Carbohydrate Research, 123 (1983) 23–29
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

THE EFFECT OF *O*-METHYLATION ON CHEMICAL SHIFTS IN THE ^{1}H- AND ^{13}C-N.M.R. SPECTRA OF CYCLIC POLYOLS*

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(Received May 6th, 1983; accepted for publication, June 6th, 1983)

ABSTRACT

The ^{1}H- and ^{13}C-n.m.r. spectra of seven inositol methyl ethers were recorded and assigned. They were classified into five types, and the effect of *O*-methylation on the chemical shifts of each type is discussed.

INTRODUCTION

For the study[2] of deuterium labelling of carbohydrates, we needed the ^{1}H- and ^{13}C-n.m.r. spectra of several mono-*O*-methylated inositols. When these spectra had been assigned, we found ourselves with a collection of data that threw some light on a much studied and often discussed subject, namely, the effect of *O*-methylation on the chemical shifts of carbon atoms and of the hydrogen atoms attached to them.

There are six possible geometrical arrangements of a methoxyl group and of one other substituent on each of the adjacent carbon atoms in a six-membered ring; they are shown in Fig. 1. Our compounds included five of these arrangements, more than those encountered in previous studies; we therefore used this opportunity to revise and update the existing data. The sixth arrangement (**F**) is not found among the (monocyclic) inositols or pyranoses; the similarity of its geometry to that of Type **C** suggests that the effect of methylation would be similar for these two types.

The ^{13}C-n.m.r. spectra of all of the inositols are well known[1,3], but the ^{1}H-n.m.r. spectrum of only one isomer (*epi*) has been described[4]; those of the others are, however, first-order at 250 MHz, and are therefore readily assigned. Among

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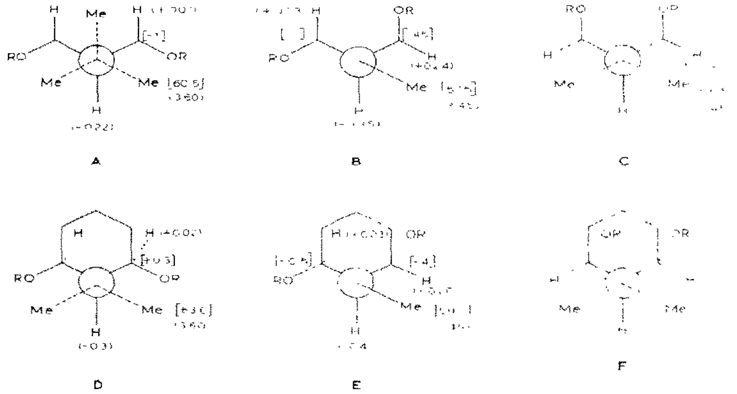


Fig. 1. The possible steric arrangements of a methoxyl group with two adjacent hydroxyl groups, viewed from the methoxyl oxygen atom along its bond to the ring-carbon atom. The effects of *O*-methylation (with + or − signs), and the chemical shifts, are indicated in square brackets for ^{13}C, and parentheses for ^{1}H, signals

the methyl ethers, the ^{13}C spectra of four isomers, and the ^{1}H spectrum of only one isomer, were previously known.

^{13}C-N.m.r. spectra

The effect, on the chemical shifts of carbon atoms in six-membered, alicyclic rings, of methylating a secondary hydroxyl group has been extensively studied$^{3,5-10}$. The signal of the carbon atom carrying the methoxyl group shifts downfield by ~10 p.p.m.; those of the adjacent carbon atoms usually shift upfield to various extents, depending on the configuration caused by the substituents. If both adjacent carbon atoms bear equatorial hydroxyl groups, the shift is small (Types **A** and **D**, Fig. 1). When one adjacent carbon atom carries an axial substituent, its signal shifts upfield by −3.5 to −4.5 p.p.m., but that of the other adjacent carbon atom shifts by$^{6-8}$ only −0.2 to −1.0 p.p.m. (**B** and **E**). The arrangements **A**–**E** show the rotational orientations of the methyl group that are most frequently populated (by dotted lines, if there are several such orientations). The effect of the methyl group on the ^{13}C-chemical shifts has been explained in terms of an interaction of the methyl group with a hydrogen atom on the carbon atom concerned^{10}; when they are in a 1,3-parallel arrangement there is a substantial, upfield shift.

