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THE 4,6-BENZYLIDENE ACETALS, AND THE CONFORMATION, OF METHYL α-D-IDOPYRANOSIDE

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ABSTRACT

Methyl α-D-idopyranoside and its 2,3-dimethyl ether give only the known 4,6-*O*-(*S*)-benzylidene acetals on benzylidenation. Methyl α-D-idopyranoside 2,3-carbonate was prepared, and it gave a small proportion of the (*R*)-benzylidene acetal, but, again, the (*S*)-isomer was the main product. Surprisingly, in chloroform solution, methyl 4,6-*O*-(*R*)-benzylidene-α-D-idopyranoside assumes the $^4C_1$(D) conformation, having an axial phenyl group, rather than the $^1C_4$(D) form (which would have an equatorial phenyl group). The $^4C_1$ forms of the (*R*) and the (*S*) derivatives are stabilized by two hydrogen bonds that can be observed in their n.m.r. spectra. In the presence of water, methyl 4,6-*O*-(*S*)-benzylidene-α-D-idopyranoside is mainly in a skew form, but methyl α-D-idopyranoside exists as a mixture of the two chair forms. Several other compounds that have three or more axially attached oxygen atoms have been studied, but none were found to be in a skew form.

INTRODUCTION

It has been widely accepted that, in solution, the pyranose forms of D-aldohexoses occur in the $^4C_1$ conformation[1]. The only exceptions are α-D-altropyranose and α-D-idopyranose; the n.m.r. spectra of these compounds show $J_{1,2}$ values too large to be compatible with the $^4C_1$ conformer[2]. It has generally been assumed that some of the $^1C_4$ form is also present in equilibrium, and that the coupling constants observed are the averages of those of the two chair forms[1]. Approximate calculations indicated that, for these two sugars[3], the free energy of the two chair forms does not differ widely. Paulsen and Friedmann[4] studied the ^{1}H-n.m.r. spectra of numerous derivatives of α-D-idopyranose, and found that the coupling constants vary widely with the nature of the solvent and the substituents; it was concluded that the $^1C_4$ form accounts for 0–75% of the equilibrium mixture.

Ever since Reeves's work[5] on cuprammonium complexes, the proportion of skew forms in the equilibria of monocyclic sugar derivatives has been regarded as negligible. Two facts emerged, however, that appeared to throw some doubt on this assumption. One is the behavior of methyl 4,6-*O*-benzylidene-α-D-idopyranoside (**1**).

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In 1968, we observed[3] that, although the compound is in the $^4C_1$ form (**1a**) in chloroform solution, it takes up a skew form when dissolved in a mixture of dimethyl sulfoxide and deuterium oxide. Paulsen and Friedmann then devoted considerable effort to examination of the behavior of this compound[6]. It appears that, in chloroform, the $^4C_1$ form (**1a**) is stabilized by hydrogen bonding between the axial oxygen atoms; when this bonding is prevented, either by the addition of water, or by methylation of the free hydroxyl groups, the $^OS_2$ conformer (**1c**) will become preponderant. The $^1C_4$ form (**1b**) would be very disfavored: as the two fused chairs would have to "flip" simultaneously, the 1,3-dioxane ring would then carry *syn*-axial phenyl and 2-hydroxypropyl groups. A closely related compound, methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-α-D-idopyranoside, was found to crystallize in the $^OS_2$ form[7].

It must be emphasized that attachment of the benzylidene group to O-4 and O-6 does not introduce any steric strain into the pyranose ring, and hence should not affect its conformation. If methyl 4,6-*O*-benzylidene-α-D-idopyranoside is partially in a skew form, the stability of the $^4C_1$ must be similar to that of the skew form; it would then be expected that methyl α-D-idopyranoside must also contain a substantial proportion of the skew form in equilibrium.

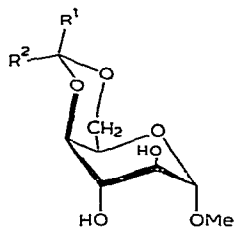
The other puzzling fact consists in the outcome of the reaction between methyl α-D-idopyranoside and benzaldehyde. Methyl 4,6-*O*-benzylidene-α-D-idopyranoside is usually prepared[8] from methyl 4,6-*O*-benzylidene-α-D-galactopyranoside by two inversions. As the configuration of the benzylic carbon atom in the starting material is[9] (*S*), and as both inversions are conducted under basic conditions, it must also be (*S*) in the idoside; that is, the phenyl group is equatorial when the pyranose is in the $^4C_1$ form (**1a**). However, were the idoside present to any great extent in the $^1C_4$ form, benzylidenation should give a substantial proportion of the (*R*) isomer (**5**), because an (*S*)-benzylidene group fused to the $^1C_4$ form would have to have an axial phenyl group, or a nonchair, 1,3-dioxane ring. Jeanloz *et al.* treated methyl α-L-idopyranoside with benzaldehyde, and obtained the enantiomer of the *known* (*S*)-benzylidene derivative[10]. We have repeated this experiment with the D enantiomer, and with its 2,3-di-*O*-methyl derivative, and obtained only the (*S*) derivative; the ^{1}H-n.m.r. spectrum showed no sign of the (unknown) (*R*) derivative.

