Conformations of Epimers of Methyl 4,6-*O*-Benzylidene-2,3-di-*O*-Methyl-α-D-Glucopyranoside. An Example of Hindered Rotation of an Axial Phenyl Group as Observed by ^{13}C Spin-Lattice Relaxation Times

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The two epimeric 4,6-*O*-benzylidene derivatives of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside were synthesised by base catalysed reaction with phenyldichloromethane. In one epimer the 1,3-dioxane ring has chair conformation with the phenyl ring in an equatorial orientation. Based on NMR arguments, the other epimer was also proved to have chair conformation with the phenyl group axially oriented. Comparison of the ^{13}C shifts of the two epimers indicated a γ-*gauche* effect due to the axial phenyl. Moreover, spin-lattice relaxation time measurements revealed an *ortho*:*para* ratio of 3 for the equatorial epimer and a ratio close to unity for the axial epimer. This strongly indicates a fast rotation around the *C*-phenyl bond for the former and almost completely hindered rotation for the latter. Nuclear Overhauser effect measurements also support the two conformations.

The acid catalysed reaction between benzaldehyde and carbohydrates yields a series of benzylidene derivatives.[1] In these reactions a new chiral centre is created. The reaction involves a series of steps. All the steps are reversible and the reaction takes place under thermodynamic control. Of the two diastereomers formed in the reaction, the more stable one will predominate. When a 1,3-dioxane ring is formed in the reaction, the product with the 2-phenyl group equatorially oriented, is strongly dominant. This feature was observed in reactions with methyl α-D-glucopyranoside (*1*) and its 2,3-di-*O*-methyl derivative (*4*) which in acid catalyzed reactions with benzaldehyde yielded exclusively *2* and *3*, respectively.[2]

Baggett *et al.*[2] have investigated the base catalysed reaction of *4* with phenyldibromomethane and found that the epimers *3* and *5* where formed in practically equal amounts. Moreover, on acid treatment, *5* was quantitatively converted into *3*. We have now reinvestigated this reaction using phenyldichloromethane and potassium *tert*-butoxide as base.

Based on the ^1H chemical shift of the benzylic proton, H-7, which was δ = 5.94 ppm (our value 6.145), it was suggested[2] that the 1,3-dioxane ring of the less stable isomer *5* had adapted a twist-boat conformation as in *5TB* in Scheme 2. This suggestion has been disputed by Stoddart[3] who argued that the conformational free energy of a phenyl ring at C-2 on a 1,3-dioxane ring is only 3.1 kcal mole^{-1} while the destabilization is 5.7 kcal/mole^{-1} when the ring adopts a twist-boat conformation. These energies suggest that the equilibrium mixture consists of 1.2 % of the boat conformer, but on the NMR time scale at room temperature, the spectrum will be time-averaged. However, it ought to be mentioned that it has recently been shown[4] that the central 1,3-dioxane

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Table 1. ^{13}C Chemical shifts for compounds *1–5* and spin-lattice relaxation times for *3* and *5*. Data for *1* and *2* were taken from Ref. 5.

	^{13}C shifts/ppm					T_1/s	
	1	*2*	*4*	*3*	*5*	*3*	*5*
C-1	99.60	99.80	97.67	98.25	98.25	–	1.3
C-2	71.90	72.20	81.92	81.97	81.48	1.2	1.4
C-3	73.60	70.40	83.44	81.28	80.02	1.3	1.3
C-4	70.10	80.60	70.38	79.68	74.22	2.0	1.3
C-5	71.60	61.90	72.08	62.08	62.52	1.7	0.7
C-6	61.20	68.40	61.12	68.91	63.11	–	1.3
C-7	–	101.40	–	101.22	96.59	1.4	1.4
(OCH_3)–1	55.30	54.80	55.17	55.16	55.11	3.3	–
(OCH_3)–2	–	–	58.73	59.21	59.26	4.9	–
(OCH_3)–3	–	–	61.75	60.87	60.96	4.2	–
Ph-C-1	–	136.80	–	137.19	136.26	14.5	–
Ph-*o*-C	–	125.80	–	125.93	127.00	3.3	1.4
Ph-*m*-C	–	127.80	–	128.07	128.90	3.3	1.4
Ph-*p*-C	–	128.70	–	128.80	128.17	1.1	1.3

