# Assignment of $^{13}C$ and $^{1}H$ Resonances of Methyl Groups in the Tri-*O*-methyl Derivatives of Methyl Pentopyranosides; Some Observations on the Methoxy $^{13}C$ Chemical Shifts

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By studies of specifically labelled trimethyl ethers of methyl β-L-arabinopyranoside, methyl α-D-lyxopyranoside, methyl β-D-ribopyranoside, and methyl α-D-xylopyranoside, in which some methyl groups are replaced by trideuteriomethyl groups, the $^{13}C$ and $^{1}H$ resonances of each of the methyl groups were identified. A rationalization is presented, in terms of *syn*-axial δ-effects and rotamer populations, for the deshielding experienced in six-membered rings by carbon-13 nuclei in equatorially disposed methoxy-groups, which are flanked by two equatorially attached methoxy(hydroxy)-groups. Benzoylation of methyl β-L-arabinopyranoside with benzoyl cyanide was shown, by $^{13}C$ n.m.r. spectroscopy, to afford the 2,4-dibenzoate as the major product.

NUCLEAR MAGNETIC RESONANCE spectroscopy has been applied widely in carbohydrate chemistry,[1] and a limited amount of work has been reported [2-11] on the use of the $^{1}H$ shifts of methoxy-groups as an aid in determining the structure of partially methylated sugars. In connection with our studies [12] on the selective reactivity of hydroxy-groups in carbohydrates, we were interested in developing a spectroscopic technique for the rapid and unequivocal identification of substitution patterns in methyl ethers of certain methyl pentopyranosides. For this purpose we have now assigned the $^{13}C$ and $^{1}H$ resonances of methyl groups in the n.m.r. spectra of the trimethyl ethers of methyl β-L-arabinopyranoside, methyl α-D-lyxopyranoside, methyl β-D-ribopyranoside, and methyl α-D-xylopyranoside [compounds (1), (5), (9), and (13), respectively].

The method used for the assignment involved the preparation of fully methylated derivatives of the glycosides in which specific methyl groups were replaced by trideuteriomethyl groups. No resonances for such groups appear in $^{1}H$ n.m.r. spectra, and in $^{13}C$ n.m.r. spectra the $^{13}C$–$^{2}H$ spin–spin coupling, quadrupole broadening, and lack of nuclear Overhauser enhancement under conditions of $^{1}H$ decoupling cause the $^{13}C$ signal for a trideuteriomethyl group to be unobserved under signal-to-noise conditions normally used.* This method for identification of resonances has been used previously to assign the $^{1}H$ resonances of methyl groups in 2,3,4,6-tetramethyl ethers of methyl α- and β-D-glucopyranoside,[4,10] and of methyl α- and β-D-galactopyranoside;[11] it was during the course of our work that the first uses of

* However, other workers [13] have noticed that deuteriation gives varying results as regards the detectability of the adjacent $^{13}C$ nucleus.

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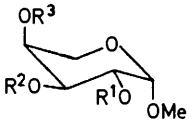
this approach for the assignment of methoxy $^{13}C$ resonances were reported.[10,11]



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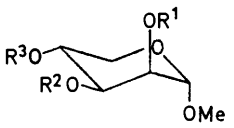
(3) $R^1 = R^2 = CD_3$, $R^3 = Me$
(4) $R^1 = R^2 = R^3 = CD_3$



(5) $R^1 = R^2 = R^3 = Me$
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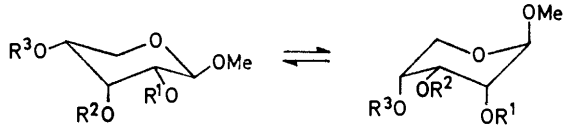

(9) $R^1 = R^2 = R^3 = Me$
(10) $R^1 = Me$, $R^2 = R^3 = CD_3$
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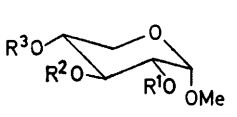
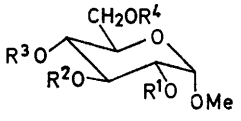


(13) $R^1 = R^2 = R^3 = Me$
(14) $R^1 = R^3 = Me$, $R^2 = CD_3$
(15) $R^1 = CD_3$, $R^2 = R^3 = Me$
(16) $R^1 = R^2 = R^3 = CD_3$



(17) $R^1 = R^2 = R^3 = R^4 = Me$
(18) $R^1 = R^2 = Me$, $R^3 = R^4 = CD_3$
(19) $R^1 = R^4 = CD_3$, $R^2 = R^3 = Me$

The substitution pattern in a partially methylated glycoside may be ascertained if the free hydroxy-groups are converted into trideuteriomethoxy-groups; comparison of the methoxy-regions of the $^1H$ and $^{13}C$ n.m.r. spectra of the compound so obtained with those of the unlabelled parent compound affords the substitution pattern in the partially methylated derivative.