A quarter of a century ago, Buchanan was puzzled[11] when he had the same experience in the benzylidenation of methyl 2-chloro-2-deoxy-α-D-idopyranoside. He suggested that the benzylic center underwent epimerization under the effect of alkali, but this explanation would now be considered very improbable. In fact, the ^{1}H-n.m.r. spectrum shows that the benzylic center in methyl 4,6-*O*-benzylidene-α-D-idopyranoside is, indeed, (*S*) (*vide infra*). This reaction, then, appears to suggest that methyl α-D-idopyranoside does not occur to any extent in the $^1C_4$ form, but in a skew form [which would give the (*S*)-benzylidene derivative, as does the $^4C_1$ form]. We therefore considered that a reinvestigation of the conformation of methyl α-D-idopyranoside was warranted.

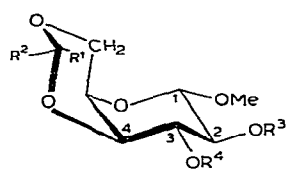
RESULTS AND DISCUSSION

Baggett *et al.*[9] prepared the (*S*)- and the (*R*)-benzylidene derivatives of methyl α-D-glucopyranoside, α-D-galactopyranoside, and β-D-galactopyranoside by treating the glycosides with benzylidene bromide in the presence of a base. One of each pair of these compounds is unstable and is converted into the other on treatment with acid*. In these cases, there is no doubt that the pyranoses are all in the $^4C_1$ form[12]; the stable benzylidene derivatives therefore have an equatorial phenyl group, and the unstable ones have an axial phenyl group. [Although it has been suggested[9] that the 1,3-dioxane ring might adopt a boat conformation, a chair form having an axial phenyl group is energetically more favored[13]. The presence of an axial phenyl group in methyl 4,6-*O*-(*S*)-benzylidene-α-D-glucopyranoside has been shown by X-ray crystal analysis[14].]

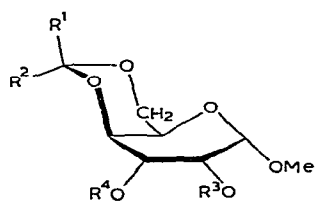
In order to learn more about equilibria and conformations in this system, we chose a different route for the synthesis of the (*R*) isomer of methyl 4,6-*O*-benzylidene-α-D-idopyranoside. Following a suggestion of the late Dr. J. A. Mills, we argued that, if methyl α-D-idopyranoside could be prevented from taking up the $^4C_1$ con-



1a R^1 = Ph, R^2 = H
5a R^1 = H, R^2 = Ph



1b R^1 = Ph, R^2 = R^3 = R^4 = H
4 R^1 = H, R^2 = Ph, R^3 R^4 = C=O
5b R^1 = H, R^2 = Ph, R^3 = R^4 = H



1c R^1 = Ph, R^2 = R^3 = R^4 = H
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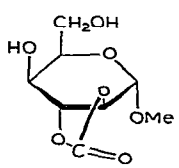

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*Baggett *et al.*[9] erroneously claimed that all of the stable isomers have the (*S*), and the unstable ones, the (*R*) configuration. Actually, in the *gluco* isomer, where the ring junction is *trans*, the stable isomer is (*R*), and the unstable one is (*S*) [see also, *Carbohydr. Res.*, 74 (1979) c14].

TABLE I

^{1}H-N.M.R. CHEMICAL-SHIFT DATA (p.p.m.) FOR SUBSTITUTED METHYL α-D-IDOPYRANOSIDES[a]

Substituent[b]	*Solvent*	*PhCH*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*Me*	*OH*
4,6-(*S*)-Bzd (**1**)	$CDCl_3$	5.52s	4.92s	3.70dqi	3.97dq	4.11m	3.90q	4.11dd	4.36dd	3.45s	3.60d, 3.64d
	Me_2SO–D_2O	5.58s	4.62d	3.48dd	3.64dd	4.05dd	3.74m	4.13m	4.13m	3.35s	
4,6-(*S*)-Bzd-2-Me	$CDCl_3$	5.51s	4.88d	3.30dd	4.02t	4.05dd	3.79q	4.13dd	4.31dd	3.45s, 3.48s	3.50?
4,6-(*S*)-Bzd-3-Me	$CDCl_3$	5.56s	4.85s	3.72dqi	3.56t	4.10m	3.90q	4.10dd	4.33dd	3.49s, 3.45s	3.26d
4,6-(*S*)-Bzd-2,3-di-Me[6]	$CDCl_3$	5.58s	4.68d	3.21dd	3.43dd	4.01dd	3.66q	4.06dd[c]	4.23dd	3.37s, 3.44s, 3.47s	
4,6-(*S*)-Bzd-2,3-CO_3 (**2**)	$CDCl_3$	5.57s	5.06d	← 4.63–4.55 →		4.28?	3.93dt	4.26dd	4.34dd	3.50s	
4,6-(*R*)-Bzd-2,3-CO_3 (**4**)	$CDCl_3$	6.04s	5.02d	4.09dd	4.56dd	4.21dd	4.33ddd	3.82dd	4.18dd	3.46s	
4,6-(*R*)-Bzd (**5**)	$CDCl_3$	6.20s	4.95s	3.68dqi	3.96?	3.96?	3.74bs	3.99dd	4.03dd	3.46s	3.87d
	Me_2SO–D_2O	5.90s	4.45d	3.20dd	3.94dd	3.80dd	4.08m	← 3.97 →		3.32s	
2,3-CO_3 (**3**)	D_2O	—	5.15d	4.47ddd	4.51dd	4.40m	4.19qi	3.62dd	3.71dd	3.44s	
None	D_2O	—	4.69d	3.52dd	← 3.74 →		4.08sp	3.78dd	3.81dd	3.45s	
None	Me_2SO–D_2O	—	4.59d	3.42ddd	3.64t	3.58dd	3.95dt	← 3.65 →		3.39s	
2-Me	D_2O	—	4.79d	3.24dd	3.85t	3.70dd	4.06ddd	← 3.75–3.78 →		3.43s, 3.46s	
3-Me	D_2O	—	4.67d		3.63t		3.92sp	3.78dd	3.83dd	3.46s, 3.54s	
2,3-di-Me	D_2O	—	4.80d	3.34ddd	3.53dt	3.80t	3.97dt	← 3.73 →		3.46(6H), 3.41s	