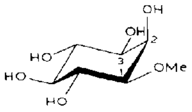
The spectra of the inositol methyl ethers have been assigned on the basis of these methylation shifts (see Table I). Those of 3-*O*-methyl-*epi*-, 2- and 3-*O*-methyl-*chiro*-, and 1-*O*-methyl-*myo*-inositol (**1**) have been previously assigned^{3}; two values for the latter had to be interchanged, consequent on the corrections re-

TABLE I

^{13}C-SHIELDINGS OF INOSITOL METHYL ETHERS IN DEUTERIUM OXIDE[a]

Inositol	*Type*[b]	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Me*
O-Methyl-*scyllo*-	**A**	84.2	73.7	74.3	74.3	74.3	73.7	60.6
D-1-*O*-Methyl-*myo*- (**1**)	**B**	81.3	[68.4]	71.8	73.1	75.2	72.4	57.5
2-*O*-Methyl-*myo*-	**D**	72.4	[83.6]	72.4	73.5	75.2	73.5	63.0
D-1-*O*-Methyl-*chiro*- (**2**)	**E**	[82.4]	71.0	73.9	73.4	71.4	[68.9]	59.4
L-2-*O*-Methyl-*chiro*-[c]	**B**	[68 2]	81.1	72.9	73.8	71.4	[72.3]	57.8
D-3-*O*-Methyl-*chiro*-[c]	**A**	[72.3]	70.7	83.5	72.9	71.4	[72.5]	60.5
3-*O*-Methyl-*epi*-[d] (**3**)	**C**	72.6	[72.6]	76.4	[72.6]	72.6	71.1	56.7

[a] In p.p.m. from external Me_4Si. Square brackets denote carbon atoms bearing axial hydroxyl (or methoxyl) groups. [b] According to Fig. 1. [c] Ref. 3. [d] Ref. 1.



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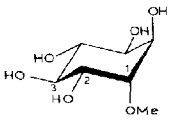

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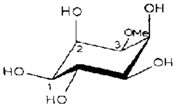

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cently made to the assignments for *myo*-inositol[2]. The spectra of the other methyl ethers could be unambiguously assigned with one exception, that of 1-*O*-methyl-*chiro*-inositol (**2**). In the nonmethylated parent compound, C-3 and C-4 are magnetically equivalent. The signal of C-4 should not be altered by methylation, owing to its distance from O-1. Blunt *et al.*[8] assumed that methylation of an axial hydroxyl group does not affect the signal of the γ-carbon atom, and we found that this was, indeed, true for 2-*O*-methyl-*myo*-inositol; hence, the signal of C-3 should not be shifted, either. However, two separate signals were found for C-3 and C-4, and they could not be assigned. Nor were the assignments of C-2 and C-5 fully convincing. We were unable to assign this spectrum until the ^{1}H-n.m.r. spectrum was assigned, and partial deuterium labelling had been performed[2].

A case of methylation shifts not previously encountered is that (C) of an equatorial methoxyl group between two axial hydroxyl groups. This occurs in 3-*O*-methyl-*epi*-inositol (**3**), and the shift of the neighboring carbon atoms is −2.9

p.p.m. Because only half the time is the methyl group close to each of the hydrogen atoms on adjacent carbon atoms, the effect is smaller than it is in Types **B** and **E**, where it is close most of the time. (See, note added in proof.)

The chemical shifts of the *O*-methyl group have been explained[10] in terms of its interaction with a substituent on the adjacent carbon atom, the δ_1 effect. The chemical-shift values are diagnostic for the orientation of the methoxyl group and of its neighboring substituents. The interaction is strong in Types **A** and **D**, and the methyl signal is found at low field (δ >60). The methyl signal is at higher field (δ 56.7) in the spectrum of 3-*O*-methyl-*epi*-inositol (**3**) than in that of any of the other isomers. In this type (**C**), there is no rotamer that has a δ_1 effect; apparently, in Type **B**, there is a small population of rotamers in which the δ_1 effect is operative.

The approximate values of the methylation effect on neighboring carbon atoms, and the chemical shifts of the methyl group, are shown (in square brackets) in Fig. 1 for each type of methyl ether. These values are also valid for carbon atoms, other than anomeric carbon atoms, in pyranoid rings, if they each bear a hydroxyl group.