The tris-*O*-trideuteriomethyl derivatives of the four pentosides [(4), (8), (12), and (16)] were required in addition to other selectively labelled ethers, in order to assign the $^{13}C$ signals for C-5 nuclei, which, unlike those from the other ring-carbon nuclei, have chemical shifts similar to those of signals of the methoxy-carbons. The syntheses of other labelled compounds were based on partially blocked derivatives of the glycosides, having well established structures. Thus methyl 2-[14] and 4-*O*-methyl-β-L-arabinopyranoside,[15] on trideuteriomethylation, afforded methyl 2-*O*-methyl-3,4-bis-*O*-trideuteriomethyl-β-L-arabinopyranoside (2) and methyl 4-*O*-methyl 2,3-bis-*O*-trideuteriomethyl-β-L-arabinopyranoside (3), respectively. The synthesis of the permethylated derivative of methyl α-D-lyxopyranoside labelled at O-4 (6) was achieved in three steps from methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside;[16] the O-3-labelled isomer (7) was obtained through trideuteriomethylation of methyl 2,4-di-*O*-methyl-α-D-lyxopyranoside.[17] Methyl 3,4- and 2,3-*O*-isopropylidene-β-D-ribopyranoside [18] provided convenient starting materials for compounds (10) and (11), containing labelled groups at O-3 and O-4, and at O-2 and O-3, respectively. The derivatives of methyl α-D-xylopyranoside labelled at O-2 (15) and O-3 (14) were obtained from the 2-toluene-*p*-sulphonate [19] and 3-benzoate [20] of the parent glycoside. In the syntheses of the ethers (6), (11), and (14), some intermediates, which were chromatographically homogeneous liquids, and which had i.r. and n.m.r. spectra in accord with their expected structures, were not characterized by elemental analysis, but were used directly in the next synthetic step.

The specifically labelled ethers in a series were compared with their parent permethyl ether by g.l.c. on two columns, and all were found to have indistinguishable retention times. The mass spectra of all these compounds were in accord with their expected substitution patterns.

TABLE 1

$^{13}C$ Chemical shift data [a] for methoxy-groups in methyl tri-*O*-methylpentopyranosides (1)—(16)

| Compd. | | 1-OMe | 2-OMe | 3-OMe | 4-OMe |
|---|---|---|---|---|---|
| (1) | *arabino* | 55.43 | 59.24 | 57.97 | 57.53 |
| (1) [b] | | 55.42 | 59.28 | 57.93 | 57.49 |
| (1) [c] | | 55.40 | 59.23 | 57.92 | 57.49 |
| (2) | | 55.43 | 59.24 | | |
| (3) | | 55.43 | | | 57.53 |
| (4) | | 55.43 [d] | | | |
| (5) | *lyxo* | 55.11 | 59.04 | 58.01 | 58.49 |
| (6) | | 55.09 | 59.03 | 58.01 | |
| (7) | | 55.10 | 59.02 | | 58.48 |
| (8) | | 55.10 [d] | | | |
| (9) | *ribo* | 56.14 | 58.74 | 59.44 | 57.49 |
| (10) | | 56.24 | 58.68 | | |
| (11) | | 56.23 | | | 57.54 |
| (12) | | 56.23 [d] | | | |
| (13) | *xylo* | 55.07 | 58.96 | 60.83 | 58.84 |
| (14) | | 55.09 | 59.00 | | 58.86 |
| (15) | | 55.10 | | 60.83 | 58.87 |
| (16) | | 55.08 [d] | | | |

[a] Chemical shifts in p.p.m. from internal $Me_4Si$; measurements were made on 0.58M-solutions (except where stated otherwise) in [$^2H$]chloroform–1,4-dioxan–tetramethylsilane (87 : 10 : 3 v/v/v). [b] At a concentration of 0.24M. [c] At a concentration of 1.30M. [d] Quartet in off-resonance, $^1H$-decoupled spectrum.

The $^{13}C$ chemical shifts of the methoxy-carbon nuclei of the ethers (1)—(16), measured in [$^2H$] chloroform–1,4-dioxan, are recorded in Table 1. A dilution study with compound (1) showed that its methoxy-carbon resonances were virtually invariant in the range 0.24—1.3M. In the Experimental section are recorded also similar shift data for methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (17) [assignments made through measurements on the 2,3-dimethyl-4,6-bis(trideuteriomethyl) ether (18) and the 3,4-dimethyl-2,6-bis(trideuteriomethyl) ether (19) of the parent glycoside] and provisional assignments for the following compounds: methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside, methyl 2,3,4,6-

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tetra-*O*-methyl-α-D-mannopyranoside, methyl 6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranoside, methyl 2,3-di-*O*-methyl-α-D-glucopyranoside, methyl 2,3-di-*O*-methyl-α-D-galactopyranoside, and methyl 2,3-di-*O*-methyl-α-D-mannopyranoside. $^{13}C$ Shift data on the *gluco*- and *galacto*- per-ethers were previously reported [10,11] for solutions in [$^2H_3$]acetonitrile. In the present work, the provisional assignments for methoxy-carbon resonances in the *galacto*- and *manno*-ethers are based on comparisons with (17), and with homomorphous derivatives (see later).

