

The Constitution and Stereochemistry of Dimeric 1,2-*O*-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose in CDCl_3 and CD_3OD Solutions. An Example of Twist-Boat Conformation

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The oxidation of 1,2-*O*-isopropylidene- α -D-glucofuranose with sodium periodate does not yield the expected 1,2-*O*-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose, but a dimer, as reported earlier. This dimer has a 1,3-dioxane ring as the central part and it contains two new chiral centres, one as an acetal and one as a hemiacetal structure. The configurations at these two centres and the conformation of the dimer in chloroform solution have been deduced by NMR spectroscopy. It has also been shown that the configuration at the acetal centre was inverted in methanol solution, and that the 1,3-dioxane ring adapted a twist-boat conformation.

In 1957 Schaeffer and Isbell¹ discovered that the periodate oxidation of 1,2-*O*-isopropylidene- α -D-glucofuranose(1) did not furnish the expected 1,2-*O*-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose(2), but a dimer.

On the basis of rates of hydrolysis of the two acetyl groups of the corresponding diacetate, the constitution was suggested to be as in 3. This constitution, which is both an acetal and a hemiacetal at the same time, has been confirmed later by Inch² who used ¹H NMR spectroscopy. He also isolated from the reaction mixture a by-product which was an

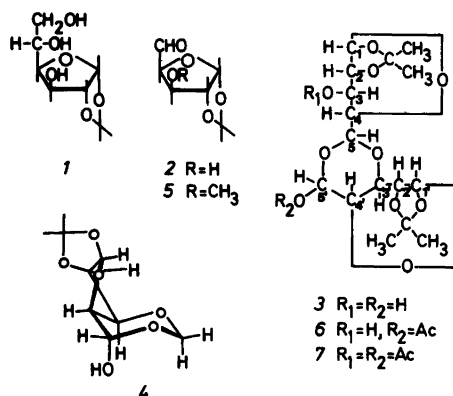


Table 1. ^1H and ^{13}C NMR data for compounds 3, 6 and 7. All chemical shifts are relative to TMS except for 3 in CD_3OD in which case $\delta_{\text{CD}_3} = 3.400$ ppm is the reference. The ^1H NMR spectra of 3 were recorded at 400 MHz and the ones of 6 and 7 at 100 MHz. All ^{13}C spectra were obtained at 25.1 MHz. The quaternary carbons of the isopropyl groups have $\delta = 112.0 \pm 0.3$ ppm. $^1J_{\text{BC,1H}}$ for C-5'-H-5' for 3 in CDCl_3 is 168.5 Hz and in CD_3OD 166.0 Hz. R=H or Ac. $J^* = J_{\text{n,(n+1)}}$ Hz.

	3 in CDCl_3			3 in CD_3OD			6 in CDCl_3			7 in CDCl_3		
	^1H	J^*	^{13}C	^1H	J^*	^{13}C	^1H	J^*	^{13}C	^1H	J^*	^{13}C
1	5.990	3.55	105.1	5.975	4.58	106.8	5.98	3.1	105.0	5.94	3.5	105.8
1'	6.001	3.65	105.1	5.985	3.74	106.6	6.00	3.4	105.0	5.99	3.7	105.7
2	4.519	~0	84.7	4.551	~0	86.9	4.50	~0	84.5	4.47	~0	83.6
2'	4.571	~0	83.3	4.551	~0	86.7	4.60	~0	83.0	4.53	~0	83.3
3	4.353	2.74	74.9	4.189	2.75	75.9	4.36	2.8	74.9	5.30	2.9	76.1
3'	4.462	2.16	76.6	4.259	2.74	84.0	4.47	2.1	76.9	4.31	1.9	77.3
4	4.143	5.51	80.2	4.017	7.33	83.4	4.12	4.8	79.3	4.23	5.8	79.3
4'	3.993	0.87	73.8	4.063	7.24	75.7	3.91	<1.0	72.4	3.88	<1.0	73.0
5	5.457		90.4	4.757		97.6	5.31		92.0	5.10		92.1
5'	5.475		89.7	4.809		97.6	6.33		88.6	6.34		89.2
OR, 3	2.670	br.					3.24			2.11		21.0, 168.3
OR, 5'	3.606	3.32					2.16		20.8, 168.3	2.16		21.2, 168.3
isoPr	1.314, 1.479		26.2, 26.7	1.384, 1.538		26.7, 27.4	1.31, 1.48		26.5, 26.7	1.30, 1.49		26.8, 27.2
isoPr	1.320, 1.496		26.3, 26.8	1.384, 1.538		26.7, 27.4	1.31, 1.49		26.0, 26.7	1.32, 1.49		26.6, 27.2

