

## CONFORMATION AND INTRAMOLECULAR HYDROGEN BONDING IN GLUCOSE AND XYLOSE DERIVATIVES\*

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**Abstract**—The nature of intramolecular hydrogen bonding in some O-methyl derivatives of glucose and xylose and related glycosides has been examined by means of IR studies of their hydroxyl stretching absorption measured in dilute solution in non-polar solvents. For most of the compounds studied the spectra are consistent with the predominance of the C1 conformation of the pyranose ring, but there is evidence of some departures from the ideal chair shape. The occurrence in 2,3-di-O-methyl-D-xylose of a lower frequency band near  $3530\text{ cm}^{-1}$  suggests the presence of hydrogen bonds between *cis meta* diaxial groups, which would be possible only if the 1C conformer were present. The bands in the crystal spectra do not correspond to those in solution, showing that the weaker intramolecular hydrogen bonds are not favoured in the solid, where strong intermolecular bonds predominate.

Now that the important role of conformation in determining the reactions of carbohydrates has been recognised, much attention is being given to studies of their detailed stereochemistry.<sup>1</sup> The determination of intramolecular hydrogen bonding by IR spectroscopy has proved of great value as a stereochemical tool<sup>2</sup> for the study of the conformations of a number of natural products and should also be useful for studies of sugar conformations. Due to strong intermolecular hydrogen bonds in the crystal, glucose and xylose are too insoluble in non-polar solvents to be studied directly. However if the intermolecular hydrogen bonding is reduced by the substitution of methoxyl for some of the hydroxyl groups, the resulting compounds are sufficiently soluble.

Since, according to Hassel and Ottar<sup>3</sup> the substitution of an oxygen atom for a carbon atom in the cyclohexane ring to form the pyranose ring (the most stable ring form found in sugars and their derivatives) causes only minor changes in geometry, general conformational similarity between the pyranose and cyclohexane rings might be expected, except that the heterocyclic ring would be slightly more prone to distortion. Thus the methods of conformational analysis<sup>4</sup> developed initially for cyclohexane rings in the steroid nucleus<sup>5</sup> have been applied successfully to pyranose ring compounds.<sup>1</sup> Reeves<sup>6</sup> obtained information about the ring shapes of various

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<sup>1</sup> R. J. Ferrier and W. G. Overend, *Quart. Rev.* **13**, 265 (1959) and Refs therein.

<sup>2</sup> M. Tichy, *Chemické Listy* **54**, 506 (1960).

<sup>3</sup> O. Hassel and B. Ottar, *Acta Chem. Scand.* **1**, 929 (1947).

<sup>4</sup> D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).

<sup>5</sup> D. H. R. Barton, *Experientia* **6**, 316 (1950).

<sup>6</sup> R. E. Reeves, *Adv. Carbohydrate Chem.* **6**, 107 (1951); *Ann. Rev. Biochem.* **27**, 15 (1958).

glycopyranosides by their ability or otherwise to complex with cuprammonium ion and was able to show that this ring could assume two chair forms and six boat forms, and that the boat forms could be interconverted through an infinite number of intermediate shapes without angular strain. More recently Isbell and Tipson<sup>7</sup> have suggested that three further forms of the pyranose ring, namely the planar, sofa and half chair forms, are possible. In cyclohexane it is clear that the chair form is strongly favoured<sup>8</sup> but since the interactions of two hydrogen atoms are eliminated when they are replaced by a lone pair of electrons in the pyranose ring, chair forms of the latter would be expected to be somewhat destabilized compared to cyclohexane. However, the presence in sugars of bulky hydroxyl or methoxyl groups attached to the ring results in the boat forms being destabilized compared to chairs on account of stronger non-bonded interactions between the bulkier substituents in the eclipsed conformation on the sides of boats. These interactions are weaker in the skew forms but they are greater than in the ideal chair in which the carbon valences are perfectly staggered. For the pyranose rings Reeves<sup>9</sup> concluded from his complexing experiments that the two chairs (which he designated C1 and 1C) were preferred to any boat form when both were structurally possible, and by ascribing instability to certain combinations of axially disposed substituents (other than hydrogen) was able to predict which chair form was favoured in a particular case. In tetrahydropyran-4-ol in dilute solution intramolecular hydrogen bonding is possible in theory but no such bonding is observed,<sup>9</sup> showing that the boat form is not present. Similarly X-ray studies<sup>10,11</sup> have shown conclusively that  $\alpha$  and  $\beta$ -glucose exist in the crystal in the C1 conformation as Reeves predicted. Moreover, signals in the PMR spectra of acetoxy and methoxy substituted pyranoses,<sup>12,13</sup> and of  $\alpha$  and  $\beta$ -glucose<sup>14</sup> have been correlated successfully with chair conformations. There was however, in the case of  $\beta$ -glucose, evidence that the pyranose ring was of somewhat flatter shape than the ideal chair.<sup>14</sup> The assumption that chair forms predominate in the O-methyl derivatives of glucose and xylose and related glycosides would therefore seem to be a reasonable basis for discussion of the results of the present study.

Recently it has been demonstrated<sup>15</sup> that in dilute solutions of cyclohexanols and triterpenoid alcohols in inert solvents, the stretching frequency may be used to characterize a free hydroxyl group as primary ( $3640\text{ cm}^{-1}$ – $3641\text{ cm}^{-1}$ ), secondary ( $3623\text{ cm}^{-1}$ – $3638\text{ cm}^{-1}$ ) and tertiary ( $3613\text{ cm}^{-1}$ – $3619\text{ cm}^{-1}$ ). Moreover it has been found that an axial hydroxyl group absorbs at approximately  $5$ – $10\text{ cm}^{-1}$  higher than its equatorial epimer<sup>16</sup> and its absorption band is more symmetrical.<sup>17</sup> Although

<sup>7</sup> H. S. Isbell and R. S. Tipson, *J. Res. Nat. Bur. Stand.* **64A**, 171 (1960).