[a]Key: b = broad, qi = quintet, and sp = septet. [b]Bzd = *O*-benzylidene; CO_3 = carbonate. [c]Erroneously recorded as 4.19 in ref. 6.

TABLE II

COUPLING-CONSTANT DATA (Hz) FOR SUBSTITUTED METHYL α-D-IDOPYRANOSIDES

Substituent	*Solvent*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{2,4}$	*Others*
4,6-(*S*)-Bzd (**1**)	$CDCl_3$	< 0.5	~3		~2	1.8	1.8	−12.6	~1	$J_{2,OH}$ 12.0, $J_{3,OH}$ 9.9, $J_{1,3}$ ~1
	Me_2SO-D_2O	3.5	6.3	3.0	2.0					
4,6-(*S*)-Bzd-2-Me	$CDCl_3$	2.9	5.0	~3	~2.5	2.4	1.6	−12.6	0.8	$J_{3,OH}$ 9?
4,6-(*S*)-Bzd-3-Me	$CDCl_3$	~1.5	~3	~3	1.4	1.8	1.8	−12.6	~1	$J_{2,OH}$ 11.7
4,6-(*S*)-Bzd-2,3-di-Me[6]	$CDCl_3$	4.3	7.7	3.2	2.3	2.3	1.4	−12.7		
4,6-(*S*)-Bzd-2,3-CO_3 (**2**)	$CDCl_3$	6.4			3.2	3.5	1.8	−13.2		
4,6-(*R*)-Bzd-2,3-CO_3 (**4**)	$CDCl_3$	6.6	12.8	7.5	4.5	7.4	6.6	−11.4		
4,6-(*R*)-Bzd (**5**)	$CDCl_3$	< 0.5	~2.5	~1.3		2.0	2.0	−12.8	~1	$J_{2,OH}$ 12.0
	Me_2SO-D_2O	5.7	8.6	7.8	4.1					
2,3-CO_3 (**3**)	D_2O	5.8	12.2	6.9	3.8	8.0	3.7	−12.6		
None	D_2O	4.2	7.2		2.9	7.5	4.9?	−12.2		
None	Me_2SO-D_2O	3.5	5.6	5.0	2.9				0.8	
2-Me	D_2O	3.0	5.3	4.9	2.9					
3-Me	D_2O	1.8	4.0	4.0	~2	7.7	4.8	−11.5		
2,3-di-Me	D_2O	2.5	4.4	4.0	2.2				0.7	$J_{3,5}$ 0.9

formation, its benzylidenation would give the (*R*) isomer. Hence, we proceeded to convert methyl 4,6-*O*-benzylidene-α-D-idopyranoside into its 2,3-carbonate and then remove, and subsequently replace, the benzylidene group.

Methyl 4,6-*O*-(*S*)-benzylidene-α-D-idopyranoside reacted readily (obviously in a skew form) with ethyl chloroformate in the presence of triethylamine[15], to give the 2,3-carbonate (**2**), together with a small proportion of a mono(ethoxycarbonyl) derivative. The n.m.r. spectrum of the latter indicated that the substituent was on O-3: the signal of a hydroxylic proton was shown to be coupled to that of H-2.

The benzylidene group was removed from carbonate **2** by hydrogenolysis, and methyl α-D-idopyranoside 2,3-carbonate (**3**) was obtained in almost quantitative yield as a nicely crystalline compound. Compound **3** cannot assume the $^4C_1$ conformation. Benzylidenation of carbonate **3** with α,α-diethoxytoluene[16] proceeded readily but, surprisingly, gave mainly the (*S*)-benzylidene derivative (from which it had been prepared); the desired (*R*) derivative (**4**) was obtained in only 10% yield. Removal of the carbonate group from **4** produced methyl 4,6-*O*-(*R*)-benzylidene-α-D-idopyranoside (**5**).

In order to study the conformations of these compounds, their ^{1}H-n.m.r. spectra were recorded, mostly at 270 MHz; the results are shown in Tables I and II. It is easy to recognize the $^4C_1$ conformation: $J_{1,2}$ is ~1 Hz, $J_{2,3}$ and $J_{3,4}$ are ~3.5 Hz, and the signals of H-2 and H-3 (which are equatorial) are at low field. It is not easy, however, to distinguish between the $^0S_2$ and the $^1C_4$ form. The most characteristic feature of the latter is that $J_{2,3} = J_{3,4}$, and therefore, in any mixture of the two chair forms, these two coupling constants are equal. A typical example is methyl α-D-idopyranosiduronic acid and its sodium salt[17]. On the other hand, in the spectrum of the skew form, $J_{2,3}$ is large (>8 Hz), but $J_{3,4}$ is small (~3.5 Hz); a typical example is methyl 4,6-*O*-(*S*)-benzylidene-2,3-di-*O*-methyl-α-D-idopyranoside[6].

