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Structural studies by ^{1}H- and ^{13}C-n.m.r. spectroscopy and circular dichroism of acetylated α- and β-D-gluco- and -manno-pyranosylarenes*

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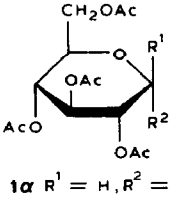
ABSTRACT

The configuration and conformation of the title compounds were investigated on the basis of ^{1}H- and ^{13}C-n.m.r. spectra, specific rotations, and circular dichroism. The ^{13}C-n.m.r. data (chemical shift of the C-1 resonances, $J_{C\text{-}1,H\text{-}1}$ values) indicate that the anomeric configuration of *C*-glycopyranosyl compounds can be assigned by using the same rules as for the corresponding glycopyranosides.

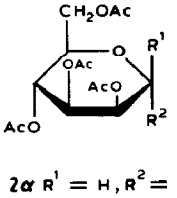
INTRODUCTION

In studies of the synthesis of *C*-glycosylarenes[1,2], several pairs of anomers were prepared for re-examination of their physical properties as related to the anomeric configuration. The tetra-acetates of α- and β-D-gluco- (**1α** and **1β**) and -manno-pyranosylbenzene (**2α** and **2β**) were chosen because these substructures are those found more frequently in natural *C*-glycosyl compounds[3], especially in *C*-flavonoids[4].

When these compounds were prepared originally[5,6], the configurations were assigned on the assumption that *C*-glycosyl compounds followed Hudson's rule[7], namely, that the more dextrorotatory isomer was the α anomer. However, there are exceptions to Hudson's rule, namely 2,3-unsaturated glycopyranosides[8], pyrimidine 2-deoxy-D-ribonucleosides[9], 2,3-unsaturated *C*-glycosyl compounds[10,11], and 2,3-*O*-isopropylidene-*C*-glycofuranosyl derivatives[12]. Therefore, the structural assignments for **1** and **2** have been re-examined by modern spectroscopic methods.



1α $R^1 = H, R^2 = Ph$
1β $R^1 = Ph, R^2 = H$



2α $R^1 = H, R^2 = Ph$
2β $R^1 = Ph, R^2 = H$

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RESULTS AND DISCUSSION

Compounds **1** and **2** were prepared as reported[5,6] and the purity of each anomer was verified by g.l.c. The high degree of purity of oily **1α** resulted in a more dextrorotatory $[\alpha]_D$ value than reported[5].

The ^{1}H-n.m.r. data for **1** and **2** are listed in Table I, and the spectra are amenable to first-order analysis. The high ^3J values (9.3–9.8 Hz) for H-1/5 of the pyranosyl ring in **1β** indicated *ax,ax* dispositions and accord with the $^4C_1$(D) conformation. For **1α**, the values (6.2–8.8 Hz) of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ in various solvents were too small for an *ax,ax* relationship of H-2/5 and too large for a $^1C_4$(D) conformation. These data suggest that there was a conformational equilibrium for **1α** in which the $^4C_1$(D) conformation preponderated and was more abundant in $CDCl_3$ and CD_2Cl_2 than in $(CD_3)_2SO$. Although the signals were not resolved when the ^{1}H-n.m.r. spectra were recorded at −70°, a distorted chair or a boat conformation was ruled out for the major conformer because all of the ^3J values depended on the solvent; the presence of a distorted conformation in the minor conformer is not precluded.

This conformational equilibrium of **1α** was also indicated by the effect of solvent on the $[\alpha]_D$ values [**1α**, +81° (chloroform), +59° (acetone), +47° (methyl sulfoxide); **1β**, −20° (chloroform), −14° (acetone), −22° (methyl sulfoxide); (*c* 0.54–0.93)].

Similar variations in ^3J and $[\alpha]_D$ values have been observed for glycopyranosides[13], and for *N*-glucopyranosyl[13] and *C*-glycopyranosyl compounds[14], and explained in terms of conformational equilibria. Since there is no anomeric effect in **1α** to stabilise the $^4C_1$ (D) conformation, it is likely that this conformational change is due to a strong *gauche* interaction of the axial phenyl group and AcO-2. The values of $J_{1,2}$ [4.6 Hz in CD_2Cl_2 and 3.7 Hz in $(CD_3)_2SO$] for **1α** accord with an *ax,eq* or *eq,ax* relationship of H-1,2 and thus confirm the α configuration.

Thus, the original assignments of configurations[5,6], based on optical rotation data, are confirmed by ^{1}H-n.m.r. data; in all of the solvents employed, the α anomer is the more dextrorotatory (see above).

