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Preliminary communication

Conformational analysis of 6-deoxy-6-fluoro-D-glucopyranose, 6-deoxy-6-fluoro-D-galactopyranose, and 4-deoxy-4-fluoro-D-glucopyranose in solution by ^{1}H-n.m.r. spectroscopy

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The replacement of a hydroxyl group by fluorine in carbohydrates and carbohydrate-containing molecules modifies their chemistry and may affect recognition in biological processes. Although there has been extensive research[1] into the synthesis, biological testing, and conformational analysis of fluorinated carbohydrates, the relationship between conformation and biological activity is little understood. For instance, the role that hydrogen bonding plays in these compounds in solution is still unclear. The difference in hydrogen-bonding capability, where a hydroxyl group can be both a donor and an acceptor, whereas a fluorine substituent can act only as a weak acceptor, is significant in the solid phase[2]. X-Ray crystallography[3] showed O-6 to be antiperiplanar to H-5 in methyl 4-deoxy-4-fluoro-α-D-glucopyranoside, and antiperiplanar to C-4 in methyl α-D-glucopyranoside. The hydrogen-bonding pattern is different in these compounds in their crystalline state, but not necessarily so in solution.

We now report on the C-5–C-6 rotamer populations of 4-deoxy-4-fluoro-D-glucopyranose (4FGlc), 6-deoxy-6-fluoro-D-glucopyranose (6FGlc), and (6-deoxy-6-fluoro-D-galactopyranose (6FGal) based on ^{1}H-n.m.r. $J_{5,6}$ data for solutions in D_2O and either acetone-d_6 or Me_2SO-d_6.

In earlier work[4] on ^{19}F- and ^{1}H-n.m.r. spectroscopy of solutions of the tetraacetates of 6FGlc in chloroform, no rotamer populations were reported, but rotamer gg[†] was thought to be preferred, in accord with the preferred conformer of 5-fluoro-1,3-dioxane. Other work on 6FGlc in aqueous solution[5] involved a first-order, approximate analysis of the second-order ^{1}H-n.m.r. spectrum, the limitations of which have been

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[†] Several nomenclatures for staggered rotamers are to be found in the literature (see ref. 16), but they have all been converted into that now in 1–3. The first letter refers to the torsional angle O-5–C-5–C-6–X-6 (X = F or OH) and the second refers to C-4–C-5–C-6–X-6.

discussed[6].

We believe that this is the first reported analysis of the ^{1}H-n.m.r. spectra of 6FGal and 4FGlc. The second-order CH–CH$_2$X (X = OH or F) spin system has been analysed using the LAOCOON[7] or PANIC851[8] programs and the results are given in Table I. The probable errors are $< \pm 0.1$ Hz for δ and J. The r.m.s. error estimation is <0.1 Hz for all but one of the iterative calculations. The prochiral protons, H-6a and H-6b are assigned following the procedure of Nishida *et al.*[9]. The relative magnitude of $J_{5,6a}$ and $J_{5,6b}$ and *not* the δ values form the basis of the assignment, and the smaller coupling is assigned to $J_{5,6b}$.

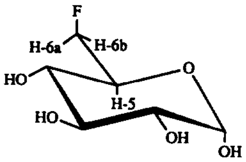
TABLE I

$^3J_{H,H}$ and $^3J_{H,F}$ values[a,b] associated with the C-5–C-6 bond in 6FGlc, 6FGal, and 4FGlc[a,b]

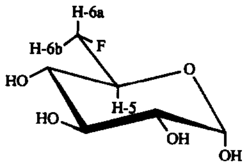
	$J_{5,6a}$	$J_{5,6b}$	*H-6a*	*H-6b*	*R.m.s. error for iterative calculation*	$J_{5,F}$
6FGlc						
D$_2$O[c]	3.60	1.77	1900.99	1864.70	0.012	29.0
Me$_2$SO[d]	4.81	1.47	1125.30	1119.67	0.049	27.7
6FGal[e]						
D$_2$O	7.78	3.49	1849.81	1866.82	0.025	16.6
Me$_2$SO	7.66	3.79	1765.80	1810.31	0.057	16.0
4FGlc[e]						
D$_2$O	5.1	2.1	1522.02	1636.20	0.255	–
Acetone	4.76	2.24	1464.56	1498.26	0.061	–

[a] For the α-pyranose form. [b] In Hz and obtained from 400-MHz spectra unless indicated otherwise. [c] Bruker AM-400 spectrometer. [d] Bruker WM250 spectrometer. [e] Bruker AMX-400 spectrometer.

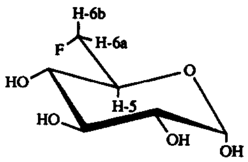
There are three non-equivalent rotamers for each compound as illustrated for 6FGlc (1–3). Thus, in order to ascertain the rotamer populations from the observed couplings, it is necessary to estimate the absolute couplings. The values used for 6FGlc and 6FGal are given in Table II and were obtained using the method of Abraham *et al.*[10]. Three sets of known[11–13] rotamer couplings were used for 4FGlc, also cited in Table II. The rotamer populations, P_{gg}, P_{gt}, and P_{tg}, which are the mole fractions (%) and are recorded in Table III, were obtained using standard equations[14]. For comparison, values for methyl α-D-glucopyranoside and methyl α-D-galactopyranoside are also given in Table III, together with energies relative to that of the most stable of the three staggered rotamers of each compound.