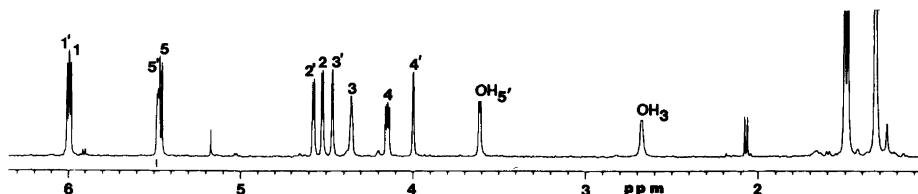


Fig. 1. The 400 MHz ^1H NMR spectrum of **3** in CDCl_3 solution.

acetal between **2** and formaldehyde formed during the periodate oxidation. The constitution and stereochemistry of this compound was shown by NMR to be **4**.

During our studies of additions of diazomethane and sulfur ylids to aldoses and ketoses we have taken interest in the aldehyde **2**.³ Reactions with the corresponding 3-*O*-methyl ether (**5**) have been studied and the results will be published shortly.

The dimer was synthesized according to known procedures^{1,2} and in an attempt to investigate the crystal structure, crystallization from various solvents was tried. We did not succeed in our efforts to grow crystals suitable for X-ray studies. For our solution studies we have extensively used ^1H and ^{13}C NMR spectroscopy. Particularly two dimensional methods like ^1H - ^{13}C shift correlated and NOE spectroscopy have been useful. The NMR data, which were obtained at 9.4 Tesla, are given in Table 1. Previously² the chemical shifts for H-3' and H-4' have been mixed up for the diacetate **7**.

Abraham *et al.*⁴ have employed proton coupling constant arguments to deduce the conformations of some simple furanosides in solutions. As judged from the coupling constants in Table 1 both furan rings in **3** are clearly in the $^3\text{T}_2$ conformation as depicted for the C-1-C-4-ring in **8**. The most prominent features are $J_{2,3}$ and $J_{2',3'}$ which are close to zero in all cases, thus indicating dihedral angles of approximately 90° (**9**). The formation of the dimer **3** produces two new chiral centra, at C-5' (hemiacetal) and C-5 (acetal) respectively. This gives four possible stereoisomers. The configuration at these two centres and the conformation of the 1,3-dioxane ring in chloroform solution have been suggested by Inch² and confirmed by us to be as depicted in **10**. The very small coupling constants $J_{2',3'}$ and $J_{4',5'}$ are compatible with a chair conformation and an axial hydroxyl group at C-5'. Moreover, the configuration as shown was strongly indicated by a nuclear Overhauser effect between H-3' and H-5 (see Fig. 1). This observation suggests an axial H-5 interacting with an axial H-3'. The ^{13}C - ^1H one bond coupling constant has been shown to be different for axial and equatorial protons at C-1 in pyranoses.⁵ The 1J coupling constant is approximately 170 Hz for α -anomers (equatorial H) and 160 Hz for β -anomers (axial H). The corresponding coupling constant for the dimer **3** was 168.5 Hz in CDCl_3 solution, thus supporting the constitution as shown in **10**. Since all ^1H coupling constants, including $J_{4',5'}$ in CDCl_3 solutions are very similar for **3**, **6** and **7**, it seems reasonable to assume that the acetates **6** and **7** have the same configurations and conformations as **3**.

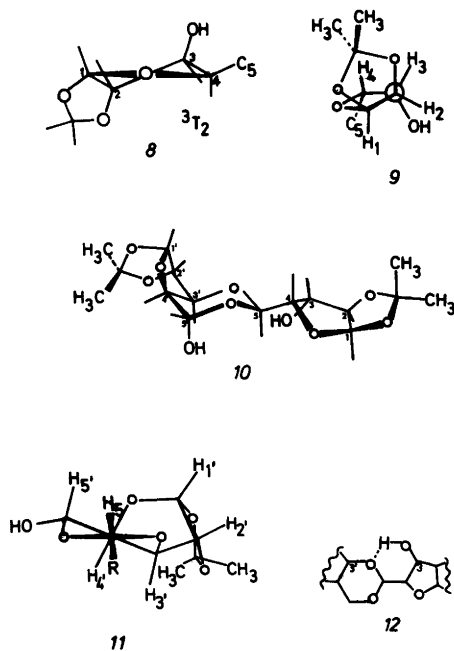
It may at first seem surprising that no trace of the C-5' epimer could be detected, *i.e.* the epimer with the hydroxyl group in the equatorial orientation. If one compares **10** with the hexopyranoses, an axial OH at C-5' is similar to an α -anomer. Moreover, the axial oxygen function at C-4' furnishes a situation comparable to the one in α -D-mannose in the $^4\text{C}_1$ conformation. This means that both the anomeric and the $\Delta 2$ effect may be operative. However, these effects alone do not seem to be sufficient to explain the strong preference for the axial OH. It is also known, that alkylation of OH groups and presence of deoxy

function influence the anomeric effect.⁶ Such effects may contribute to the equilibrium structure of the dimer (3).