Baggett *et al.*[9] found that the benzylic proton resonates at δ ~5.6 for the stable benzylidene derivatives, where this proton is axial, and at ~6.3 for the unstable ones, the proton being equatorial.

Perusal of the n.m.r. data in Table II gives some information on the conformations of our compounds. The (*S*)-benzylidene carbonate can only be in a skew conformation (**2**): the carbonate group prevents it from taking up the $^4C_1$ form, and the benzylidene group precludes the $^1C_4$ form. After removal of the benzylidene group, methyl α-D-idopyranoside 2,3-carbonate (**3**) could be in the $^1C_4$ or in the skew form. The values of $J_{1,2}$ and $J_{3,4}$ are not quite large enough for the $^1C_4$ form (they should be ~8 and 10 Hz) and indicate the presence of a considerable proportion of the skew form.

It would be tempting to conclude that the low yield of the (*R*) isomer on benzylidenation is due to the low proportion of the $^1C_4$ form in the equilibrium of carbonate **3**. However, under the acid-catalyzed conditions of the reaction, the products are undoubtedly formed in equilibrium proportion. In fact, when the (*S*)-benzylidene derivative was submitted to the same reaction conditions, a 9:1 mixture of the (*S*) and (*R*) derivatives was obtained. A little consideration shows that an

(*R*)-benzylidene group *cis*-linked to a D-hexopyranoside is inherently less stable than an (*S*)-benzylidene group, even when linked to a $^1C_4$ conformer: in that chair form of the 1,3-dioxane ring in which the phenyl group is equatorial, the (*R*) derivative has an axial carbon atom (C-3, as in **5b**), whereas the (*S*) derivative has only an axial oxygen atom (O-5, as in **1a**), and the axial oxygen atom is in the position of the dioxane ring in which axial interactions are small (*meta* to the oxygen atoms). Therefore, even if the pyranose ring cannot adopt the $^4C_1$ form, the (*S*)-benzylidene derivative will be the major product (as long as the skew form of the pyranose has a stability comparable to those of the chair forms).

The new benzylidene carbonate has the (*R*) configuration: the n.m.r. signal of the benzylic proton appears at δ 6.01, whereas that of the (*S*) isomer is at δ 5.57. The compound is mainly in the $^1C_4$ conformation, with an equatorial phenyl group on the 1,3-dioxane ring; the shift of the benzylic proton to low field is then due to its being *syn*-axial with a carbon atom; in the unstable, benzylidene compounds described by Baggett *et al.*[9], the pyranose ring is fixed in the $^4C_1$ form, and the benzylic proton is equatorial, resulting in a somewhat greater downfield shift.

Methyl 4,6-*O*-(*R*)-benzylidene-α-D-idopyranoside (**5**) is also clearly an (*R*) compound: the benzylic proton was found at δ 6.20. However, to our great surprise, in chloroform solution, we found it to be in the $^4C_1$ conformation (**5a**): the coupling constants are similar to those of the (*S*) isomer, but H-4, H-5, H-6, and H-6′ are at higher field, owing to the effect of the phenyl group, which is now axial. The hydrogen bonds appear to be strong enough to overcome the stabilizing effect of the benzylidene group. It transpires that only the phenyl group of the (*S*)-benzylidene ring has a strong, anchoring effect; in the (*R*) derivative, the two chair forms of the 1,3-dioxane ring have either an axial phenyl group on C-2′ (ΔG^0 13.0 kJ.mol^{-1}), or an axial carbon atom, bearing two substituents, on C-4 (ΔG^0 for methyl, 12.1 kJ.mol^{-1}); there is, therefore, little difference between the stabilities of the two chair forms.

Once the hydrogen bonds are broken, however, by the use of dimethyl sulfoxide–water as solvent, the (*R*) derivative has its pyranose ring mainly in the $^1C_4$ form (**5b**): $J_{2,3}$ and $J_{3,4}$ are both large; H-1, H-2, and H-4 are at higher field than for the (*S*) isomer (because they are axial); and H-5 is at lower field (because it is equatorial). However, $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ are not quite so large as they should be for the $^1C_4$ form: some of the $^4C_1$, or the $^0S_2$, or both, is also present.

It was assumed[6] that, in chloroform solution, methyl 4,6-*O*-benzylidene-α-D-idopyranoside is held in the $^4C_1$ conformation by hydrogen bonds between its axial oxygen atoms; evidence for these bonds can, in fact, readily be observed in the n.m.r. spectrum. That of the (*S*) isomer shows two sharp doublets that disappear on deuterium exchange, and therefore are the signals of hydroxylic protons; the signals of H-2 and H-3 are split, and this splitting also disappears on deuteration. The coupling between H-2 and the hydroxylic proton is very large (12.0 Hz); such large coupling indicates[18] that the hydrogen atom is held in a fixed position, antiperiplanar to H-2, by the hydrogen bond (which must be strong). The coupling between H-3 and the hydroxylic proton is smaller (9.9 Hz), indicating a somewhat weaker hydrogen-bond.