^{1}H-N.m.r. spectra

The effect of *O*-methylation on the ^{1}H-n.m.r. spectra of sugars has been studied much less than that on ^{13}C spectra, probably because fully resolved, ^{1}H spectra of sugars have become readily available only recently. Correlations have been established concerning the chemical shifts of the methyl protons[11,12], but there has been only one detailed study of the methylation shifts of ring protons[13]. After methylation, the signal of the β-hydrogen atom (that is, the one attached to the same carbon atom as the methoxyl group) shifts by ~ −0.3 p.p.m., the γ-hydrogen atom shifts to a varied extent, mostly downfield, depending on the configu-

TABLE II

^{1}H SHIELDINGS OF INOSITOLS AND THEIR METHYL ETHERS IN DEUTERIUM OXIDE^a

Inositol	*Type*^{b}	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*Me*
scyllo		3.36	3.36	3.36	3.36	3.36	3.36	
—, *O*-methyl-	**A**	3.13	3.43	3.36	3.36	3.36	3.43	3.60
myo-		3.54	[4.06]	3.54	3.63	3.28	3.63	
—, D-1-*O*-methyl- (**1**)	**B**	3.22	[4.31]	3.52	3.62	3.29	3.66	3.44
—, 2-*O*-methyl-	**D**	3.56	[3.75]	3.56	$3.58^{?}$	3.23	$3.58^{?}$	3.59
chiro-		[4.03]	3.75	3.56	3.56	3.75	[4.03]	
—, D-1-*O*-methyl- (**2**)	**E**	[3.64]	3.78	3.49	3.56	3.66	[4.22]	3.46
—, L-2-*O*-methyl-	**B**	[4.26]	3.40	~3.62	~3.59	3.74	[4.06]	3.45
—, D-3-*O*-methyl-	**A**	[4.00]	3.81	3.34	3.65	~3.75	[4.00]	3.59
epi-		3.47	[4.05]	3.72	[4.05]	3.47	3.85	
—, 3-*O*-methyl-^{c} (**3**)	**C**	3.45	[4.24]	3.37	[4.24]	3.45	3.85	3.44

^{a}In p.p.m. from internal sodium 4,4-dimethyl-4-silapentane-1-sulfonate. Square brackets denote equatorial hydrogen atoms. The coupling constants are listed in the Experimental part. ^{b}According to Fig. 1. ^{c}Ref. 4.

ration, and the δ-hydrogen atom shows a small upfield shift if it is *syn*-axial with the methoxyl group.

On the basis of these correlations, and after matching the coupling constants, it was possible to assign the signals in the ^{1}H-n.m.r. spectra of all of the inositol methyl ethers (see Table II). Two signals in the spectrum of 2-*O*-methyl-*myo*-inositol were very close to each other, even at 250 MHz, and the chemical-shift values are only approximate. Several signals in the spectrum of 1-*O*-methyl-*chiro*-inositol have similar chemical shifts, and the assignments were therefore checked by progressive decoupling; they proved to be correct.

De Bruyn *et al.*[13] discussed the correlation between conformation and methylation shifts as applied to five monomethylated aldoses. The γ-effect, that is, the change in the shift of a hydrogen atom on the adjacent carbon atom, depends on the proximity of the methyl group to that hydrogen atom. De Bruyn *et al.* treated the γ-effect semi-quantitatively by the use of methylation shift-increments derived from various derivatives of cyclohexane and 1,3-dioxane; the values of these increments were: $\sim +0.03$ for $H(g,a)CH_3$, -0.22 for $H(a,g)CH_3$, 0 for $H(a,a)CH_3$, $+0.25$ for $H(g^+,g^-)CH_3$, and between -0.13 and -0.30 p.p.m. for $H(g^+,g^+)CH_3$. (The symbols describe the rotameric orientations, *gauche* or *anti*, along the C–C and the C–O bonds, viewed from the hydrogen atom.)

The methylation shifts due to the γ-effect in the various types of inositol methyl ethers are shown in Fig. 1, in parentheses. In Types **B** and **E**, where only one rotamer needs to be considered, the increments are $H(g^+,g^-)CH_3$ and $H(g,a)CH_3$ for the equatorial and the axial neighboring hydrogen atoms, respectively, and these are in good agreement with our observed data (see Fig. 1). Similar values were found by De Bruyn *et al.* for 3-*O*-methyl-β-D-gulopyranose.