Deductions of relationships between molecular environment and chemical shift require a knowledge of the conformations adopted by the molecules under consideration. Although the conformations of compounds (1), (5), (9), and (13) have not been specifically investigated previously, all available evidence strongly suggests that in solution the β-L-*arabino*-, α-D-*lyxo*-, and α-D-*xylo*-glycoside derivatives (1), (5), and (13) respectively, exist predominantly in the $^4C_1$ conformation, whereas the β-D-*ribo*-derivative (9) exists in an equilibrium mixture which contains substantial amounts of both $^4C_1$ and $^1C_4$ forms. Thus, in aqueous solution, methyl β-L-arabinopyranoside,[21-23] and methyl [24] and benzyl [25] α-D-lyxopyranoside appear to exist predominantly in $^4C_1$ conformations. Also there is little doubt that methyl α-D-xylopyranoside adopts a $^4C_1$ conformation in solution, in view of the fact that α-D-xylose exists in the $^4C_1$ form,[26,27] and that glycoside formation increases the magnitude of the anomeric effect; [27] this deduction is fully supported by the $^{13}C$ chemical shift of its methoxy-carbon atom.[22,23] Methyl β-D-ribopyranoside appears [21] to be a mixture of about equal amounts of $^4C_1$ and $^1C_4$ forms in aqueous solution. Further, it has been observed [27] that the anomeric effect increases with the extent of methylation of the hydroxy-groups in a sugar, and in general that it is greater in non-aqueous media than in water. Therefore, for the ethers (1), (5), and (13), when dissolved in organic solvents, an even greater preference for the $^4C_1$ conformation would be expected in comparison with that of the parent glycoside in aqueous solution; on the other hand, the reverse would be predicted in the case of (9). Finally, the $J_{1,2}$ values in [$^2H_3$]acetonitrile of compounds (1),* (5), and (13) were all close to 3 Hz, which is a reasonable value if they adopt $^4C_1$ conformations; in the alternative $^1C_4$ form, values of 1.0—1.5, 7—10, and 1.0—1.5 Hz, respectively, would be expected.[29] For compound (9), the $J_{1,2}$ value of 7 Hz suggests that an appreciable proportion of the $^4C_1$ conformer is present.†

The similarity of the $^{13}C$ shifts of the methoxy-carbon nuclei at the anomeric centres in compounds (1), (5), and (13) to that in the *gluco*-derivative (17) further supports the existence of these compounds predominantly in the $^4C_1$ conformation. Significantly, the corresponding resonance of (9) lies *ca.* 1 p.p.m. to lower field, consistent [22,23] with a major contribution of the $^4C_1$ form to the conformational equilibrium. This deduction is also supported [23] by the fact that C-1 in (9) is considerably deshielded in comparison with C-1 in the other stereoisomers; the resonance of the anomeric carbon nucleus is readily identified since it is the most deshielded of all the carbon nuclei in these compounds.

The $^{13}C$ resonances of certain non-anomeric methoxy-groups show an interesting dependence on molecular geometry. Thus the methoxy-groups at C-3 in (1) and (5), which in both cases are situated between an equatorially and an axially attached methoxy-group, resonate *ca.* 2.8 p.p.m. to higher field of the C-3 methoxy-group in (13), which has two equatorially attached methoxy-groups at the adjacent carbon atoms. Analogous shift differences have been observed by Haverkamp and his co-workers,[10,11] who compared methoxy-carbon resonances at C-2 in the anomeric forms of the tetramethyl ether of methyl D-glucopyranoside and methyl D-galactopyranoside, and at C-3 in the *gluco*- and *galacto*-stereoisomers having the same configuration at the anomeric centres. This type of $^{13}C$ shift appears to have some generality (and therefore analytical value as regards stereochemistry and conformational analysis) and to suggest a rationalization in terms of preferred rotamer populations,[32] and deshielding δ-effects,[33-35] which have only recently been recognized. The common structural units which are compared in each of the above cases are (A) and (B). The major rotamers about the MeO–C(2′) bond in (A) will be (C) and (D), whereas that for (B) will be (E). The relative orientation of the methyl group,

* The value of $J_{1,2}$ given for (1) assumes $J_{1,3} = 0$; virtual coupling [28] of H-1 to H-3 was apparent, since the signal for H-1 was not a simple doublet.