For **2α** and **2β**, the high values of $J_{3,4}$ and $J_{4,5}$ indicated $^4C_1$(D) conformations. Due to the axial location of AcO-2, the configuration at C-1 could be deduced from the $J_{1,2}$ values (3.1 Hz for **2α** and 1.3 Hz for **2β**).

According to Booth's rule[15], a *gauche* coupling $^3J_{A,B}$ decreases with increasing electronegativity of the substituent S in the fragment H_A–C(S)–C–H_B, provided that S is antiperiplanar to H_B.

The Newman projections along C-1–C-2 for **2α** and **2β** (**3** and **4**, respectively) show that, in **2β**, H-1,2 are each antiparallel to an electronegative atom (O-2 and O-5, respectively). Consequently the observed small $J_{1,2}$ value (1.3 Hz) accords with previous observations of this phenomenon[16]. In **2α**, the higher value for $J_{1,2}$ (3.1 Hz) is accounted for by the fact that only H-2 is antiparallel to an oxygen atom.

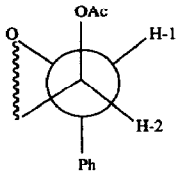
These observations, together with the fact that **2α** is the more dextrorotatory, confirm the assigned structures. The axial location of AcO-2 allows the $^4C_1$(D) conformation for **2α**. Moreover, the chemical shifts of the H-1 resonances in **2α** and **2β** accord

TABLE I

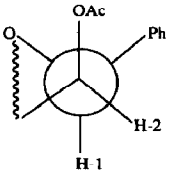
^{1}H-N.m.r. data (δ in p.p.m., J in Hz) for 2,3,4,6-tetra-*O*-acetyl-α- (1α) and -β-D-glucopyranosylbenzene (1β) and the α- (2α) and β-D-mannopyranosyl (2β) analogues

Compound	*Solvent*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*AcO*	*Ph*
1α	$CDCl_3$	5.35 (m)	5.35 (m)	5.60 (m)[a]	5.13 (dd)	3.73 (ddd)	4.29 (dd)	4.06 (dd)	2.00, 2.02 2.09, 2.10 (4 s)	7.28–7.45 (m, 3 H), 7.54–7.62 (m, 2 H)
				$J_{3,4}$ 7.7	$J_{4,5}$ 8.8	$J_{5,6a}$ 5.1	$J_{5,6b}$ 2.9	$J_{6a,6b}$ 12.2		
1α	$(CH_3)_2SO$	5.29 (d)	5.14 (dd)	5.22 (dd)	4.96 (dd)	3.93 (ddd)	4.38 (dd)	4.11 (dd)	1.86, 2.00 2.01, 2.08 (4 s)	7.24–7.40 (m)
		$J_{1,2}$ 3.7	$J_{2,3}$ 6.2	$J_{3,4}$ 6.2	$J_{4,5}$ 6.2	$J_{5,6a}$ 7.1	$J_{5,6b}$ 3.3	$J_{6a,6b}$ 12.2		
1α	CD_2Cl_2	5.29 (br. d.)	5.25 (dd)	5.45 (dd)	5.83 (dd)	3.86 (ddd)	4.32 (dd)	4.09 (dd)	1.95, 2.02 2.06, 2.10 (4 s)	7.28–7.43 (m, 3 H) 7.51–7.57 (m, 2 H)
		$J_{1,2}$ 4.6	$J_{2,3}$ 7	$J_{3,4}$ 6.9	$J_{4,5}$ 7.4	$J_{5,6a}$ 6.2	$J_{5,6b}$ 3.3	$J_{6a,6b}$ 12.1		
1β	$CDCl_3$	4.40 (d)	5.14 (dd)	5.35 (dd)	5.24 (dd)	3.84 (ddd)	4.28 (dd)	4.18 (dd)	1.80, 2.01 2.06, 2.09 (4 s)	7.34 (m)
		$J_{1,2}$ 9.8	$J_{2,3}$ 9.3	$J_{3,4}$ 9.3	$J_{4,5}$ 9.7	$J_{5,6a}$ 4.7	$J_{5,6b}$ 2.2	$J_{6a,6b}$ 12.3		
2α	$CDCl_3$	5.13 (d)	6.01 (dd)	5.17 (dd)	5.36 (dd)	3.77 (ddd)	4.38 (dd)	4.13 (dd)	2.02, 2.06 2.14, 2.17 (4 s)	7.3–7.55 (m)
		$J_{1,2}$ 3.1	$J_{2,3}$ 3.1	$J_{3,4}$ 9.1	$J_{4,5}$ 8.8	$J_{5,6a}$ 6	$J_{5,6b}$ 2.8	$J_{6a,6b}$ 12.2		
2β	$CDCl_3$	4.77 (d)	5.56 (dd)	5.27 (dd)	5.35 (dd)	3.82 (ddd)	4.34 (dd)	4.26 (dd)	1.92, 1.99 2.09, 2.10 (4 s)	7.32 (m)
		$J_{1,2}$ 1.3	$J_{2,3}$ 3.2	$J_{3,4}$ 9.8	$J_{4,5}$ 9.6	$J_{5,6a}$ 5.7	$J_{5,6b}$ 2.6	$J_{6a,6b}$ 12.2		

[a] The signal of H-3 comprised at least 9 lines.