In Type **C**, there are two equivalent rotamers, and the increment should be the average of $H(g^+,g\ )CH_3$ and $H(g,a)CH_3$; the value found is slightly higher. A similar value could be expected for (the as-yet-unexplored) Type **F**.

In the case of Type **A**, there are three rotamers to be considered (see Fig. 1). Dorman and Roberts[6] concluded, from the observed chemical-shift changes of the carbon atoms, that the population of the *gauche-gauche* rotamer must be substantially smaller than that of the two other rotamers. Yet it is hard to see why it should not make a significant contribution to the equilibrium, as its two *gauche* interactions are less unfavorable than the 1,3-parallel interactions in the other two rotamers. If only the two *gauche* rotamers contributed to the equilibrium, the γ-shift would be negative, being the average of $H(g^+,g^+)CH_3$ and $H(g,a)CH_3$. In fact, the value is positive ($+0.07$), indicating the presence of the *gauche-gauche* rotamer, which causes a (positive) $H(g^+,g^-)CH_3$ increment. Using De Bruyn's increment values, the γ-shift observed would indicate that between 40 and 55% of the methoxyl groups are in the *gauche-gauche* orientation.

There is also an indication in Haines and Shandiz's work[10] for the presence of the *gauche-gauche* rotamer in Type **A** compounds. The three-bond coupling ($^3J_{C,H}$) between the methoxyl-carbon atom and the closest ring-hydrogen atom in *r*-1-methoxy-*t*-2,*t*-6-dimethylcyclohexane[*] was found to be 7.3 Hz. This value is far too large for a *gauche* relationship[14], and suggests that the methyl group and the hydrogen atom are *antiperiplanar*, as they would be in the *gauche-gauche* rotamer of Type **A**. A further indication of the presence of the *gauche-gauche* rotamer is given by some methylation shifts in the ^{13}C-n.m.r. spectra. The methylation shift of the adjacent carbon atom that bears an axial hydrogen atom is −1.0 in Type **B**, presumably due to the γ-*trans*-effect of the methyl group[15]. Because, in Type **A**, the methyl group is *trans* to each axial hydrogen atom for only half the time, the effect should be only −0.5 p.p.m.; the larger effect found can be explained by the presence of the *gauche-gauche* rotamer.

In Type **D**, the γ-effect should also be negative, the average of $H(a,g)CH_3$ and $H(a,a)CH_3$; in fact, a small positive value was found. This discrepancy suggests that the preponderant orientation may not be one of the *gauche* orientations shown in Fig. 1 (which have severe steric interactions), but, rather, one in which the methyl group and the ring-hydrogen atom are almost eclipsed. No increment value is known for such an orientation. This suggestion is supported by the finding[10] that $^3J_{C,H}$ for *r*-1-methoxy-*c*-2,*c*-6-dimethylcyclohexane (also a Type **D** compound) is particularly large (9.2 Hz). This value cannot reflect a 180° dihedral angle (the *gauche-gauche* rotamer being particularly hindered), but probably corresponds to an angle of 0°. Several similar cyclohexane derivatives have large $^3J_{C,H}$ values[10]. However, in the spectrum of such an eclipsed rotamer, the methylation shift of the β-hydrogen atom should be larger[16] than the value observed. Clearly, the rotameric distribution of Type **D** requires further examination.

The β-effect of methylation, that is, the shift of the hydrogen atom geminal to the methoxyl group, is caused by the methyl group's being *syn-clinal* to the hydrogen atom, and has a value of −0.3 to −0.4 p.p.m. in most cases. Only in Type **A** is it smaller, ~ -0.22 p.p.m., again suggesting that there is a considerable contribution of the *gauche-gauche* rotamer, in which the methyl group is antiperiplanar to the hydrogen atom, and therefore causes a downfield shift[16].

The δ-effect is small; when the methoxyl group is equatorial, it is negligible (between −0.03 and +0.03 p.p.m.), but, when it is axial, there is a clearly distinguishable, upfield shift of the signal of the *syn*-axial hydrogen atom (−0.04 to −0.09 p.p.m.).

The chemical shift of the methyl group is also characteristic. In types **A** and **D**, it is δ 3.60, but, in the other types, it is δ 3.45. The former value reflects the effect of steric crowding.