† If we assume the values of $J_{1,2}$ for the $^4C_1$ and $^1C_4$ conformers of (9) to be the same as those found for β-D-ribopyranose tetra-acetate [30] (8 and *ca.* 1 Hz, respectively), (9) appears to consist of 86% of the $^4C_1$ conformer, which is a greater proportion than would be predicted from the foregoing argument on the effect of methylation and solvent change on the magnitude of the anomeric effect. It appears that destabilization of the $^1C_4$ conformer by the axial substituents at C-2 and C-4 is greater in the case of the permethylated compound than in the parent glycoside, a result which could be explained if intramolecular hydrogen bonding occurred between the two *syn*-axial hydroxy-groups in the latter compound. Although this appears unlikely in aqueous solution, the stereochemistry is particularly favourable for such bonding, and one of the rare examples of a carbohydrate showing intramolecular hydrogen bonding within a monosaccharide unit in the crystalline state involves the *syn*-axial hydroxy-groups at C-2 and C-4 in a ribopyranoside derivative (methyl 1-thio-α-D-ribopyranoside).[31]


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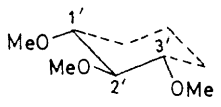
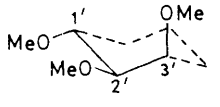
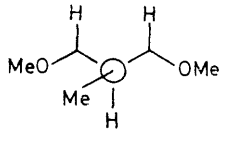
the nearest oxygen atom on an adjacent ring carbon atom, and the four intervening bonds in (C) and (D) is essentially that of the *syn*-axial [33] arrangement of a methyl group and an oxygen atom occupying 1,3-diaxial positions on a cyclohexane ring. It has been shown that such an arrangement produces, with few exceptions,[35] appreciable *downfield* shifts in the $^{13}C$ resonance of a methyl group (δ-effects), which are to be compared with the *upfield* shifts produced by steric compression of a carbon nucleus by an atom other than hydrogen in the



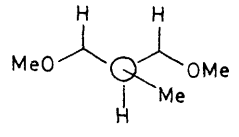

(A)



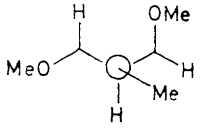

(B)




(C)




(D)




(E)

γ-position.[36,37] By contrast, in rotamer (E) the stereorelationship with the nearest adjacent oxygen atom is of the *gauche, gauche* [33] type, which usually leads to only small (generally $<1$ p.p.m.), variable shifts.*

The groups neighbouring the central methoxy-group need not, necessarily, be methoxy-groups for similar effects to be observed. Thus it has already been noted [38,39] that the methoxy-carbon nuclei in partially *O*-methylated inositols absorb near $\delta_C$ 60 if flanked by two equatorial hydroxy-groups, but at $\delta_C$ 58 if flanked by one axial and one equatorial group. The fact that a general equivalence of hydroxy and methyl shielding effects has been recognized [40] suggests that 1-methoxy-2,6-dimethylcyclohexanes and related compounds should also show similar changes in the $^{13}C$ methoxy-carbon resonance with changes in configuration at the 2- and 6-positions.

In the *ribo*-derivative (9), the signal for the methoxy-carbon at C-3 is deshielded by *ca.* 1.4 p.p.m. relative to the resonances for similar carbon nuclei in the *arabino*-(1) and *lyxo*-ethers (5) affording further evidence that the $^1C_4$ conformation is not strongly favoured for this compound. In this conformation of (9) the two preferred rotamers about the C(3)–OMe bond would both involve the methyl group in *syn*-axial interactions with a hydrogen atom, and thus the methoxy-carbon nucleus might reasonably be expected to have a chemical shift value similar to those at C-3 in (1) and (5) [note rotamer (E)]. Interestingly, in the $^4C_1$ conformation, the methyl group of the axially disposed methoxy-group at C-3 is subject, in each of the favoured rotamers, to a *syn*-axial interaction with an oxygen atom, but further study is required to ascertain if a correlation exists between expected rotamer populations and $^{13}C$ chemical shifts for axially situated methoxy-groups.

Our values for the chemical shifts of the methoxy-carbon nuclei in methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (17) in [$^2H$]chloroform–dioxan solution are similar to those reported [10] for this compound in [$^2H_3$]acetonitrile, the most notable difference being 0.6 p.p.m. for the methoxy-group at C-2. Interestingly, the methoxy-carbon resonances in methyl 2,3-di-*O*-methyl-α-D-glucopyranoside were close (differences less than 0.4 p.p.m.) to three of those for methoxy-carbon nuclei in (17). A similar correspondence between $^{13}C$ signals was observed in the case of methyl 2,3-di-*O*-methyl-α-D-galactopyranoside and methyl 2,3-di-*O*-methyl-α-D-mannopyranoside, and the corresponding per-methylated glycopyranosides. A reasonable, self-consistent deduction is that for a given glycoside, the chemical shift of a methoxy-carbon nucleus at a particular ring position is largely independent of substitution at the other hydroxy-groups, for a given solvent and solute concentration. Therefore when the separations between methoxy-carbon resonances in a fully methylated glycoside are greater than *ca.* 0.5 p.p.m., partially methylated derivatives of the glycoside may be useful in assigning methoxy-resonances. The comparison of homomorphous sugar derivatives is also useful in this respect. Thus the resonance positions for methoxy-carbon nuclei at C-1, C-2, and C-3 in the *xylo*-ether (13) are very close (differences less than 0.05 p.p.m.) to those of similarly placed carbon nuclei in the *gluco*-ether (17).