In the spectrum of the (*R*) isomer, the same, strong, hydrogen bond involving H-2 is seen ($J_{2,OH}$ 12.0 Hz), but the signal of OH-3 is not clearly defined.

It appears, therefore, that the hydrogen bond from O-2 to O-4 is stronger than that from O-3 to O-1. To confirm this conclusion, we inspected the n.m.r. spectra of the 2- and 3-methyl ethers of methyl 4,6-*O*-(*S*)-benzylidene-α-D-idopyranoside. The latter showed the hydroxylic proton strongly coupled to H-2, and the conformation was found to be mainly $^4C_1$ ($J_{1,2}$ ~1.5 Hz). On the other hand, in the spectrum of the 2-methyl derivative, the signal of the hydroxylic proton was indistinct, and a considerable proportion of the molecules was found to be in the skew form ($J_{1,2}$ 2.9 Hz). The hydrogen bond to O-1 is, therefore, less effective in keeping the molecule in the chair form than is that to O-4. As the geometry of the two hydrogen-bonds is the same, we conclude that the benzylidene substituent (on O-4) increases the electron density to a greater extent than does the methyl group (on O-1).

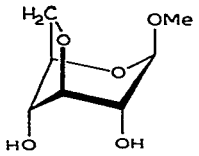
Of the 4,6-benzylidene glycosides described by Baggett *et al.*[9], the (*R*) isomers are more dextrorotatory than the (*S*) isomers. This is also true of the methyl 4,6-*O*-benzylidene-α-D-idopyranosides in chloroform solution, although the difference in the rotation of the two isomers is much smaller. However, in Me_2SO–H_2O, the (*S*) isomer has the higher rotation. [The (*S*) isomer has[6] $[\alpha]_D$ +47.5° in chloroform, and +84.2° in Me_2SO–H_2O.] The (*S*) isomer of the 2,3-carbonate is also more dextrorotatory than the (*R*) isomer. This "discrepancy" is obviously attributable to the fact that the two isomers do not assume the same conformation.

The totality of these data does not define the conformation of methyl α-D-idopyranoside itself. Its n.m.r. spectrum was therefore studied, but the (crucial) value of $J_{3,4}$ could not be determined, because, even at 270 MHz, the signals of H-3 and H-4 were very close together. To shift these signals farther apart, the spectra of the 2-*O*-methyl, 3-*O*-methyl, and 2,3-di-*O*-methyl derivatives were studied. All the coupling constants of the ring protons could be obtained from the spectra of these compounds (see Table II), but, in each case, the value of $J_{1,2}$ was smaller than that of the parent idoside, indicating that methylation shifts the equilibrium in favor of the $^4C_1$ conformation. As calculated from the $J_{1,2}$ values, the proportion of this form in the aqueous solution of methyl α-D-idopyranoside is 54%; of the 2-methyl ether, 73%; of the 3-methyl ether, 93%; and of the dimethyl ether, 82%. (The limiting values used for this calculation were 1.4 Hz for the $^4C_1$ form, as for α-D-mannopyranose, and 7.5 Hz for the $^1C_4$ form, as for 6-deoxy-5-*C*-methyl-β-D-*xylo*-hexopyranose[19].) Methylation on O-2 probably shifts the equilibrium, because it increases the anomeric effect[20]. The greater shift caused by methylating O-3 is probably due to lessened interaction between the axial methoxyl groups on C-1 and C-3. Paulsen and Friedmann[4] observed that the interaction between two axial methoxyl groups is considerably diminished in aqueous solution, probably by the formation of bridges by hydrogen atoms of water molecules[21]. Methyl tetra-*O*-methyl-α-D-idopyranose is almost completely in the $^4C_1$ form in aqueous solution, in contrast to its conformation in nonhydroxylic solvents[4].

It was later observed that the spectrum of methyl α-D-idopyranoside is well

resolved in mixtures of Me_2SO and water, although here, again, the equilibrium shifts towards the $^4C_1$ form (65%). The values of $J_{2,3}$ and $J_{3,4}$ have thus been obtained in a number of instances, but the forms other than the $^4C_1$ were always minor components. It is not, therefore, possible to determine from them how much of the skew form is present in equilibrium; the value of $J_{3,4}$ is always less than that of $J_{2,3}$, but the difference is small. It may be concluded that the equilibrium mixture consists mainly of the $^4C_1$ and $^1C_4$ forms; if the skew is present, it constitutes only a minor component.

Other compounds in skew forms? — To extend this investigation, we examined some other compounds that have serious, nonbonded interactions in their chair forms. An obvious example is methyl 3,6-anhydro-β-D-glucopyranoside (**6**), which can only adopt the $^1C_4$ form, in which every substituent is axial; the other chair form is precluded by the anhydro ring. The α anomer has been shown to exist, at least in the crystalline state, in the $^1C_4$ form[22].