<sup>8</sup> S. J. Angyal and J. A. Mills, *Rev. Pure. Appl. Chem.* **2**, 185 (1952).

<sup>9</sup> S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen and G. Zweifel, *Tetrahedron* **7**, 10 (1959).

<sup>10</sup> T. R. R. McDonald and C. A. Beevers, *Acta Cryst.* **5**, 654 (1952).

<sup>11</sup> W. G. Ferrier, *Acta Cryst.* **16**, 1023 (1963).

<sup>12</sup> R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Amer. Chem. Soc.* **80**, 6098 (1958).

<sup>13</sup> S. A. Barker, J. Homer, M. C. Keith and L. F. Thomas, *J. Chem. Soc.* 1538 (1963).

<sup>14</sup> R. W. Lenz and J. P. Heeschen, *J. Polymer. Sci.* **51**, 247 (1961).

<sup>15</sup> A. R. H. Cole, *Elucidation of Structures by Physical and Chemical Methods* (Edited by K. W. Bentley) Vol. XI; Part I of *Technique of Organic Chemistry* (Edited by A. Weissberger) Interscience, New York—London (1963).

<sup>16</sup> A. R. H. Cole, P. R. Jefferies and G. T. A. Muller, *J. Chem. Soc.* 1222 (1959).

similar frequency correlations might be expected to be applicable to pyranose sugars the differentiation of axial and equatorial secondary hydroxyls is of most practical importance, as tertiary hydroxyl groups occur rather infrequently and the primary hydroxyl on C<sub>6</sub> in the hexopyranoses is always suitably placed to bond to the ring oxygen if no other oxygen atoms are more favourably situated (cf. the spectrum of 2-hydroxymethyl tetrahydropyran in which there is no evidence of any free hydroxyl absorption;<sup>9</sup> as can be seen from a model, hydrogen bonding is possible in both the axial and equatorial epimers of this compound). The free secondary hydroxyl stretching frequencies of sugar derivatives and related alcohols recorded in the literature<sup>9,18-23</sup> do indeed occur in the range 3620 cm<sup>-1</sup>–3640 cm<sup>-1</sup>, which would be predicted from the cyclohexanol and triterpenoid work.<sup>15</sup> However no distinction can be made between axial and equatorial hydroxyls on this basis. This is probably because the frequency differences between primary, secondary and tertiary alcohols are caused by the differing bond polarities—O<sup>-</sup>—H<sup>+</sup>, whereas the difference in frequency between epimers appears to be due to steric factors.<sup>17,24</sup> If the replacement of the methylene hydrogens by oxygen lone pair electrons lessens steric interactions then the frequency difference between epimers based on the pyranose ring would be expected to be less than for their cyclohexane analogues. A further difficulty in distinguishing between free equatorial and axial hydroxyls on the basis of their stretching frequency is that very few free axial hydroxyl frequencies are recorded because the axial hydroxyl is more prone to be bonded than its equatorial epimer.

Since the energy of interconversion of the two chair forms of cyclohexanol is only about 0.8 kcal mole<sup>-1</sup><sup>25</sup> and the energy of an intramolecular O—H...O hydrogen bond is at least of the same order, the possibility of the formation of such a bond can clearly influence the conformations of cyclohexane alcohols. Indeed the observed conformation of cyclohexane *cis*-1,3 diol is not the chair in which the hydroxyl groups are in a *cis* diequatorial relationship as might be inferred from simple considerations of instability factors,<sup>9</sup> but rather the chair in which they are related in a *cis* diaxial way, and in which they are hydrogen bonded.<sup>26</sup> Little is known about the energies of interconversion of pyranose conformations,<sup>1</sup> except that they are expected to be lower than for their cyclohexane analogues, and therefore the conformational equilibria would be even more sensitive to hydrogen bonding. Moreover, for  $\alpha$  and  $\beta$  pyranose sugars in aqueous solutions Ferrier and Overend<sup>1</sup> suggest that the energy difference between anomers of two of the compounds included in this study, namely 2,3-di-O-methyl-D-xylose and 2,3,4,6-tetra-O-methyl-D-glucose is only of the order of 0.5 kcal/mole. Since water, by virtue of its hydrogen bonding ability,

<sup>17</sup> H. S. Aaron and C. P. Rader, *J. Amer. Chem. Soc.* **85**, 3046 (1963).

<sup>18</sup> J. S. Brimacombe, A. B. Foster, M. Stacey and D. H. Whiffen, *Tetrahedron* **4**, 351 (1958).

<sup>19</sup> N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey and D. H. Whiffen, *J. Chem. Soc.* 2574 (1960).

<sup>20</sup> H. Spedding, *J. Chem. Soc.* 3617 (1961).

<sup>21</sup> N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann and J. M. Webber, *J. Chem. Soc.* 4151 (1963).

<sup>22</sup> S. A. Barker, A. B. Foster, A. H. Haines, J. Lehmann, J. Webber and G. Zweifel, *J. Chem. Soc.* 4161 (1963).

<sup>23</sup> A. B. Foster, R. Harrison, J. Lehmann and J. M. Webber, *J. Chem. Soc.* 4471 (1963).

<sup>24</sup> A. R. H. Cole, G. T. A. Muller, D. W. Thornton and R. L. S. Willix, *J. Chem. Soc.* 1218 (1959).

<sup>25</sup> R. C. Cookson, *Ann. Reports* **54**, 170 (1957).

<sup>26</sup> L. P. Kuhn, *J. Amer. Chem. Soc.* **74**, 2492 (1952); *Ibid.* **76**, 4323 (1954).

displaces intramolecular hydrogen bonds in aqueous solution,<sup>27</sup> this energy difference could be appreciably changed in non-polar solvents (e.g. CCl<sub>4</sub> and CS<sub>2</sub>).