By applying these principles to methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside, the methoxy-carbon resonances at C-1, C-2, C-3, C-4, and C-6 may tentatively be assigned to the signals at 55.35, 59.00, 58.25, 61.31, and 59.16 p.p.m., respectively, with the possibility that the second and last figures may be interchanged. The agreement between this allocation and that reported [11] from studies of labelled compounds in [$^2H_3$]acetonitrile as solvent is satisfactory. Comparison of the methoxy-carbon resonances for methyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside with those of the homomorphous *lyxo*-derivative (5) and those of methyl 2,3-di-*O*-methyl-α-D-mannopyranoside, suggest the assignment of methoxy-carbon resonances at C-1, C-2, C-3, C-4, and C-6 as

* The methyl group in (C), (D), and (E) is also *gauche,trans* [33] to the furthest adjacent oxygen atom. Shielding effects induced by such an arrangment might reasonably be expected to be similar in the three rotamers, and since shift differences are considered here, they should cancel.

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54.78, 58.92, 57.66, 60.41, and 59.15 p.p.m. Although the second and last values may be interchanged, the order given is preferred, as the chemical shift of the methoxy-carbon at C-6 should be close to that in the *gluco*-ether (17). Assignments for methyl 6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranoside follow from reasoning similar to that outlined above. On the basis of the above signal allocations, the per-methylated derivatives of the D- and L-mannopyranosides provided further examples of the large upfield shift observed in the resonance of a methoxy-carbon nucleus (that at C-3), when the adjacent methoxy-substituents occupy an equatorial and an axial position, in comparison with the case when the neighbouring substituents are both equatorially disposed.

Assignments of the methoxy-proton resonances in the $^1$H n.m.r. spectra of the ethers (1), (5), (9), and (13), measured in [$^2H_3$]acetonitrile, are noted in Table 2. In

TABLE 2

Some $^1$H n.m.r. parameters [a] (δ values; $J$ in Hz) for methyl tri-*O*-methylpentopyranosides (1), (5), (9), and (13) in $CD_3CN$

| Compd. | 1-OMe | 2-OMe | 3-OMe | 4-OMe | H-1 | $J_{1,2}$ |
|---|---|---|---|---|---|---|
| (1) | 3.309 | 3.360 | 3.347 | 3.347 | 4.77 | 3.3 [b] |
| (5) | 3.313 | 3.379 | 3.370 | 3.362 | 4.62 | 3.0 |
| (9) | 3.366 | 3.377 | 3.449 | 3.334 | 4.43 | 7.0 |
| (13) | 3.310 | 3.378 | 3.480 | 3.392 | 4.74 | 3.1 |

[a] Methoxy-chemical shifts were measured at 50 Hz sweep width. [b] Assuming $J_{1,3} = 0$.

the case of the *arabino*-ether (1), the signals for the methoxy-protons at C-3 and C-4 were not resolved, illustrating an advantage of $^{13}$C n.m.r. spectroscopy where accidental shift equivalence is less likely, as a result of the wider range of chemical shifts normally encountered.

In $^1$H n.m.r. spectroscopy, many examples have been reported [4,8-11] of protons in an equatorially disposed methoxy-group on a six-membered ring, situated between two equatorially attached methoxy(hydroxy)-groups [as in (A)] resonating at a significantly lower field than protons in a similar group having one axial and one equatorial neighbouring methoxy(hydroxy)-group [as in (B)]. The present data are in full accord with these previous findings, and there appears to be, from our own results and those of others,[10,11] a direct connection between the $^1$H and $^{13}$C methoxy-shifts induced by the changes in configuration which may be depicted as (A) ⟶ (B). Especially noteworthy is that both $^1$H and $^{13}$C chemical shifts of the proton and carbon nuclei of the central methoxy-group exhibit chemical shift changes *in the same direction*, that is upfield, in going from the stereoarrangement (A) to (B). It has been noted [41] that in many instances, when $^{13}$C nuclei exhibit enhanced shielding due to steric hindrance, for example through *gauche* interactions of methyl groups (*γ-gauche* interaction), then the appended protons are deshielded; that is, inverse shielding patterns are observed for the two types of nuclei. This phenomenon has been rationalized [42] in terms of a change in charge polarization of C–H bonds. It has also been observed [33] that current notions regarding the origins of γ-effects in $^{13}$C spectra, in terms of steric polarization, appear to fail for *syn*-axial δ-effects, which are generally deshielding, since the non-bonded interatomic distances for the *syn*-axial arrangement are little different from those in γ-gauche orientations. The similar directions of chemical shift changes for protons and $^{13}$C nuclei noted in this work support the idea that the origins of γ- and δ-effects are different.

*Selective Acylation of Methyl* β-L-*Arabinopyranoside.*—An illustration of the utility of $^{13}$C n.m.r. spectroscopy for glycoside ether identification was provided during selective benzoylation studies on methyl β-L-arabinopyranoside. Treatment of the glycoside with 2 mol. equiv. of benzoyl cyanide in *NN*-dimethylformamide containing a trace of triethylamine afforded, as the major product, a dibenzoate which was different from the known [15] 2,3-dibenzoate. Its structure was proved by sequential methylation with diazomethane–boron trifluoride reagent, de-esterification, and then trideuteriomethylation. The $^{13}$C n.m.r. spectrum of the product in [$^2$H]chloroform–dioxan included peaks at $\delta_C$ 55.42, 57.93, and 58.78 (C-5), indicating the original diester to be the 2,4-derivative. The $^1$H n.m.r. spectrum in [$^2H_3$]acetonitrile did not allow an unequivocal identification, since the resonances for methoxy-groups at C-3 and C-4 were not resolved under these conditions.