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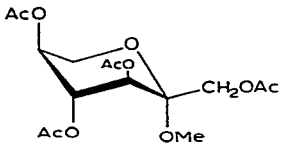

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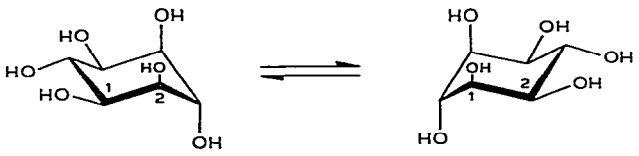

8

The β anomer, however, has more-serious, nonbonded interactions, and it has been suggested[23] that it would occur mainly in a flexible form. The n.m.r. spectrum of the β anomer was well resolved at 270 MHz, and the values of $J_{1,2}$ (<1 Hz) and $J_{2,3}$ (3.8 Hz) leave no doubt that the compound is completely in the $^1C_4$ form (**6**).

Another compound of interest is methyl β-L-sorbopyranoside[24]. It has four axial oxygen atoms in one of its chair forms, and an axial hydroxymethyl group in the other, just like methyl α-D-idopyranoside. Its tetraacetate gave a well defined, n.m.r. spectrum; its coupling constants, particularly the long-range couplings between H-3 and H-5, and H-4 and H-6, showed that the preponderant conformation is $^5C_2$ (**7**). Not all of the compound is, however, in this conformation: $J_{3,4}$, $J_{4,5}$, $J_{5,6a}$, and $J_{5,6e}$ are all appreciably greater than the values expected for the $^5C_2$ form[25]; they agree well with the assumption that about 1/4 of the compound is in the $^2C_5$ con-

formation. By contrast, the n.m.r. spectrum of methyl tetra-*O*-acetyl-α-D-idopyranoside is completely in accordance with its being in the $^4C_1$ form[4]. It appears, therefore, that the ketopyranoses have a greater tendency than the aldopyranoses to avoid *syn*-axial interactions of the anomeric oxygen atom.

Unfortunately, the n.m.r. spectrum of methyl β-L-sorbopyranoside is not well resolved. Even at 270 MHz, three of the proton signals almost coincide, and two other signals are, therefore, affected by virtual coupling; only the signals of H-1 and H-1′ are clear doublets. However, comparison with the spectrum of the acetate shows that the chemical shifts do not have the values expected for the $^5C_2$ form; they are, however, compatible with the $^2C_5$ form, as shown by comparison with the spectrum of benzyl β-D-xylopyranoside[25]. The signal at lowest field (δ 3.95) shows a coupling of 12 Hz and a total width of 16.5 Hz, in agreement with its being that of H-6*e*; a complex multiplet at δ 3.50, with a total width of 22 Hz, seems to be the signal of H-6*a*. It appears, therefore, that, in aqueous solutions of methyl β-L-sorbopyranoside, that chair form having an axial hydroxymethyl group is preponderant. The optical rotation of this compound varies greatly with the solvent[24], an indication of an equilibrium mixture whose composition is affected by the medium.

Methyl α-D-fructopyranoside[26] is a closely related compound that, in the $^5C_2$ form, has three axial oxygen atoms and, in the other chair form, an axial hydroxymethyl group. The spectrum is well resolved, and we found that the coupling constants (which are listed in the Experimental part) are readily compatible with a 2:1 mixture of the $^5C_2$ and $^2C_5$ forms, without the need to invoke any skew forms. In contrast to the aldopyranosides, even one pair of *syn*-axial oxygen atoms shifts the equilibrium substantially towards the other chair form. The optical rotation of this compound also varies greatly with the solvent[27].

muco-Inositol (**8**) is another compound for which a flexible conformation has been suggested[28]. In each of its two (equivalent) chair forms, it has three axial hydroxyl groups, whereas a boat form would have only equatorial substituents. A recent, X-ray structure investigation, however, found the inositol to exist in the chair form in the crystalline state[29]. Owing to its high degree of symmetry, its n.m.r. spectrum does not provide all the coupling constants; it consists of a doublet and a triplet only, both having a splitting of 5.8 Hz. We therefore investigated 1-*O*-methyl-*muco*-inositol[30]; introduction of the methyl group shifts the signal of H-1 downfield, and destroys the symmetry of the molecule. Although some of the signals still overlap, the values of $J_{1,2}$ (3.1 Hz), and $J_{6,1}$ and $J_{5,6}$ (both 6.6 Hz) can be determined. They indicate that *muco*-inositol in aqueous solution consists of a mixture of the two chair forms; for the all-equatorial, boat form, the coupling constants would be much greater, and for the most favored skew form, $J_{6,1}$ and $J_{5,6}$ would be smaller. The same coupling-constants were found for the pentaacetate of 1-*O*-methyl-*muco*-inositol.

It therefore appears that an accumulation of axial substituents will not, in itself, cause the preponderance of a skew form. Methyl 4,6-*O*-benzylidene-α-D-idopyranoside is exceptional; the greater electron-density generated on O-4 by the benzylidene group seems to increase the interaction between O-2 and O-4 to such

an extent that the $^4C_1$ form becomes similar in energy to the skew; the $^1C_4$ form is, of course, particularly disfavored.

EXPERIMENTAL

General. — Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Solutions were evaporated in rotary evaporators under diminished pressure. Optical rotations were determined with a Bendix automatic polarimeter. N.m.r. spectra were recorded with a Jeol JNM-4H-100S spectrometer at 25° in Sydney, and a Brucker HX-270 spectrometer at 23° at the National NMR Centre in Canberra.