All of these methylation changes are shown in Fig. 1, in parentheses, classified according to types of orientation. It is to be hoped that these values will also be found valid for pyranoses, but, apart from the examples given by De Bruyn *et al.*[13], there seem to be few data against which they could be checked. Again, these values do not apply to anomeric hydrogen atoms.

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[*] Notation: *c* = *cis*, *r* = reference, *t* = *trans*

EXPERIMENTAL

N.m.r. spectra were recorded with a Cameca 250 spectrometer in Grenoble, and with a JEOL JNM-FX-100 spectrometer in Sydney. For the ^{13}C spectra, 1,4-dioxane (δ_C 67.4) was used as the internal standard. The coupling constants, not shown in Table II, are listed here: for the methyl ether of *scyllo*-inositol, J 9.2 Hz; for those of *myo*-inositol, $J_{1,2}$ 2.75, $J_{1,6}$ 9.9, and $J_{4,5}$ 9.2 Hz; for those of *chiro*-inositol, $J_{1,2}$ 3.0, $J_{2,3}$ 9.5, $J_{3,4}$ 9.5, and $J_{1,6}$ 3.2 Hz; and, for that of *epi*-inositol, $J_{2,3}$ 3.2, $J_{1,2}$ 2.75, and $J_{1,6}$ 10.0 Hz.

ACKNOWLEDGMENTS

The authors are grateful to Professor M. Anteunis, Dr. A. De Bruyn, and Dr. A. H. Haines for helpful discussions.

NOTE ADDED IN PROOF

Type **F**, not encountered in our work, occurs in 1,6-anhydro-3-*O*-methyl-β-D-glucopyranose; the γ-effect is −3.6 and −3.7 p.p.m. The pyranoid chair is, however, somewhat distorted in this compound.

REFERENCES

1 S. J. Angyal and L. Odier, *Carbohydr. Res.*, 100 (1982) 43–54.
2 S. J. Angyal and L. Odier, *Carbohydr Res.*, 123 (1983) 13–22.
3 D. E. Dorman, S. J. Angyal, and J. D. Roberts, *J. Am. Chem Soc.*, 92 (1970) 1351–1354.
4 S. J. Angyal and R. J. Hickman, *Aust. J. Chem.*, 28 (1975) 1279–1287.
5 D. E. Dorman and J. D. Roberts, *J. Am. Chem Soc.*, 92 (1970) 1355–1361.
6 D. E. Dorman and J. D. Roberts, *J Am Chem. Soc.*, 93 (1971) 4463–4472.
7 W. Voelter, E. Breitmaier, E. B. Rathbone, and A. M. Stephen, *Tetrahedron*, 29 (1973) 3845–3848.
8 J. W. Blunt, M. H. G. Munro, and A. J. Paterson, *Aust. J. Chem.*, 29 (1976) 1115–1118.
9 S. A. Abbas, A. H. Haines, and A. G. Wells, *J. Chem. Soc., Perkin Trans. 1*, (1976) 1351–1357.
10 A. H. Haines and M. S. Shandiz, *J. Chem. Soc., Perkin Trans. 1*, (1981) 1671–1678.
11 E. B. Rathbone, A. M. Stephen, and K. G. R. Pachler, *Carbohydr. Res.*, 20 (1971) 357–367; 23 (1972) 275–282.
12 J. Haverkamp, J. C. P. M. Van Dongen, and J. F. G. Vliegenthart, *Carbohydr. Res.*, 33 (1974) 319–327.
13 A. De Bruyn, M. Anteunis, and P. Kováč, *Collect. Czech. Chem. Commun.*, 42 (1977) 3057–3068.
14 G. K. Hamer, F. Balza, N. Cyr, and A. S Perlin, *Can. J. Chem* , 56 (1978) 3109–3116.
15 E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, 97 (1975) 322–330.
16 M. Anteunis and D. Daneels, *Org. Magn. Reson.*, 7 (1975) 345–348.
17 H Paulsen, V. Sinnwell, and W. Greve, *Carbohydr Res* , 49 (1976) 27–35; N. Gullyev, A. Ya. Shmyrina, A. F Sviridov, A. S. Shashkov, and O. S. Chizhov, *Bioorg. Khim.*, 3 (1977) 50–54, *Chem. Abstr.*, 86 (1977) 121,647*a*