## EXPERIMENTAL

T.l.c. was performed on Kieselgel $GF_{254}$ and preparative layer chromatography (p.l.c.) on Kieselgel $PF_{254}$. G.l.c. was performed on a Perkin-Elmer F-11 instrument, with carrier gas nitrogen at 16 lb in$^{-2}$, and detection by flame ionization [column (A) 2 m, i.d. 2mm, Carbowax 20M, on Chromosorb-W, column temperature 215 °C; column (B) 2 m, i.d. 2 mm, silicone gum-rubber E301 on Chromosorb-GAW-DMCS, column temperature 140 °C]. Optical rotations were measured in chloroform on a Perkin-Elmer 141 polarimeter. $^1$H N.m.r. spectra were measured at 100 MHz with a Varian HA-100 spectrometer, with tetramethylsilane as internal reference. Methoxy-proton chemical shifts were measured for 0.1M-solutions in [$^2H_3$]acetonitrile, at a sweep-width of 50 Hz; spectra were calibrated by using a pen-coupled, digital frequency-counter. $^{13}$C N.m.r. spectra were recorded at 25.16 MHz on a Varian XL-100-15 spectrometer in the Fourier transform mode; spectra were measured for 0.58M-solutions in [$^2$H]chloroform, with 1,4-dioxan and tetramethylsilane as internal standards ([$^2$H]chloroform–1,4-dioxan–tetramethylsilane, 87 : 10 : 3 v/v/v). $^{13}$C Shifts were initially calculated with reference to 1,4-dioxan, and converted $\delta_C$ values (from $Me_4Si$) by addition of 67.15 p.p.m. For proton noise-decoupled spectra, typically, 2 000 transients were collected with a pulse width of 10 μs and an acquisition time of 1.6 s (8 K data points) at a spectral width of 2 500 Hz. Off-resonance decoupled spectra were recorded with a single frequency decoupling signal, offset 1 000 Hz to high field of the frequency used for proton noise-decoupling, and, typically, 15 000 transients were collected. Mass spectra were measured with a Hitachi–Perkin-Elmer RMU-6E spectrometer, using an electron beam ionization energy of 70 eV and an accelerating potential of 1 800 V.

Unless stated otherwise, the physical constants of previously reported compounds which were prepared again for use in this work were in agreement with the literature values.

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The purities of all of the per-methylated glycosides were established by g.l.c. analysis on columns (A) and (B). In a given stereochemical series, the retention times of the labelled compounds were indistinguishable from that of the unlabelled ether. In addition, the labelled and unlabelled per-ethers of a given stereo-series had, with one exception,* similar values of specific rotation, and, except for expected differences in the regions of the methoxy-resonances, similar n.m.r. spectra.

2,3,4-Trimethyl ethers of methyl β-L-arabinopyranoside,[44] methyl α-D-lyxopyranoside,[45] methyl α-D-xylopyranoside,[46] and methyl 6-deoxy-α-L-mannopyranoside,[47] and the 2,3,4,6-tetramethyl ethers of methyl α-D-glucopyranoside,[48] methyl α-D-galactopyranoside,[49] and methyl α-D-mannopyranoside [50] were prepared by application of the methylation procedure described below to the parent glycosides. *Methyl 2,3,4-tri-O-methyl-β-D-ribopyranoside*, prepared by similar methylation of methyl β-D-ribopyranoside,[51] had b.p. 49—50° at 0.06 mmHg, $[\alpha]_D$ −81.1° (*c* 1.2) (Found: C, 52.1; H, 9.0. $C_9H_{18}O_5$ requires C, 52.4; H, 8.8%). The 2,3-dimethyl ethers of methyl α-D-glucopyranoside,[52] methyl α-D-galactopyranoside,[53] and methyl α-D-mannopyranoside [54] were prepared from the 4,6-*O*-benzylidene derivatives of the parent glycosides through methylation, followed by hydrogenolytic removal of the acetal group.

*Methylation Procedure.*—This procedure was used for all methylations unless stated otherwise. Sodium hydride, supplied as a 60% dispersion in oil, was freed from oil by washing with light petroleum; weights of this reagent refer to oil-free material.

A solution of the carbohydrate derivative (0.01 mol) in 1,2-dimethoxyethane (DME) (10 ml per g of solute) was added cautiously to a stirred suspension of sodium hydride (0.02 mol per hydroxy-group) in DME (10 ml per g of carbohydrate derivative), and when effervescence had ceased, methyl iodide (trideuteriomethyl iodide) (0.013 mol per hydroxy-group) was added, and the solution then stirred for 12 h. Methanol was then added until effervescence ceased, followed by an equal volume of water; solid carbon dioxide was then added until the solution remained cold. The mixture was concentrated to a thick slurry, after which more methanol was added, and the solution was again concentrated. The slurry was partitioned between water and chloroform, and the aqueous layer extracted with several portions of chloroform. The combined extracts were washed with water, dried ($Na_2SO_4$), and then concentrated to give material which was usually distilled under reduced pressure to afford the methylated derivative.