Methyl 4,6-*O*-(*S*)-benzylidene-α-D-idopyranoside and its 2-methyl, 3-methyl, and 2,3-dimethyl ethers were prepared by Dr. J. L. Frahn by an improved method[31] based on Sorkin and Reichstein's work[8].

Methyl 4,6-O-(S)-benzylidene-α-D-idopyranoside 2,3-carbonate (**2**). — To a stirred mixture of methyl 4,6-*O*-(*S*)-benzylidene-α-D-idopyranoside[8] (4.0 g), ethyl chloroformate (40 mL), and 1,4-dioxane (20 mL), cooled in an ice-bath, was added, dropwise, a solution of trimethylamine (22 mL) in benzene (130 mL). After 1 h at ~6°, the mixture was washed with M hydrochloric acid and then repeatedly with water, dried, and evaporated. The syrupy residue crystallized from chloroform–petroleum ether, to give fine crystals (2.8 g in three crops, 64%) of carbonate **2**, m.p. 205–212°, $[\alpha]_D^{24}$ +76.5° (*c* 1.2, chloroform); ν_{max}^{Nujol} 1850 and 1820 cm^{-1} (characteristic of *trans*-fused, cyclic carbonates[15]).

Anal. Calc. for $C_{15}H_{16}O_7$: C, 58.45; H, 5.25. Found: C, 58.55; H, 5.25.

The mother liquors were combined, and evaporated, and the residue was chromatographed on a column of silica gel (150 g) with 4:1 benzene–ethyl acetate, fractions being collected that showed a spot at R_F 0.43 on t.l.c. plates (9:1 benzene–acetone). The content of these fractions was twice recrystallized from ethanol, to give methyl 4,6-*O*-(*S*)-benzylidene-3-*O*-(ethoxycarbonyl)-α-D-idopyranoside (0.4 g), m.p. 117–120°, $[\alpha]_D^{24}$ +73° (*c* 1.1, chloroform); n.m.r. data (Me_2SO-d_6): δ 5.58 (s, Ph*CH*), 5.43 (d, $J_{2,OH}$ 6.3 Hz, OH), 4.67 (dd, $J_{2,3}$ 7.8, $J_{3,4}$ 3.7 Hz, H-3), 4.60 (d, $J_{1,2}$ 4.2 Hz, H-1), 4.23–4.02 (m, 5 H), 3.72 (broad d, H-5), 3.55 (ddd, H-2), 3.33 (s, Me), and 1.21 (t, CMe). These assignments were made as follows: the d at δ 5.43 disappeared on deuterium exchange, and hence it must represent a hydroxyl group; irradiation of this signal caused the collapse of the ddd at δ 3.55 to dd; irradiation of the latter signal caused collapse of the dd and d at δ 4.67 and 4.60 to d and s, respectively.

Anal. Calc. for $C_{17}H_{22}O_8$: C, 57.6; H, 6.3. Found: C, 57.5; H, 6.3.

A sample of the ethoxycarbonate (100 mg) was acetylated with acetic anhydride–pyridine in the cold. On pouring the mixture into water, a white powder (87 mg) separated; this crystallized from ethanol as long needles of methyl 2-*O*-acetyl-4,6-*O*-(*S*)-benzylidene-3-*O*-(ethoxycarbonyl)-α-D-idopyranoside, m.p. 128–130°, $[\alpha]_D^{24}$

+81° (*c* 1.2, chloroform); ν_{max}^{Nujol} 1762 cm^{-1} (characteristic of acyclic carbonate groups[15]).

Anal. Calc. for $C_{19}H_{24}O_9$: C, 57.5; H, 6.1. Found: C, 57.2; H, 6.3.

Methyl α-D-idopyranoside 2,3-carbonate (**3**). — A solution of the benzylidene carbonate **2** (2.4 g) in acetic acid (65 mL) and anhydrous methanol (95 mL) was stirred under hydrogen with 10% palladium-on-carbon catalyst (0.5 g) for 14 h. The catalyst was removed by filtration and the filtrate evaporated; the residual solid was triturated with chloroform, and recrystallized from ethanol–ether, giving fine needles (1.46 g, 85%; in three crops) of carbonate **3**, m.p. 138–142°, $[\alpha]_D^{24}$ +82.5° (*c* 0.3, ethanol).

Anal. Calc. for $C_8H_{12}O_7$: C, 43.7; H, 5.5. Found: C, 43.4; H, 5.5.

Methyl 4,6-O-(R)-benzylidene-α-D-idopyranoside 2,3-carbonate (**4**). — A mixture of **3** (475 mg), *N*,*N*-dimethylformamide (2 mL), α,α-diethoxytoluene (0.4 mL), and *p*-toluenesulfonic acid (~1.2 mg) was heated for 1 h under reflux in an evacuated, rotary evaporator at 65–70°, cooled, and evaporated to dryness; the residue was triturated with a saturated solution of sodium hydrogencarbonate, the suspension was diluted with water, and the solid (579 mg) was filtered off. At this stage, n.m.r. spectroscopy showed the presence of 88% of the original benzylidene derivative and 12% of an isomer. Recrystallization from chloroform–petroleum ether gave crystals (434 mg) of the (*S*) isomer, m.p. 208–213°. The contents of the mother liquor were chromatographed on a column of silica gel (100 g) with 9:1 benzene–ethyl acetate, and the fractions having R_F 0.78 (t.l.c., 9:1 benzene–acetone), which contained the (*R*) isomer (64 mg, 9.5%), were recrystallized from ethanol; m.p. 162–165°, $[\alpha]_D^{24}$ +64.5° (*c* 0.5, chloroform).