In the cyclohexane ring the requirements of the tetrahedral distribution of carbon valencies restricts the number of possible combinations of *cis*, *trans*, equatorial and axial substituents for a given conformation. The allowed combinations for chair and boat forms are shown in Table 1. In the chair forms of cyclohexane diols only

TABLE 1. STERICALLY PERMISSIBLE COMBINATIONS OF PAIRS OF SUBSTITUENTS FOR SIX MEMBERED RINGS IN CHAIR AND BOAT CONFORMATIONS

Conformation		Permitted relationships*		
		<i>ortho</i>	<i>meta</i>	<i>para</i>
Chairs	<i>cis</i>	<i>ae</i>	<i>aa, ee</i>	<i>ae</i>
	<i>trans</i>	<i>aa, ee</i>	<i>ae</i>	<i>aa, ee</i>
Boats	<i>cis</i>	<i>aa, ee</i>	<i>ae</i>	<i>aa, ee</i>
	<i>trans</i>	<i>ae</i>	<i>aa, ee</i>	<i>ae</i>

\* *a* and *e* designate axial and equatorial dispositions of the oxygen atoms.

oxygen atoms having *cis ortho* axial-equatorial, *trans ortho* di-equatorial and *cis meta* di-axial relationships are sufficiently close together to be able to participate in hydrogen bonds. Such bonded hydroxyls absorb near 3585, 3600 and 3550 cm<sup>-1</sup> respectively.<sup>28,28</sup> These facts, together with the non-bonded frequencies previously discussed, have been used to obtain valuable information<sup>2</sup> about the stereochemistry of simple cyclohexane alcohols,<sup>15,26,28,29</sup> and of more complex systems such as steroids<sup>30-35</sup> and triterpenoids.<sup>36</sup>

The possibilities for intramolecular hydrogen bonding in pyranose compounds in chair conformations may be explored on the basis of the relationships given in Table 1, and of the distances between oxygen atoms attached directly to the ring, as in sugars or their O-methyl derivatives. For hydrogen bonds between hydroxyl and methoxyl groups the O...O distances and the relative orientations of the C—O bonds determine the possibilities of hydrogen bond formation.<sup>28</sup> In the hexopyranoses further possibilities exist for intramolecular hydrogen bonds involving the primary hydroxyl at C<sub>6</sub> (or, in derivatives, O<sub>6</sub> as acceptor). Since there is free rotation about the C<sub>6</sub>—C<sub>5</sub> bond, the O<sub>6</sub>...O distances and relative orientations of the C—O bonds are not fixed. The relative oxygen dispositions, dihedral angles between C—O bonds, O...O distances and the size of the rings formed are shown in Table 2 for the only hydroxyl groups which can participate in intramolecular hydrogen bonding in either the C1 or 1C chair conformations. All the other O...O distances are too large,

<sup>27</sup> G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond*, p. 179. Freeman, San Francisco (1960).

<sup>28</sup> A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.* 4391 (1956).

<sup>29</sup> L. P. Kuhn, P. von R. Schleyer, W. F. Baitinger and L. Ebersson, *J. Amer. Chem. Soc.* **86**, 650 (1964).

<sup>30</sup> R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2820 (1952).

<sup>31</sup> H. B. Henbest and B. J. Lovell, *J. Chem. Soc.* 1459 (1957).

<sup>32</sup> S. J. Angyal and R. J. Young, *J. Amer. Chem. Soc.* **81**, 5251 (1959).

<sup>33</sup> F. Dalton, G. D. Meakins, J. H. Robinson and W. Zaharia, *J. Chem. Soc.* 1566 (1962).

<sup>34</sup> F. Dalton, J. I. McDougall and G. D. Meakins, *J. Chem. Soc.* 4068 (1963).

<sup>35</sup> J. Fajkos, J. Joska, J. Pitha and F. Sorm, *Coll. Czech. Chem. Comm.* **28**, 2337 (1963).

<sup>36</sup> A. R. H. Cole and G. T. A. Muller, *J. Chem. Soc.* 1224 (1959).

TABLE 2. OXYGEN-OXYGEN INTERATOMIC DISTANCES, DIHEDRAL ANGLE BETWEEN C—O BONDS, SIZE OF RINGS FORMED AND ABSORPTION FREQUENCIES OF BONDED HYDROXYLS ATTACHED TO PYRANOSE RINGS

Relative oxygen disposition	Interatomic* distance (Å°)	Dihedral angle between C—O bonds	Size of ring	Frequency in reference compound	Reference
<i>cis meta aa</i>	2.51	0°	6 membered	3533 cm <sup>-1</sup> ; methyl 4,6-O-benzylidene- $\alpha$ -D-idoside	20
<i>cis ortho ae</i>	2.83	60°	5 membered	3583 cm <sup>-1</sup> ; 1,5-anhydro-2-deoxy-L-erythro-pentitol	18
<i>trans ortho ee</i>	2.83	60°	5 membered	3608 cm <sup>-1</sup> ; 1,5-anhydro-2-deoxy-D-threo-pentitol	18
O <sub>1</sub> (a)—O <sub>2</sub> †	2.92	60°	5 membered	3604 cm <sup>-1</sup> ; tetrahydropyran-3-ol	9
O <sub>1</sub> (a)—O <sub>2</sub> †	2.92	60°	5 membered	3604 cm <sup>-1</sup> ; tetrahydropyran-3-ol	9
O <sub>4</sub> (e or a)—O <sub>5</sub>	2.67§	v	5 membered	3607 cm <sup>-1</sup> ; Et 2,3-dideoxy- $\alpha$ -D-erythro hexopyranoside	23
O <sub>4</sub> (e)—O <sub>4</sub> (e)	2.32§	v	6 membered	3548 cm <sup>-1</sup> ; Et 2,3-dideoxy- $\alpha$ -D-erythro hexopyranoside	23
O <sub>5</sub> (a)—O <sub>4</sub> (a)†	1.31§	v	7 membered	†	
O <sub>5</sub> (a)—O <sub>1</sub> (a)†	1.31§	v	7 membered	†	

\* B. J. Poppleton—unpublished calculations, based on tetrahedral ring angles and bond lengths C—C = 1.54Å° and C—O = 1.43Å°