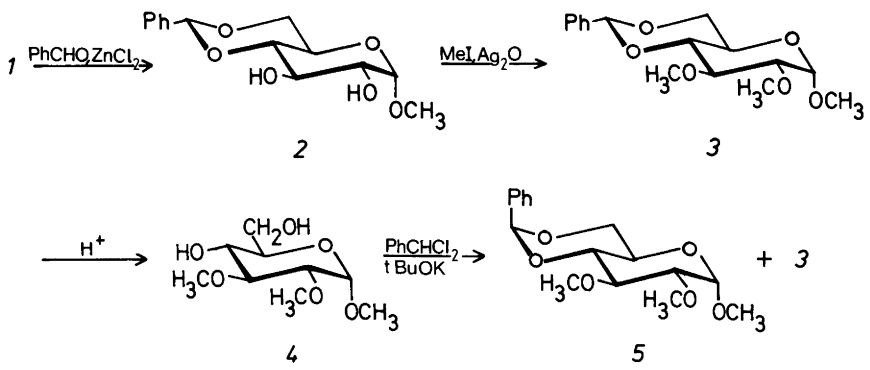
ring of dimeric 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose changes its conformation from being a chair in $CDCl_3$ solution to a twist-boat in CD_3OD solution.

We now present conclusive evidence for the conformation of *5* as being a chair (5C in Scheme 2) with an axial phenyl group. The proof rests on three points; i) ^{13}C chemical shifts, ii) nuclear Overhauser effect measurements and iii) ^{13}C spin-lattice relaxation times.

Between the two epimers, *3* and *5*, there are significant differences in the ^{13}C NMR spectra (Table 1). Particularly important are the shifts on the 1,3-dioxane ring, C-4 +5.46 ppm, C-5 −0.44 ppm, C-6 +5.80 ppm and C-7 +4.63 ppm. Compound *3*, with the equatorial phenyl group, has the largest number of downfield shifts for C-4,6 and 7. These shift differences, which are due to replacement of the smaller γ-*trans* effect in the equatorial isomer *3* with the larger γ-*gauche* effect in the axial isomer *5*, are also easily recognizable between anomers of carbohydrates.[5] In agreement with earlier observations of twist-boat conformation of 1,3-dioxane derivatives,[4] such a conformation for *5* is not expected to show the observed shifts.

Moreover, differentiated nuclear Overhauser enhancement experiments, which demonstrate spatial relationship between protons, also support the chair conformation. Irradiation of H-7 influences the intensity of the aromatic *ortho*-protons only. As indicated in Scheme 2, a significant contribution of the *5TB* conformation should show an increased intensity of the H-5 resonance and perhaps of the more distant H-3 resonance (dotted line). On the other hand, irradiation of the *ortho*-protons influenced not only H-7, but also to a great extent the resonances of H-4 and the axial one of the two H-6 protons as indicated in *5C* (Scheme 2).

The final point in our proof rests on the measurement of the ^{13}C spin-lattice relaxation times T_1. Assuming that the dominant relaxation mechanism for the protonated aromatic carbons is due to dipol-dipol interactions with the directly bonded protons, and moreover, that the molecules tumble rapidly in solution allowing the extreme narrowing approximation, then increased motion of the molecule as a whole or of a part of the molecule, will lead to less effective spin-lattice relaxation. A preferred rotation of a phenyl group as indicated in *5TB* will lead to shorter correlation times (τ_c) for the *ortho* and *meta* protons than for the *para* proton. This in turn leads to longer T_1's for the two former. Such anisotropic tumbling has been observed for a number of monosubstituted benzenes[6] and $T_{1dd}^{o,m}/T_{1dd}^{p}$-values in the range 1.3–4.9 have been recorded. Although these values are quite far from the theoretical maximum of 64 for extreme anisotropic



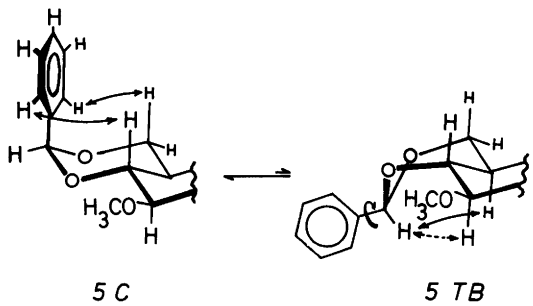
Scheme 1

behaviour, they clearly show a preferred axis of rotation in phenyl groups.

The spin-lattice relaxation times for epimers *3* and *5*, which were measured by the inversion recovery method, are presented in Table 1. The relaxation ratio for the aromatic carbons in the equatorial epimer *3* was 2.9 while the value for *5* was 1.1. These values indicate that while there is a significant anisotropic tumbling of the phenyl group in *3*, the rotation of the phenyl group in *5* is practically blocked. Model studies show that an axial phenyl group is expected to behave in this way, thus strongly supporting the conformation of *5* being a chair.