*Deacetonation Procedure.*—The method is a slight modification of that previously reported.[55] The isopropylidene derivative (1 g) was dissolved in trifluoroacetic acid–water (9 : 1 v/v; 10 ml). The solution was then concentrated (bath <40 °C) to yield material which was dissolved in methanol (10 ml). This solution was placed on a column (3 × 20 cm) of Amberlite IRA-400 ($OH^-$) resin (prewashed with methanol). The column was eluted with methanol (300 ml), and the eluate was concentrated to yield a solid (which was recrystallized) or a syrup (which was distilled under reduced pressure).

*Synthesis of Specifically Labelled Methyl Ethers of the Glycopyranosides.*—(a) *From methyl β-L-arabinopyranoside.* Trideuteriomethylation of the glycoside and its 2-[14] and 4-methyl [15] ethers afforded the ethers (4), (2), and (3) respectively.

(b) *From methyl α-D-lyxopyranoside.* Methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside [16] was trideuteriomethylated, and the product deacetonated; after p.l.c. the 4-ether was methylated to afford (6). Trideuteriomethylation of the glycoside and its 2,4-dimethyl ether [17] gave (8) and (7), respectively.

(c) *From methyl β-D-ribopyranoside.* Trideuteriomethylation of the glycoside gave (12). Methyl 2,3-*O*-isopropylidene-β-D-ribopyranoside [18] was sequentially methylated, deacetonated, and trideuteriomethylated to yield (11). Methylation of methyl 3,4-*O*-isopropylidene-β-D-ribopyranoside [18] afforded the *2-methyl ether*, b.p. 74° at 0.2 mmHg, $[\alpha]_D$ −114.8° (*c* 1.5) (Found: C, 54.9; H, 8.1. $C_{10}H_{18}O_5$ requires C, 55.0; H, 8.3%). Deacetonation of the above ether gave *methyl 2-O-methyl-β-D-ribopyranoside*, b.p. 85° (bath temp.) at 0.02 mmHg, $[\alpha]_D$ −113.4° (*c* 0.95) (Found: C, 46.9; H, 8.05. $C_7H_{14}O_5$ requires C, 47.2; H, 7.9%). Trideuteriomethylation of the 2-methyl ether yielded (10).

(d) *From methyl α-D-xylopyranoside.* The 3-benzoate [20] of the glycoside was methylated with the diazomethane–boron trifluoride reagent [56] to give the *3-O-benzoyl-2,4-di-O-methyl derivative*, m.p. 48—52° (from ether–light petroleum) $[\alpha]_D$ +108° (*c* 0.66) (Found: 60.8; H, 6.6. $C_{13}H_{10}O_6$ requires C, 60.8; H, 6.8%). Debenzoylation of this compound and trideuteriomethylation of the product gave (14). On methylation with methyl iodide–silver oxide, methyl 2-*O*-*p*-tolylsulphonyl-α-D-xylopyranoside [19] gave the *3,4-dimethyl ether*, m.p. 66—68° (from ether–light petroleum), $[\alpha]_D$ +82.6° (*c* 1.2) (Found: C, 52.1; H, 6.6. $C_{15}H_{22}O_7S$ requires C, 52.0; H, 6.4%). De-esterification of this compound with sodium amalgam in methanol, and crystallisation of the crude product from ethyl acetate–light petroleum, gave *methyl 3,4-di-O-methyl-α-D-xylopyranoside*, m.p. 36—40°, $[\alpha]_D$ +138.5° (*c* 1.3) (Found: C, 49.7; H, 8.2. $C_8H_{10}O_5$ requires C, 50.0; H, 8.4%). Trideuteriomethylation of this material gave (15).

(e) *From methyl α-D-glucopyranoside.* Methyl 2,3-di-*O*-methyl-α-D-glucopyranoside [52] and methyl 3,4-di-*O*-methyl-α-D-glucopyranoside [57] were trideuteriomethylated to afford (18) and (19), respectively.

* In the *xylo*-series, the 2,3,4-tris(trideuteriomethyl) ether (16) had $[\alpha]_D$ + 98.3° (*c* 1.2). The values of $[\alpha]_D$ for the other members (13)—(15) were 127.7°, 123.4°, and 126.0°, respectively. G.l.c. indicated (16) to contain 8% of another compound, which was shown to be the β-anomer by an acid-catalysed equilibration study on (13). The low value of the specific rotation of the 2,3,4-tris(trideuteriomethyl) ether, together with the known [43] rotation of the β derivative (unlabelled), suggested (16) to be contaminated with 11% of the β-anomer. Equilibration of glycosides does not occur under the basic conditions of the alkylation, and a slightly impure batch of the α-glycoside was responsible for the anomalous rotation.