† No examples in the pyranose series are known to the authors, but the bonding situation is somewhat similar to that in the cyclohexane 1,2-dimethanols<sup>26</sup> in which the bonded hydroxyls absorb near 3500 cm<sup>-1</sup>

‡ IC conformation only

§ Distance of closest approach

|| C1 conformation only

v Variable owing to rotation about C<sub>5</sub>—C<sub>4</sub> bond

except in the case of  $O_1 \cdots O_5$ , in which the determining factor would seem to be the unfavourable  $O-C-O$  bond angle ( $\sim 109^\circ$ ) (cf. tetrahydropyran-2-ol<sup>9</sup> in which no hydrogen bond is evident). The absorption frequencies of bonded hydroxyls have been examined by Foster *et al.* in tetrahydropyrans, 1,3-dioxan-5-ols<sup>9,18,19,21,22</sup> and ethyl-deoxy- $\alpha$ -D-erythro and threo-hexopyranosides,<sup>23</sup> and by Spedding<sup>20</sup> in methyl 4,6-O-benzylidene-D-aldohexosides. As a result of these works a number of useful correlations similar to those obtained for cyclohexanols<sup>2</sup> may be made when the pyranose ring can be assumed to exist in one of the chair forms. These correlations are shown in Table 2. Since hydrogen bonds between *cis ortho ae* and *trans ortho ee* groups would be of identical length and have equal  $O-H \cdots O$  bond angles it might be thought that the associated hydroxyl frequencies would also be identical. The difference in bonded hydroxyl frequencies ( $25 \text{ cm}^{-1}$ ) between 1,5-anhydro-2-deoxy-L-erythro- and 1,5-anhydro-2-deoxy-D-threo-pentitols is therefore evidence of some distortion of the ideal chair shapes in these compounds. A similar, although lesser, difference ( $15 \text{ cm}^{-1}$ ) in frequencies has been noted previously in the cyclohexanol series by Kuhn<sup>26</sup> who suggested that it could be explained by the ring system in the *cis* compound being more planar, and in the *trans* compound more puckered, as a result of the formation of an intramolecular hydrogen bond. The lower frequency found for the *cis meta aa* bonded hydroxyl groups in methyl 4,6-O-benzylidene- $\alpha$ -D-idoside compared with cyclohexane *cis*-1,3-diol also suggests some puckering of the ring. No definite frequency correlations have been proposed for sugars or their derivatives in conformations other than chairs, but Spedding<sup>20</sup> does discuss a number of examples in which the frequencies do not appear to correspond well to either chair conformation.

Table 3 shows the band frequencies, shifts from the frequency of the free primary or secondary hydroxyl group, as appropriate, and optical densities of solutions of the compounds ( $< 0.005 \text{ M}$ ) in carbon tetrachloride, as well as the frequencies of some of the compounds in carbon disulphide solution and in the solid state in KCl discs and 'Nujol' mulls.

Since even the O-methyl derivatives were only slightly soluble in carbon tetrachloride only the upper limits of the concentrations were known and thus the extinction coefficients could not be determined. Peak optical densities however have been included to enable intensity comparisons to be made between different bands in the spectrum of the same compound.

A test for the presence of intermolecular hydrogen bonding was carried out by making measurements on solutions of the compounds over a four-fold range of concentrations. As the peak frequencies and relative intensities varied little during these experiments no appreciable intermolecular hydrogen bonding could have been present. Moreover, preliminary intensity measurements on the compounds in tetrachloroethylene over the temperature range  $25^\circ$  to  $90^\circ$  also showed much less variation than would be expected if the lower frequencies represented self associated species.

The absence of bands in Table 3 representing free hydroxyls is noteworthy but is not surprising since for each hydroxyl there is at least one acceptor oxygen atom closer than the maximum distance at which hydrogen bonding is feasible.<sup>26</sup>

For those preparations which were not known definitely to consist of only one anomer an indication of the predominant anomer was obtained from the spectra in

TABLE 3. BAND FREQUENCIES, PEAK OPTICAL DENSITIES AND FREQUENCY SHIFTS FOR METHYL DERIVATIVES OF GLUCOSE, XYLOSE AND RELATED GLYCOSIDES

Compound	CCl <sub>4</sub> soln.		Frequency shifts <sup>a</sup> (cm <sup>-1</sup> )	CS <sub>2</sub> soln.		Mull
	Frequencies (cm <sup>-1</sup> )	Peak optical densities		Frequencies (cm <sup>-1</sup> )	Frequencies (cm <sup>-1</sup> )	
Methyl 2,3,4-tri-O-methyl- $\alpha$ -D-glucoside	3614	0.23	26 p	3601	3458 <sup>b</sup>	•
Methyl 2,3,4-tri-O-methyl- $\beta$ -D-glucoside	3609	0.22	31 p	•	{3350 3263	•
Methyl 4,6-di-O-methyl- $\beta$ -D-glucoside	3611	0.32	18	•	{3492 3392 3332	•
Methyl 4,6-O-benzylidene- $\alpha$ -D-glucoside	{3606 3578	0.23	23	•	{3463 3360	•
Methyl 4-O-methyl- $\beta$ -D-glucoside	{3611 3611	0.20 0.30	51 18	•	{3265 3369	•
2,3,4,6-tetra-O-methyl-D-glucose	{3610 3571	0.15 0.12	19 58	3600	{3245 3420 3362	3413
2,3,4-tri-O-methyl-D-xylose	{3614 3572	0.28 0.24	15 57	3600	3413	3412
2,3,6-tri-O-methyl-D-glucose	{3576 sh 3535	0.15 0.12	53 94	3593	3393	3384
2,3-di-O-methyl-D-xylose	{3613 3536	0.19 0.22	16 93	3579	{3407 3367	3411 3361
Benzyl 4-O-methyl- $\beta$ -D-xyloside	{3610 3521	0.09 0.17	19 108	3594	{3478 3411 3356 3277	3472 3413 3361 3276

<sup>a</sup> Difference between frequency of bonded hydroxyl and a standard free primary or secondary hydroxyl group. Differences refer to the secondary group unless indicated as primary.