Experimental

TLC was performed on "Merck DC-Alufolien Kieselgel 60 F_{254}" (0.2 mm). As ion-exchange resin was used "Amberlite MB 3", activated by treatment with 0.1 M NaOH and then with water. The ^{1}H NMR spectra were recorded at 400 MHz on a Bruker WM 400. The ^{13}C spectra were recorded using a Jeol FX 100 at 25.1 MHz. Measurements of ^{13}C T_1 values were done by the inversion recovery method (180-τ-90-PD) with PD = 40 s and τ values of 1, 2, 4 and 8 s for epimer *3* and PD = 10 s and τ values of 0.1, 0.3, 0.6, 1.0, 1.5 and 2 s for epimer *5*. All NMR measurements were done in $CDCl_3$ solutions.



Scheme 2

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (2). Methyl α-D-glucopyranoside (*1*) (5.0 g, 25.7 mmol), finely powdered anhydrous zinc chloride (3.75 g, 27.5 mmol) and benzaldehyde (12.5 ml) were stirred at ambient temperature for 5 h. The mass was washed with cold water and then with petroleum ether; yield 3.8 g, 13.5 mmol, 53 %. ^{1}H NMR: 4.784 d J = 3.90 Hz (H-1), 3.630 m (H-2), 3.924 t J = 9.25 Hz (H-3), 3.488 t J = 9.26 Hz (H-4), 3.804 dt J = 4.2 and 10.3 Hz (H-5), 3.783 t J = 10.30 Hz (H-6a), 4.291 dd J = 4.21 and 9.59 Hz (H-6e), 5.528 s (H-7), 3.453 s (OCH_3), 7.493 m (*o*-Ph-H), 7.359–7.387 m (*m, p*-Ph-H).

Methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside (*3*). Dry methyl 4,6-*O*-benzylidene- α-D-glucopyranoside (*2*) (1.5 g, 5.3 mmol). finely divided silver oxide (1.25 g, 5.4 mmol) and freshsly distilled methyl iodide (100 ml) were heated under reflux for 24 h. A new portion of silver oxide (1.25 g, 5.4 mmol) was added and the heating continued for another 24 h. After cooling the mixture was filtered and the silver salts were extracted with dichloromethane under reflux. The combined filtrate and extracts were evaporated under reduced pressure;

yield 1.34 g, 4.3 mmol, 81 %. ^{1}H NMR: 4.858 d J = 3.68 Hz (H-1), 3.302 dd J = 3.70 and 9.22 Hz (H-2), 3.531 t J = 9.32 Hz (H-3), 3.690 t J = 9.37 Hz (H-4), 3.816 dt J = 4.50 and 9.56 Hz (H-5), 3.730 t J = 10.13 Hz (H-6a), 4.283 dd J = 4.49 and 9.84 Hz (H-6e), 5.545 s (H-7), 3.447 s (OCH_3-1), 3.552 s (OCH_3-2), 3.635 s (OCH_3-3), 7.493 m (*o*-Ph-H), 7.346–7.395 m (*m,p*-Ph-H).

*Methyl 2,3-di-*O*-methyl-α-*D*-glucopyranoside* (*4*). A solution of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (*3*) (1.0 g, 3.2 mmol) in water (40 ml) and sulfuric acid (2.0 ml, 0.1 N) was heated for 1 h in a water bath at 60 °C. The easily liberated benzaldehyde was removed by distillation under reduced pressure, and the remainder of the solution was deacidified by passing it through ion-exchange resin. The neutral solution was concentrated under reduced pressure, and the resulting thick syrup was used in the next step without further purification.

*7-Epimers of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside* (5 + 3). The syrup from the previous step, containing methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*4*) (*ca.* 0.7 g), was dissolved in a mixture of a 1 M solution of potasium *tert*-butoxide in *tert*-butanol (15 ml) and toluene (15 ml). This solution was added dropwise to a boiling solution of phenyldichloromethane (1.0 ml, 6.4 mmol) in benzene (185 ml) for 2 h. The mixture was boiled overnight and after cooling, washed with water, dried over $MgSO_4$ and evaporated to give a residue (*ca.* 0.5 g) which was fractionated by preparative TLC. Elution with benzene-diethyl ether (4:1) gave *3* (R_f=0.4) 48 mg, 0.15 mmol and *5* (R_f=0.5) 42 mg, 0.14 mmol; total yield 90 mg, 0.29 mmol, 9 % based on *3*. ^{1}H NMR for *5*: 4.736 d J = 3.67 Hz (H-1), 3.130 dd J = 3.67 and 9.18 Hz (H–2), 3.645 t J = 9.27 Hz (H-3), 3.438 t J = 9.42 (H-4), 3.847 dt J = 4.92 and 10.07 Hz (H-5) 3.592 t J = 10.23 Hz (H-6a), 3.925 dd J = 4.90 and 9.95 Hz (H-6e), 6.145 s (H-7), 3.425 s (OCH_3-1), 3.504 s (OCH_3-2), 3.740 s (OCH_3-3), 7.496 d (*o*-Ph-H), 7.441 t (*m*-Ph-H), 7.356 t (*p*-Ph-H).

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