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*Selective Benzoylation of Methyl β-L-Arabinopyranoside with Benzoyl Cyanide.*—To a stirred suspension of methyl β-L-arabinopyranoside (0.82 g, 5 mmol) in *NN*-dimethylformamide (20 ml) was added triethylamine (0.05 ml), and then a solution of benzoyl cyanide (1.31 g) in *NN*-dimethylformamide (20 ml) was added in two portions, separated by a 20 min interval. T.l.c. (benzene–ethyl acetate, 3 : 1) indicated the presence of four components (W)—(Z) in order of increasing mobility; (Y) was the major component. The solvent was removed under reduced pressure, methanol (2 × 5 ml) was added and evaporated off, and the crude mixture was separated into its components by p.l.c.

Component (W) (0.3 g), when subjected to t.l.c. with repeated elution, was seen to consist of two components and was not investigated further. Component (X) (0.43 g) was identified as the 2,3-dibenzoate, m.p. 142—143° (from ether–light petroleum), $[\alpha]_D$ +212.5° (*c* 1.1) (lit., [58] m.p. 141.5—142.5°), $[\alpha]_D$ +210° (*c* 1.0). Component (Z) (0.41 g) was isolated as a foam, and was presumed to be the 2,3,4-tribenzoate on the basis of its i.r. and $^1$H n.m.r. spectra.

Component (Y) (0.71 g) was crystallised from ethyl acetate–light petroleum to afford prisms of a *dibenzoate*, m.p. 155—157°, $[\alpha]_D$ + 241.3° (*c* 1.0) (Found: C, 64.4; H, 5.2. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%), identified as follows. A sample (2 g) was methylated with diazomethane–boron trifluoride [56] in dichloromethane; two treatments were necessary to achieve complete alkylation. The syrup (1.98 g) isolated was homogeneous by t.l.c. (toluene–ethyl acetate, 4 : 1) and showed no i.r. absorption near 3 600 $cm^{-1}$; it had $[\alpha]_D$ +197.8° (*c* 0.5). This material was immediately debenzoylated by base catalysed transesterification in methanol, and the material so obtained was subjected to trideuteriomethylation. The product, which crystallised, was distilled to afford an oil (0.63 g), b.p. *ca.* 120° (bath temp.) and 0.4 mmHg, which crystallized to give a solid, m.p. 38—42°, $[\alpha]_D$ +211.7° (*c* 0.3). Values for the ethers (1)—(4) were, respectively: m.p. 46—47°, $[\alpha]_D$ +217° (*c* 1.1); m.p. 42—45°, $[\alpha]_D$ +209° (*c* 1.1); m.p. 43—45°, $[\alpha]_D$ +209° (*c* 0.9); m.p. 40—44°, $[\alpha]_D$ +207° (*c* 1.0).

The methoxy-region of its $^1$H n.m.r. spectrum contained peaks at δ 3.310 and 3.350. The methoxy-region of its $^{13}$C n.m.r. spectrum contained peaks at $\delta_C$ 55.42, 57.93, and 58.78 (C-5) indicating it to be the 3-methyl-2,4-bistrideuteriomethyl ether; the original diester from which it is derived is thus methyl 2,4-di-*O*-benzoyl-β-L-arabinopyranoside.

$^{13}$C *Chemical Shift Data for Methoxy-groups in Some Methylated Methyl Hexopyranosides.*—$\delta_C$ Values are given in parentheses. Except for (17)—(19), assignments are provisional. Assignments designated with an asterisk may be reversed.

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (17): 1-OMe (55.11), 2-OMe (58.96), 3-OMe (60.79), 4-OMe (60.43), 6-OMe (59.20); methyl 2,3-di-*O*-methyl-4,6-bis-*O*-trideuteriomethyl-α-D-glucopyranoside (18): 1-OMe (55.11), 2-OMe (58.88), 3-OMe (60.75); methyl 3,4-di-*O*-methyl-2,6-bis-*O*-trideuteriomethyl-α-D-glucopyranoside (19): 1-OMe (55.15), 3-OMe (60.79), 4-OMe (60.39); methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside: 1-OMe (55.35), 2-OMe (59.00),* 3-OMe (58.25), 4-OMe (61.31), 6-OMe (59.16); * methyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside: 1-OMe (54.78), 2-OMe (58.92),* 3-OMe (57.66), 4-OMe (60.41), 6-OMe (59.15); * methyl 6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranoside: 1-OMe (54.67), 2-OMe (58.88), 3-OMe (57.61), 4-OMe (60.75); methyl 2,3-di-*O*-methyl-α-D-glucopyranoside: 1-OMe (55.19), 2-OMe (58.61), 3-OMe (61.15); methyl 2,3-di-*O*-methyl-α-D-galactopyranoside: 1-OMe (55.33), 2-OMe (58.95), 3-OMe (57.79); methyl 2,3-di-*O*-methyl-α-D-mannopyranoside: 1-OMe (54.87), 2-OMe (59.07), 3-OMe (57.33).

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