<sup>b</sup> Liquid film.

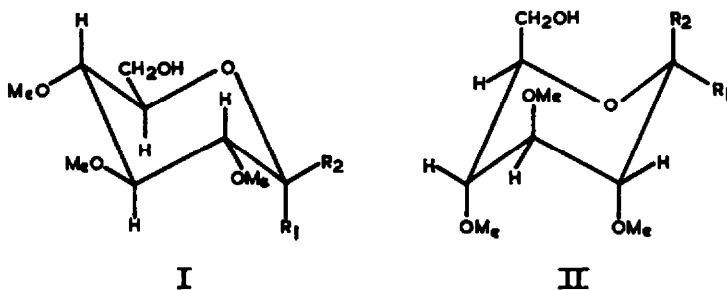
• Not measured owing to limited quantity of compound available.

p Referred to primary hydroxyl group.

sh Shoulder.

the region below  $900\text{ cm}^{-1}$  by using the correlations established by Barker *et al.*<sup>37,38</sup> However as this method is based on measurements in KCl discs it was of interest to test whether there was any change in solution in carbon disulphide. Although the spectra were of low intensity, because of low solubility, no differences in the region below  $900\text{ cm}^{-1}$  were detected. Further, to check that there was no mutarotation in carbon tetrachloride, the solutions were vacuum evaporated rapidly after the measurements and their spectra re-measured in a KCl disc. The spectra were identical with those shown by the pure compounds in the disc.

The two possible chair conformations I and II of methyl 2,3,4-tri-O-methyl- $\alpha$ -D-glucoside ( $R_1 = \text{OMe}$ ,  $R_2 = \text{H}$ ) are shown below



In the conformation I the primary hydroxyl could bond either to the oxygen on  $C_4$  (6-membered ring) or to the ring oxygen (5-membered ring) and the respective absorption frequencies would be ca.  $3550\text{ cm}^{-1}$  and  $3600\text{ cm}^{-1}$ . In conformation II bonding to the ring oxygen is again possible, but so is bonding to the oxygen on  $C_3$ . In the latter case, in which the hydrogen bond is involved in a 7-membered ring, absorption near  $3500\text{ cm}^{-1}$  would be expected by analogy with the results for cyclohexane 1,2-dimethanols.<sup>20</sup> Since the only hydroxyl absorption shown by this compound is near  $3614\text{ cm}^{-1}$ , the primary hydroxyl must be completely bonded to the ring oxygen, but since this seems equally possible in both conformations (cf. 2-hydroxymethyl-tetrahydropyran<sup>9</sup>) no discrimination between the conformers is possible on this basis. However the conformation I, which has four of the five bulky substituents equatorially disposed, is to be preferred on the basis of Reeves' instability criteria.<sup>6</sup>

Methyl 2,3,4-tri-O-methyl- $\beta$ -D-glucoside ( $R_1 = \text{H}$ ,  $R_2 = \text{OMe}$ ) may also exist in the forms I and II. For this compound a single absorption is found near  $3609\text{ cm}^{-1}$ , indicative of bonding of the primary hydroxyl to the ring oxygen, as for the  $\alpha$  compound. Such bonding is again possible in both chair forms, but the 1C conformation (I) is to be preferred even more strongly than in the case of the  $\alpha$  anomer because all the substituent groups are equatorial, whereas in the 1C conformation (II) they are all axial. The higher frequencies shown by both anomers compared with that of 2-hydroxymethyl-tetrahydropyran<sup>9</sup> are probably the result of some distortion of the ideal chair form due to the bulky methoxyl substituents. Furthermore, the higher frequency found for the  $\alpha$  anomer compared with the  $\beta$  anomer reflects a longer hydrogen bond, probably because of the non-bonded interactions of the axial methoxyl group on  $C_1$ .

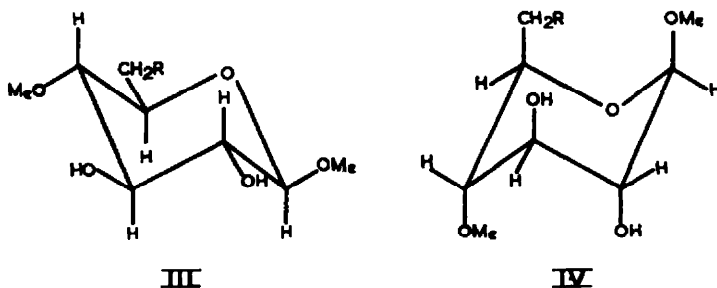
<sup>37</sup> S. A. Barker, E. J. Bourne, M. Stacey and D. H. Whiffen, *J. Chem. Soc.* 171 (1954).

<sup>38</sup> S. A. Barker, E. J. Bourne, R. Stephens and D. H. Whiffen, *J. Chem. Soc.* 3468 (1954).



The two possible chair conformations of methyl 4,6-di-O-methyl- $\beta$ -D-glucoside (R = OMe) are shown as III and IV below.

In conformation III the bonding situation is closely analogous to that in 1,5-anhydro-2-deoxy-D-threopentitol<sup>18</sup> except that there is no free hydroxyl absorption because of chain bonding either of the type  $O_2-H_2 \cdots O_3-H_3 \cdots O_4$  or of the type  $O_3-H_3 \cdots O_2-H_2 \cdots O_1$  (both *trans ortho ee* and spectroscopically indistinguishable).



The single absorption found near  $3611\text{ cm}^{-1}$  is in accord with such bonding. In the other chair form (IV) there is the possibility of bonding  $O_2-H_2 \cdots O_5$  (cf. tetrahydropyran-3-ol<sup>9</sup>,  $3604\text{ cm}^{-1}$ ) or  $O_2-H_2 \cdots O_4$  (*cis meta aa*,  $3530\text{ cm}^{-1}$ ) and  $O_3-H_3 \cdots O_6$  (cf. cyclohexane 1,2-dimethanols,<sup>20</sup>  $\sim 3500\text{ cm}^{-1}$ ) or  $O_3-H_3 \cdots O_1$  (*cis meta aa*,  $3530\text{ cm}^{-1}$ ).