3 (2α)



4 (2β)

with this assignment. As found for cyclohexane derivatives[17] and several *C*-glycopyranosyl compounds[18,19], the equatorial H-1 of **2α** (δ 5.13) is more deshielded than the axial H-1 of **2β** (δ 4.77).

Circular dichroism (c.d.) has been used frequently to detect differences in configuration and conformation, especially in cyclic molecules[20], including phenyl glycopyranosides and 1-thioglycopyranosides[21], for which α anomers gave positive Cotton effects and β anomers gave negative effects.

The c.d. curves for **1** and **2** are shown in Fig. 1 in the 250-nm region. The c.d. curve for **1β** shows a well-defined negative Cotton effect, whereas that for **1α** exhibits a positive Cotton effect, but the structure is not well defined, which accords with a conformational equilibrium for this compound (see above)[22]. The signs of these Cotton effects are identical to those for acetylated phenyl α- and β-D-glucopyranosides[23]. For **2α** and **2β**, both c.d. curves are well resolved, with a negative Cotton effect for the β anomer and a positive effect for the α anomer. Thus, modification of the configuration at C-2 on going from **1** to **2**, although close to the chromophore, does not affect the Cotton effect. For other *C*-glycosylated aromatic compounds[10,24], the sign of the Cotton effect was not influenced by changes in conformation nor by different substitution at C-3 and C-4. Therefore, the signs of the Cotton effect for **1** and **2** appear to be determined essentially by the anomeric configuration.

The ^{13}C-n.m.r. spectra of **1** and **2** are of interest in terms of a comparison of the chemical shifts and $J_{C\text{-}1,H\text{-}1}$ values with the corresponding data for the glycosides[25,26]. The data for **1** and **2** are assembled in Table II. The ^{13}C chemical shifts were assigned on the basis of the results of a heteronuclear shift-correlated 2D-n.m.r. experiment[27], and the C-3 and C-5 signals for **1α** were assigned on the basis of appropriate cross-sections along the ^{1}H dimension of the contour map.

Systematic shielding of C-1 was observed in comparison with the acetylated phenyl glycopyranosides[25]. According to the rule[28] for γ-effects, the signals for C-5 and C-1 appear at lower field for the β- than for the α-D anomer. These observations parallel those for the corresponding glycopyranosides[25,26] and accord with data for other *C*-glycopyranosyl compounds[29]. The $J_{C\text{-}1,H\text{-}1}$ values were smaller (10–12 Hz) for the β- than for the α-D anomers in the $^{4}C_{1}$ conformation, as observed for other *C*-glycopyranosyl compounds[29] and glycopyranosides[25,26].

Thus, the chemical shifts of C-1 and the $J_{C\text{-}1,H\text{-}1}$ values are of value for the stereochemical assignment of the anomeric configuration of *C*-glycopyranosyl compounds.