When the dimer 3 was dissolved in CD₃OD, the NMR spectra gradually changed to the spectra of a different compound. This phenomenon was observed by the appearance of a set of new peaks at the cost of the original ones. It is therefore not a matter of conformational averaging, in which case one should expect to observe a gradual shift of the peaks. The conversion took three days, but addition of one drop of DCl completed the reaction in two h. The most remarkable difference between the ¹H chloroform-*d*₃ and methanol-*d*₄ spectra, is the H-4'–H-5 coupling constant. From being less than 1 Hz in CDCl₃ it increased to 7.24 Hz in CD₃OD solution (see Table 1). The only reasonable explanation for this observation seems to be that the 1,3-dioxane ring had adapted a twist-boat conformation as shown in 11. Further evidence was found by 2D NOE spectroscopy. There was no nuclear Overhauser effect between H-3' and H-5. An effect between H-5 and H-5' was uncertain due to small chemical shift difference. The ¹J coupling constant at C-5' was reduced to 166.0 Hz, which is in between the values expected for axial and equatorial orientations on a chair.

During the reaction following the solvent change, there were significant shifts of the ¹³C resonances (see Table 1). Particularly important were the shifts for the carbons on the 1,3-dioxane ring, they were as follows: C-3' 7.4, C-4' 1.9, C-5' 7.9 and C-5 7.2 ppm. All the shifts were downfield.

It is well documented that an axial substituent on a cyclohexane ring causes an upfield shift at the 3- and 5-positions, relative to a similar equatorial substituent, due to the γ -gauche effect.⁷ For instance, this may be seen in the ¹³C NMR spectra of methyl α - and β -glucosides. Going from a chair like 10, with an axial hydroxy group at C-5', to a twist-boat like 11, would be expected to lead to downfield shifts of magnitudes such as observed. A difference between shifts calculated on the basis of chair conformation for *trans*-2,4,4,6-tetramethyl-



1,3-dioxane and the observed ^{13}C shifts, has led to the suggestion of a twist-boat conformation for this compound.⁸

The conversion of the dimer structure *10* into *11* upon solvent change probably proceeds through an aldehydic intermediate. In some of the NMR spectra recorded during the interconversion, aldehyde protons were observed ($\delta \sim 10$ ppm). A question may be raised concerning the driving force for the transformation. After all, it involves a chair-twist-boat interconversion with a difference in free energy of $\Delta G^\circ = 5.7$ kcal/mol.⁹ The necessary energy is probably provided by interaction with the polar solvent.

From modelbuilding it may be inferred that in the chair form in chloroform solution there is an excellent arrangement for hydrogen bonding between OH-3 and O-3' as shown in *12*. This hydrogen bonding is similar to the one postulated to be important for the secondary structure of cellulose.

When the ^1H NMR spectra were recorded with decreasing concentrations from 9.4 to 0.7 mg/ml CDCl_3 , the OH-5' resonance shifted upfield by 0.6 ppm while the OH-3 resonance remained almost constant. When the temperature was increased from 20 to 60 °C, the OH-5' moved upfield by 0.4 ppm compared with 0.1 ppm for OH-3. These observations seem to confirm an intramolecular hydrogen bond for OH-3 as suggested.

In the twist-boat form in methanol solution the hydrogen bonding preferably takes place with the solvent. Among other effects, this leads to a different situation around the C-4-C-5 bond, and this is reflected in a significant increase in the vicinal coupling constant. Furthermore, modelbuilding also indicates that in methanol solution, the molecule as a whole is bent and exposing the oxygens to the solvent. In chloroform the molecule seems to be more stretched out. A part of this work has been published previously.¹⁰

EXPERIMENTAL

TLC was performed on "Merck Fertigplatten" (0.25 mm SiGel GF 254) and preparative separations on column (i.d. 50 mm) packed with Merck SiGel 60. The ^1H spectra of *3* and the 2D spectra were recorded at 400 MHz on a Bruker WM 400. Other ^1H NMR spectra and the ^{13}C spectra were recorded using Jeol FX 100 at 100 MHz for ^1H and 25.1 MHz for ^{13}C . The spectra of *3* in methanol- d_4 were recorded minimum three days after dissolution. The 2D NMR spectroscopy was done with the following sequences: COSY 90- t_1 -90- t_2 (acq), NOESY 90- t_1 -90- t_m -90- t_2 (acq). The mixing delay t_m was 1 s.