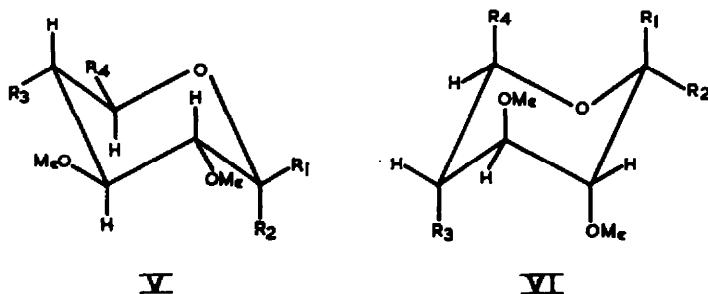
Since hydrogen bonding  $O_3-H_3 \cdots O_5$  is not a possibility (cf. tetrahydropyran-4-ol<sup>9</sup>) there should either be free  $O_3-H_3$  absorption near  $3630\text{ cm}^{-1}$  or bonded  $O_3-H_3$  absorption near  $3550\text{ cm}^{-1}$  or  $3500\text{ cm}^{-1}$  if methyl 4,6-di-O-methyl- $\beta$ -D-glucoside exists in the form IV. The absence of absorption in these regions is clear evidence that conformation IV is not present and III is the preferred form.

Methyl 4-O-methyl- $\beta$ -D-glucoside (R = OH) may also exist in the forms III and IV. The same possibilities for hydrogen bonding as in methyl-4,6-di-O-methyl- $\beta$ -D-glucoside exist in this compound in both forms, together with the added possibility of bonds involving the primary hydroxyl on C<sub>6</sub>. For the conformation III the added possibilities are  $O_6-H_6 \cdots O_5$  and  $O_6-H_6 \cdots O_4$ . These possibilities have been discussed earlier in connection with the methyl 2,3,4-tri-O-methyl-D-glucosides. A single absorption band near  $3611\text{ cm}^{-1}$  is again in accordance with the bonding of the primary hydroxyl to the ring oxygen  $O_5$ , and with bonding of  $O_2-H_2$  and  $O_3-H_3$  as in methyl 4,6-di-O-methyl- $\beta$ -D-glucoside. For the other conformation (IV)  $O_3-H_3$  still cannot be bonded to a vicinal oxygen and therefore must either be free or involved in a 6- or 7-membered ring. The absence of absorption other than that at  $3611\text{ cm}^{-1}$  again rules out these possibilities, so that the conformation III must be preferred.

Methyl 4,6-O-benzylidene- $\alpha$ -D-glucoside, which absorbs near  $3606$  and  $3578\text{ cm}^{-1}$ , has been studied previously by Spedding.<sup>20</sup> Since the benzylidene ring can form only if the glucose molecule is in the C1 conformation, when the acetal oxygens are equatorially disposed, the first frequency can be assigned to the bonded  $O_3-H_3 \cdots O_2$  (*trans ortho ee*), and the second to bonded  $O_2-H_2 \cdots O_1$  (*cis ortho ae*).

From the spectrum near  $900\text{ cm}^{-1}$  in both  $\text{CS}_2$  and in the solid phase of the sample of 2,3,4,6-tetra-O-methyl-D-glucose ( $R_1 = \text{H}$  or  $\text{OH}$ ,  $R_2 = \text{OH}$  or  $\text{H}$ ,  $R_3 = \text{OMe}$  and  $R_4 = \text{CH}_2\text{OMe}$ ) the  $\alpha$  anomer appears to predominate. The two chair forms (V and

VI) are depicted below. For the  $\alpha$  anomer in both the chair forms (V and VI) the only possible hydrogen bonds are between the hydroxyl group at  $C_1$  and the methoxyl at  $C_2$  (*cis ortho ae*). Such bonded hydroxyls have previously<sup>18</sup> been shown to absorb near  $3583\text{ cm}^{-1}$  (Table 2). If some of the  $\beta$  anomer were also present then in conformation V a hydrogen bond  $O_1-H_1 \cdots O_2$  (*trans ortho ee*) could be expected to form



and absorb near  $3608\text{ cm}^{-1}$ . In form VI, however,  $O_1-H_1$  in the  $\beta$  anomer can be bonded only if it participates in a six or seven membered ring. In both cases it would be expected to absorb in the range  $3500-3550\text{ cm}^{-1}$ , but since there is no absorption in this region the  $\beta$  anomer cannot exist in this conformation. Thus it would seem most likely that this sample of the compound is a mixture of  $\alpha$  and  $\beta$  anomers in the conformation V.

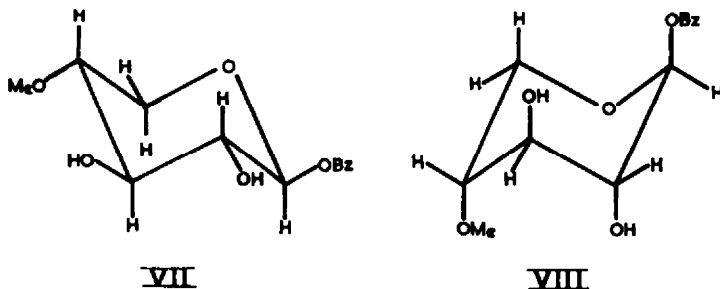
2,3,4-Tri-O-methyl-D-xylose (V; VI;  $R_1 = \text{H or OH}$ ,  $R_2 = \text{OH or H}$ ,  $R_3 = \text{OMe}$ , and  $R_4 = \text{H}$ ) has a similar oxygen disposition to the previous compound 2,3,4,6-tetra-O-methyl-D-glucose and shows similar absorption near  $3614\text{ cm}^{-1}$  and  $3572\text{ cm}^{-1}$ . Although from an examination of the spectrum near  $750\text{ cm}^{-1}$  this compound appears to be mainly the  $\alpha$  anomer the above absorption bands as in the previous case can be most plausibly explained as being due to  $O_1-H_1 \cdots O_2$  bonded hydroxyls in both  $\alpha$  and  $\beta$  anomers in the C1 conformation (V).