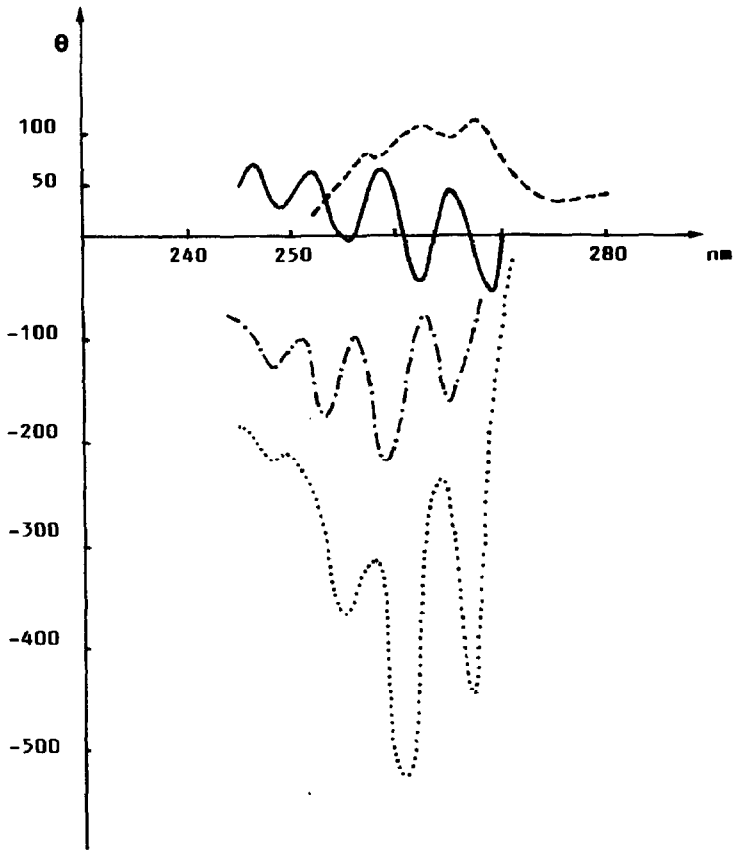


Fig. 1. C.d. spectra of **1α** (----), **1β** (-·-·), **2α** (—), and **2β** (····) recorded for solutions in aqueous 95% ethanol.

TABLE II

^{13}C-N.m.r. data (δ in p.p.m., $^{1}J_{C,H}$ values in Hz) for **1** and **2**

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
1β	80.22 (144)	72.71 (154)	74.30 (152)	68.67 (154)	76.16 (144)	62.37 (150)
1α	72.91[a] (156)	70.73[a] (152)	70.40 *b*	68.63 (153)	70.35 *b*	61.94 (148)
2β	78.09 (140)	70.54 (153)	72.36 (148)[c]	66.16 (155)[c]	76.28 (143)	62.86 (149)
2α	75.37 (150)	69.06 (152)	69.42 (151)[c]	66.79 (156)[c]	71.16 (145)[c]	62.18 (148)

[a] Assignments may be reversed. [b] $^{1}J_{C,H}$ not measurable (H strongly coupled). [c] Measured from the centre of a broad multiplet.

EXPERIMENTAL

General methods. — Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. N.m.r. spectra (internal Me_4Si) were recorded with a Bruker AM-250 instrument (^1H, 250 MHz; ^{13}C, 63 MHz). The chemical shifts of the ^{13}C resonances were measured from proton-decoupled spectra relative to internal $CDCl_3$ (77.0 p.p.m.). The $J_{C\text{-}1,H\text{-}1}$ values were measured on undecoupled spectra obtained with a gated-decoupling technique[30]. C.d. spectra were recorded with a Jobin et Yvon dichrograph III at room temperature with 1- or 2-cm cells on solutions (~0.6 mg/mL) in aqueous 95% EtOH. Elemental analyses were performed at the Service de Microanalyse of the Université P. et M. Curie. G.l.c. was performed with a Girdel 75 FD instrument fitted with a 1-m column of 3% of phenyldiethanolamine succinate (PDEAS) on Chromosorb WAW DMCS. T.l.c. was performed on Silica Gel $60F_{254}$ (Merck), using 2:1 ether–light petroleum (b.p. 40–65°). Silica Gel 40 (Merck, 70–230 mesh ASTM) was used for column chromatography with 1:1 ether–light petroleum.

A mixture of **1α** and **1β** was obtained, according to Bonner[5], by reaction of the acetylated glycosyl bromide with phenylmagnesium bromide and reacetylation. Crystallisation of the crude mixture from 2-propanol gave pure 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylbenzene (**1β**), m.p. 156–158°, $[\alpha]_D^{20}$ −20° (*c* 0.94, chloroform), R_F 0.36; lit.[5] m.p. 155–156°, $[\alpha]_D^{20}$ −18.6° (chloroform). Pure 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylbenzene (**1α**), obtained after column chromatography of the crude residue, was an oil, $[\alpha]_D^{20}$ +81° (*c* 0.93, chloroform), R_F 0.37; lit.[5] $[\alpha]_D$ +39.9° (chloroform). The purity of each anomer was verified by g.l.c. at 155° (*T* 15.4 min for **1β**, 14 min for **1α**).

Crystallisation from 2-propanol of the crude mixture of **2α** and **2β**, obtained by the above procedure[6], gave 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylbenzene (**2β**), m.p. 108–109°, $[\alpha]_D^{20}$ −23° (*c* 0.86, chloroform), *T* 17.8 min (at 155°), R_F 0.31; lit.[6] m.p. 107–108°, $[\alpha]_D$ −25.6° (chloroform).

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosylbenzene (**2α**), obtained by column chromatography, had m.p. 135–136° (from 2-propanol), $[\alpha]_D^{20}$ +53° (*c* 0.98, chloroform), *T* 14 min (at 155°), R_F 0.35; lit.[6] m.p. 139.5–140°, $[\alpha]_D$ +53.6° (chloroform).

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