Anal. Calc. for $C_{15}H_{16}O_7$: C, 58.4; H, 5.3. Found: C, 58.1; H, 5.3.

When methyl α-D-idopyranoside was treated in the same way, only the (*S*)-benzylidene compound was obtained. The signals of the (*R*) isomer were not detected in the n.m.r. spectrum.

Methyl 4,6-O-(R)-benzylidene-α-D-idopyranoside (**5**). — To a solution of the (*R*)-carbonate **4** (170 mg) in acetone (230 mL) was added a 1% solution of barium hydroxide (26 mL); after 1 h, the base was neutralized with solid carbon dioxide, the suspension was filtered, and the filtrate was evaporated to dryness. Crystallization of the residue from ethanol gave fine needles (80 mg, 50%), m.p. 123–125°, $[\alpha]_D^{24}$ +83° (*c* 1.1, ethanol), +59° (*c* 0.7, chloroform), and 74° (*c* 0.7, in 4:1 Me_2SO–H_2O).

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.6; H, 6.5. Found: C, 59.3; H, 6.6.

Methyl 3,6-anhydro-β-D-glucopyranoside (**6**). — This compound[23] gave the following n.m.r. data (D_2O): δ 3.45 (s, Me), 3.77 (d, $J_{2,3}$ 3.8 Hz, H-2), 3.94 (dd, $J_{5,6exo}$ 2.9, $J_{6exo,6endo}$ −10.4 Hz, H-6*exo*), 4.17 (d, $J_{5,6endo}$ 0 Hz, H-6*endo*), 4.19 (dd, $J_{2,3}$ 3.8, $J_{3,4}$ 5.5 Hz, H-3), 4.32 (dd, $J_{4,5}$ 3.1 Hz, H-4), 4.34 (t, H-5), and 4.80 (s, $J_{1,2}$ <1 Hz, H-1). Apart from that of $J_{1,2}$, the values of these coupling constants are similar to those recorded for the diacetate of methyl 3,6-anhydro-α-D-glucopyranoside[32].

Methyl tetra-O-acetyl-β-L-sorbopyranoside (7). — This compound[24] gave the following n.m.r. data ($CDCl_3$): δ 2.08 (Ac), 2.09 (2 Ac), 2.11 (Ac), 3.32 (s, Me), 3.76 (ddd, $J_{4,6e}$ 0.9, $J_{5,6e}$ 3.5, $J_{6a,6e}$ −12.9 Hz, H-6*e*), 4.05 (dd, $J_{5,6a}$ 3.2 Hz, H-6*a*), 4.18 (d, $J_{1,1'}$ −12.2 Hz, H-1), 4.33 (d, H-1'), 4.85 (dq, $J_{3,5}$ 0.9, $J_{4,5}$ 4.6 Hz, H-5), 5.03 (dd, $J_{3,4}$ 5.0 Hz, H-3), and 5.07 (dt, H-4).

Methyl β-L-sorbopyranoside. — This compound[24] gave the following n.m.r. data (D_2O): δ 3.95 (pair of indistinct 3-peak signals, *J* 12 Hz, H-6*e*?), 3.83 (d, $J_{1,1'}$ −12.7 Hz, H-1), 3.72 (d, H-1'), 3.70 (m, 3 H), 3.50 (m, H-6*a*?), and 3.33 (s, Me).

Methyl α-D-fructopyranoside. — This compound[26] gave the following n.m.r. data (D_2O): δ 3.32 (s, Me), 3.63 (d, $J_{1,1'}$ −12.6 Hz, H-1'), 3.65 (dd, $J_{6,6'}$ −11.7, $J_{5,6'}$ 5.1 Hz, H-6'), 3.70 (dd, $J_{5,6}$ 8.0 Hz, H-6), 3.73 (d, H-1), 3.90 (dd, $J_{3,4}$ 5.3, $J_{4,5}$ 3.4 Hz, H-4), 3.95 (d, H-3), and 3.99 (sept, H-5).

1-O-Methyl-muco-inositol. — This compound[30] gave the following n.m.r. data (D_2O): δ 4.06 (t, $J_{6,1} = J_{5,6}$ = 6.6 Hz, H-6), 4.00–3.95 (m, 2 H), 3.86–3.81 (m, 2 H), 3.50 (dd, $J_{1,2}$ 3.1 Hz, H-1), and 3.43 (s, Me). By decoupling, it was ascertained that the triplet assigned to H-6 is coupled to the signal of H-1.

Penta-*O*-acetyl-1-*O*-methyl-*muco*-inositol gave the following n.m.r. data ($CDCl_3$): δ 5.44 (t, $J_{6,1} = J_{5,6}$ = 6.5 Hz, H-6), 5.43 (t, $J_{2,3} = J_{3,4}$ = ~6.6 Hz, H-3), 5.28–5.22 (m, 3 H), 3.65 (dd, $J_{1,2}$ 3.4 Hz, H-1), 3.42 (s, Me), and 2.12, 2.11, 2.09, 2.07, and 2.06 (5 OAc).

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