2,3-Di-O-methyl-D-xylose (V; VI;  $R_1 = \text{H or OH}$ ,  $R_2 = \text{OH or H}$ ,  $R_3 = \text{OH}$ ,  $R_4 = \text{H}$ ) appears to be mainly the  $\beta$  anomer, since there is no band near  $750\text{ cm}^{-1}$  in the KCl disc spectrum.<sup>39</sup> In the  $\beta$  compound in the conformation V  $O_1-H_1 \cdots O_2$  and  $O_4-H_4 \cdots O_3$  hydrogen bonds which would be expected to absorb near  $3608\text{ cm}^{-1}$  (*trans ortho ee*) may occur. In the  $\alpha$  anomer in this conformation an  $O_1-H_1 \cdots O_2$  bond would absorb near  $3583\text{ cm}^{-1}$  (*cis ortho ae*) as against  $3608\text{ cm}^{-1}$  for the  $\beta$  anomer (*trans ortho ee*). In conformation VI the hydrogen bonds  $O_1-H_1 \cdots O_3$ ,  $O_4-H_4 \cdots O_2$  and  $O_4-H_4 \cdots O_5$ , corresponding to O—H absorptions near  $3530$  and  $3610\text{ cm}^{-1}$  respectively, are possibilities for the  $\beta$  anomer. In the case of the  $\alpha$  anomer in conformation VI possible hydrogen bonds are  $O_1-H_1 \cdots O_2$  and  $O_4-H_4 \cdots O_2$ , and the corresponding OH stretching bands should lie near  $3608$  and  $3530\text{ cm}^{-1}$  respectively. Thus the observed absorption bands at  $3613$  and  $3536\text{ cm}^{-1}$  respectively are consistent with the presence of both  $\alpha$  and  $\beta$  anomers in the 1C conformation (VI). There may also be some of the  $\beta$  anomer present in the C1 conformation, but the lower intensity of the  $3613\text{ cm}^{-1}$  band compared to the  $3536\text{ cm}^{-1}$  band (Table 3) suggests that the 1C conformer must be predominant. The absence of absorption near  $3583\text{ cm}^{-1}$  denies the possibility of the presence of any of the  $\alpha$  anomer in the C1 conformation. This compound is therefore an example of the apparently less stable

conformation, on the basis of Reeves' instability factors,<sup>6</sup> being nevertheless preferred because of the favourable possibilities for hydrogen bonding.

2,3,6-Tri-O-methyl-D-glucose (V; VI;  $R_1 = \text{H}$  or  $\text{OH}$ ,  $R_2 = \text{OH}$  or  $\text{H}$ ,  $R_3 = \text{OH}$ ,  $R_4 = \text{OMe}$ ) shows absorption at 3609, 3576 and 3535  $\text{cm}^{-1}$ . For both anomers in the C1 conformation (V) possible hydrogen bonds are  $\text{O}_1\text{—H}_1 \cdots \text{O}_2$  (*cis ortho ae*),  $\text{O}_4\text{—H}_4 \cdots \text{O}_3$  (*trans ortho ee*) and  $\text{O}_4\text{—H}_4 \cdots \text{O}_6$  (six-membered ring), which should correspond to OH stretching bands near 3583, 3608 and 3530  $\text{cm}^{-1}$  respectively. For the 1C conformation (VI) hydrogen bonding possibilities differ between the two anomers. These possibilities are, for the  $\alpha$ -anomer:  $\text{O}_1\text{—H}_1 \cdots \text{O}_2$  (*cis ortho ae*),  $\text{O}_4\text{—H}_4 \cdots \text{O}_5$  and  $\text{O}_4\text{—H}_4 \cdots \text{O}_2$  (*cis meta aa*), which should correspond to absorption bands near 3583, 3610 and 3530  $\text{cm}^{-1}$  respectively; for the  $\beta$ -anomer:  $\text{O}_1\text{—H}_1 \cdots \text{O}_3$  (*cis meta aa*),  $\text{O}_4\text{—H}_4 \cdots \text{O}_2$  (*cis meta aa*) and  $\text{O}_4\text{—H}_4 \cdots \text{O}_5$ , which should correspond to absorptions near 3530, 3530 and 3610  $\text{cm}^{-1}$  respectively. The observed absorption band at 3576  $\text{cm}^{-1}$  would not be present in the  $\beta$ 1C compound. The spectrum in the 900  $\text{cm}^{-1}$  region indicates that the material is predominantly the  $\alpha$ -anomer. The only plausible explanation for the three observed OH stretching bands requires the postulate that the proton on  $\text{O}_4$  is involved in hydrogen bonds to two acceptor oxygen atoms. For the C1 conformation these would have to be  $\text{O}_3$  and  $\text{O}_6$ , and in the 1C conformation  $\text{O}_2$  and  $\text{O}_5$ . Such an explanation is not without precedent, since the hydrogen bonding pattern in ethyl 2,3-dideoxy- $\alpha$ -D-erythrohexopyranoside has been explained in a similar way.<sup>28</sup> Some support for this proposal is provided by the observation that the optical density of the 3535  $\text{cm}^{-1}$  band is less than that of either the 3609 or 3583  $\text{cm}^{-1}$  bands, whereas in 2,3-di-O-methyl-D-xylose it is greater than that of the 3613  $\text{cm}^{-1}$  band.

Benzyl 4-O-methyl- $\beta$ -D-xyloside may exist in the conformations VII and VIII.



