful to the D.S.I.R. and Colonial Products Research Council for the award of research studentships. All are indebted to numerous chemists for the gift of reference samples.

Chemistry Department, The University,
Edgbaston, Birmingham, 15. [*Received, September 10th*, 1962.]