Mass spectra were recorded on an AEI MS 902 under electron impact (70 eV).

Dimeric 1,2-O-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose (3). To a mixture of 1,2-isopropylidene- α -D-glucofuranose (*I*) (12.5 g, 56.8 mmol) and NaHCO_3 (2.76 g, 32.9 mmol) in H_2O (60 ml), was added dropwise under vigorous stirring and cooling in ice, a solution of NaIO_4 (12.5 g, 63.2 mmol) in H_2O (60 ml). After stirring at room temp. for 12 h the reaction mixture was extracted with diethyl ether (3 \times 50 ml). The extract was dried over Na_2SO_4 , filtered and the solvent was evaporated under reduced pressure, yield 7.2 g, 38.7 mmol, 68 % as colourless syrup. The syrup (2.2 g) was applied on a column and eluted with hexane: diethyl ether 50:50. Fractions à 15 ml were collected. Fractions 3–6 contained the formaldehyde adduct (*4*) (1 g) and fractions 12–14 the dimer *3* (1.1 g). Crystals of *3* were obtained from hexane, mp. 174–176°. Optical rotation was measured immediately after dissolution of the crystals in methanol, $[\alpha]_D^{25} = 25.5^\circ$ (CH_3OH , c 0.275). After 3 days the rotation had changed to $[\alpha]_D^{25} = -28.5^\circ$.

MS showed no M^+ . Important fragment ions were: m/z 173 (30 %) $\text{CHO, OH}[\text{C}_4\text{H}_4\text{O}] \text{O}-\text{C}=\text{O}^+$, CH_3 , m/z 159 (65 %) $[\text{C}_4\text{H}_5\text{O}^+]\text{OH, O}_2\text{C}(\text{CH}_3)_2$, m/z 101 (8 %) $[\text{C}_4\text{O}^+\text{H}_3\text{O}]\text{OH}$, m/z 85 (38 %) $[\text{C}_3\text{H}_2\text{OO}^+]\text{CH}_3$, m/z 59 (100 %) $\text{HO}^+ = \text{C}(\text{CH}_3)_2$.

Diacetate (7). The dimer (*3*) (50 mg, 0.13 mmol) was dissolved in a mixture of pyridine (1 ml) and acetic anhydride (1 ml). After standing at room temp. for 12 h, the mixture was

evaporated under reduced pressure. Purification on preparative TLC gave a yellow syrup of 7, 45 mg, 0.1 mmol, 76.9 %.

Monoacetate (6). The dimer (3) (0.36 g, 0.97 mmol) was dissolved in an ice cooled mixture of pyridine (4 ml) and acetic anhydride (4 ml) and stirred on ice. After 9 min. the reaction was stopped by addition of crushed ice (80 g). The mixture was extracted with CHCl_3 (3×100 ml), the extracts washed with NaHCO_3 solution (3×50 ml), dried over Na_2SO_4 , filtered and evaporated under reduced pressure to yield a mixture of 3, 6 and 7 (0.38 g). TLC ($\text{CHCl}_3:\text{CH}_3\text{OH}=97:3$) showed the composition of the mixture to be as follows: 3, 30 % (R_f 0.22), 6, 50 % (R_f 0.47) and 7 20 % (R_f 0.77). Preparative TLC was performed with the same solvent system.

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REFERENCES

1. Schaeffer, R. and Isbell, H.S. *J. Am. Chem. Soc.* 79 (1957) 3864.
2. Inch, T.D. *Carbohydr. Res.* 5 (1967) 53.
3. Hagen, S., Lwande, W., Kilaas, L. and Anthonson, T. *Tetrahedron* 36 (1980) 3101.
4. Abraham, R.J., Hall, L.D., Hough, L. and McLaughlan, K.A. *J. Chem. Soc.* (1962) 3699.
5. Bock, K. and Pedersen, C. *J. Chem. Soc. Perkin Trans. 2* (1974) 293.
6. Angyal, S.J. *Angew. Chem.* 81 (1969) 172.
7. Wehrli, F.W. and Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*, Heyden, London 1976, p. 45.
8. Riddell, F.G. *J. Chem. Soc. B* (1970) 331; Kelly, G.M. and Riddell, F.G. *J. Chem. Soc. B* (1971) 1030.
9. Pihlaja, K. and Luoma, S. *Acta Chem. Scand.* 22 (1968) 2401.
10. Kilaas, L. and Anthonson, T. *XII. Intern. Carbohydr. Symp. Utrecht 1984, Abstr.* D 9.4.

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