In the conformation VII the possible hydrogen bond systems are  $\text{O}_3\text{—H}_3 \cdots \text{O}_2\text{—H}_2 \cdots \text{O}_1$  and  $\text{O}_2\text{—H}_2 \cdots \text{O}_3\text{—H}_3 \cdots \text{O}_4$  which would all be expected to absorb near 3608  $\text{cm}^{-1}$  (*trans ee*). A further possibility involves a bond from  $\text{O}_2\text{—H}_2$  to the  $\pi$ -electron cloud of the benzene ring, and this bonded hydroxyl might be expected to absorb at a frequency near 3550  $\text{cm}^{-1}$  (cf. *trans* 1,2-diaryl-acenaphthene diols<sup>29</sup>). In the 1C chair conformation (VIII)  $\text{O}_2\text{—H}_2 \cdots \text{O}_5$  and  $\text{O}_2\text{—H}_2 \cdots \text{O}_4$ ,  $\text{O}_3\text{—H}_3 \cdots \text{O}_1$ , which might be expected to absorb near 3610, 3530 and 3530  $\text{cm}^{-1}$  respectively, are possible hydrogen bonds. The spectroscopic data do not enable any discrimination to be made between the conformers but on steric grounds the conformer VII in which the benzyl group is equatorial would seem to be preferred.

<sup>29</sup> E. J. Moriconi, W. F. O'Connor, L. P. Kuhn, E. A. Keneally and F. T. Wallenberger, *J. Amer. Chem. Soc.* **81**, 6472 (1959).

The compounds studied show some differences in frequency from the model compounds listed in Table 2. Although these differences do not appear to be great enough to invalidate considering the conformations in terms of the two chairs, they do suggest that appreciable distortion from the ideal shape may occur.

Values of the frequencies observed for some of the compounds in carbon disulphide solution are also included in Table 3, from which it may be seen that the lower frequency bands are less solvent sensitive.<sup>40</sup> Although the optical densities in carbon disulphide are not quoted, no appreciable changes in the relative peak densities were noted compared with those in carbon tetrachloride.

In all the solution spectra the hydroxyl bands are at much higher frequencies than those in the solid, and there seems to be no correlation between the number of bands evident in each phase. To test whether the bands at lower frequencies in the solid phase were due to environmental effects in the KCl disc or to intermolecular hydrogen bonding, measurements were made of the spectrum of 2,6-di-*t*-butyl-*p*-cresol, in which intramolecular hydrogen bonding is not possible and intermolecular bonding is drastically hindered by the bulky *t*-butyl substituents. In carbon tetrachloride this compound absorbs at 3647  $\text{cm}^{-1}$  and in a KCl disc at 3627  $\text{cm}^{-1}$ . The corresponding frequencies for phenol, in which again there is no acceptor atom for intramolecular bonding, but in which intermolecular bonding is unhindered by substituents, are 3612 and 3270  $\text{cm}^{-1}$  respectively. Clearly, since similar dielectric factors would be operative in both cases, the large frequency shift in phenol must be due to intermolecular hydrogen bonding and not to dielectric effects. Thus the bands in the solution spectra represent hydroxyls intramolecularly bonded in a way which is dependent on molecular geometry, whereas those in the solid spectra are due to intermolecularly bonded hydroxyls incorporated into a crystal (cf. Ref. 26).

#### EXPERIMENTAL

**Materials.** Pure samples of methyl 2,3,4-tri-*O*-methyl- $\alpha$ -D-glucoside, 2,3,6-tri-*O*-methyl-D-glucose and 2,3-di-*O*-methyl-D-xylose were supplied by Prof. T. E. Timell; methyl 4,6-di-*O*-methyl- $\beta$ -D-glucoside and methyl 4-*O*-methyl- $\beta$ -D-glucoside by Dr. H. O. Bouveng; methyl 2,3,4-tri-*O*-methyl- $\beta$ -D-glucoside by Dr. M. Gee, benzyl 4-*O*-methyl- $\beta$ -D-xyloside by Prof. B. Lindberg, 2,3,4,6-tetra-*O*-methyl-D-glucose by Dr. C. M. Stewart, 2,3,4-tri-*O*-methyl-D-xylose by Dr. E. F. L. Anet and 2,6-di-*t*-butyl-*p*-cresol by Dr. F. R. Hewgill. The sample of methyl 4,6-*O*-benzylidene- $\alpha$ -D-glucoside was obtained from Calbiochem.

$\text{CCl}_4$  was A. R. material which had been distilled from  $\text{CaSO}_4$ ;  $\text{CS}_2$  was redistilled A. R. material and tetrachloroethylene was May and Baker laboratory chemical which had been fractionally crystallized, and dried over  $\text{K}_2\text{CO}_3$ , from which it was decanted and filtered before use. As the solutes rarely dissolved completely, the concentration was not measured precisely but was always less than 0.005M.

The heated cell used in the temp. measurements was a double beam adaption of that described by Cole and MacRitchie.<sup>41</sup>

**Spectroscopy.** "Infrasil" cells of 2 cm path length were used for the hydrogen bonding studies and the spectra were measured on a Grubb Parsons double beam S4 spectrometer which was equipped with silica and rocksalt prisms. The frequency calibration was checked against water vapour and ammonia bands, and spectra of MeOH (3643  $\text{cm}^{-1}$ ) and menthol (3626  $\text{cm}^{-1}$ ) were also measured to verify that under the experimental conditions it was possible to differentiate primary from secondary hydroxyl groups.

**Acknowledgements**—The authors are grateful to all those people mentioned who kindly supplied compounds, and to Dr. A. R. H. Cole for the loan of the heating box used in the temperature measurements.

<sup>40</sup> For a discussion of the effect of solvents on hydrogen bonded hydroxyl groups see A. Allerhand and P. von R. Schleyer, *J. Amer. Chem. Soc.* **85**, 371 (1963).

<sup>41</sup> A. R. H. Cole and F. MacRitchie, *Spectrochim. Acta* **15**, 6 (1959)