1(gg)



2(gt)



3(tg)

TABLE II

$^3J_{H,H}$ values for the rotamers about the C-5–C-6 bond in 4FGlc and 6FGlc/6FGal

	tg	*gg*	*gt*
4FGlc			
Method 1 (ref. 11)			
$J_{5,6a}$	5.0	0.9	10.7
$J_{5,6b}$	10.7	0.9	2.8
Method 2 (ref. 12)			
$J_{5,6a}$	5.8	1.3	11.5
$J_{5,6b}$	11.7	1.3	2.7
Method 3 (ref. 13)			
$J_{5,6a}$	3.8	1.4	10.5
$J_{5,6b}$	10.6	2.3	2.6
6FGlc/6FGal			
Method 4 (ref. 10)			
$J_{5,6a}$	5.4	−0.2	10.0
$J_{5,6b}$	10.0	1.7	3.5

TABLE III

Rotamer populations (%) and relative energies of the three staggered rotamers about the C-5–C-6 bond in 6FGlc, 6FGal, 4FGlc, and their non-fluorinated analogues[a]

	Rotamer populations (%)			*Relative energy (kcal/mol)*		
	P_{gt}	P_{gg}	P_{tg}	*gt*	*gg*	*tg*
6FGlc						
D_2O	42	66	−8	0.3	0	>2
Me_2SO	5	58	−15	0.01	0	>2
6FGal						
D_2O	76	19	5	0	0.8	1.6
Me_2SO	74	16	11	0	0.9	1.1
4FGlc						
D_2O	41	59	1	0.2	0	>2
Acetone	36	62	2	0.3	0	>2
Methyl α-D-glucopyranoside[a]						
D_2O	38	57	5	0.2	0	1.4
Me_2SO	47	53	0	0.1	0	>2
Methyl α-D-galactopyranoside[a]						
D_2O	47	14	39	0	0.7	0.1

[a] Unless indicated otherwise, calculated using the data of Table I.

Assisted by 2D homocorrelated experiments (COSY) and ^{1}H-n.m.r. difference spectra, it was possible to analyse the α- and β-pyranose forms for each sugar[15]. Crystalline 6FGlc and 6FGal exist as α-pyranose forms, whereas 4FGlc exists as the β-pyranose form. On dissolution, 6FGlc and 4FGlc mutarotated to give a mixture of the α- and β-pyranose forms, but 6FGal yielded a mixture of α- and β-pyranose and furanose forms at equilibrium.

The rotamer tg is particularly disfavoured for each sugar: 6FGlc $P_{gg} > P_{gt} \gg P_{tg}$, 6FGal $P_{gt} \gg P_{gg} > P_{tg}$, and 4FGlc $P_{gg} > P_{gt} \gg P_{tg}$. These trends were found for solutions in Me_2SO and H_2O and are independent[15] of the configuration at C-1. For methyl α-D-glucopyranoside, the trend $P_{gg} > P_{gt} \gg P_{tg}$, identical to those of 6FGlc and 4FGlc, has been reported$_9$. For methyl α-D-galactopyranoside, the trend $P_{gt} > P_{tg} \gg P_{gg}$ has been reported[9], so that, as for 6FGal, gt is the preferred conformation, whereas gg is the least favourable conformation.

1,3-*syn*-Diaxial interaction of HO-4,6 has been invoked to account for the unfavourable rotamers tg in D-glucopyranose and gg in D-galactopyranose. This interaction has been observed in crystallography studies[16] of cyclic and acyclic carbohydrates, but it is uncertain whether it is steric or dipolar in nature. It is similar to the steric interaction of 1,3-diaxial groups in cyclohexane structures, although modified in cyclohexane-*cis*-1,3-diol[17] by OH···O hydrogen bonding. Jeffrey[16] noted that the tg rotamer in the $^4C_1$-D-*gluco* and the gg rotamer in the $^4C_1$-D-*galacto* configurations are observed only where they are stabilised by intramolecular hydrogen bonding, as also concluded[18] for a solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol in the non-hydrogen bonding solvent 1,2-dichloroethane.

The unfavourability of the rotamer tg suggests the absence of any intramolecular hydrogen bonding involving the 4,6-substituents in 6FGlc, 6FGal, and 4FGlc. This situation is not surprising, since OH···F hydrogen bonding does not occur in solutions of 2-fluoroethanol[19]. The early work of Evelyn and Hall[4] on solutions in chloroform (poor hydrogen-bond donor) gave $J_{5,6a}$ and $J_{5,6b}$ values of 4.2 and 2.8 Hz, respectively, for the tetra-acetate of β-6FGlc, which suggest that the rotamer populations in $CHCl_3$ do differ significantly from those obtained here. These data correspond to 55% gg, 41% gt, and 4% tg, *cf.* (Table III) approximately 60% gg and 40% gt for a solution of α-6FGlc in water. Presumably, then, intramolecular hydrogen bonding plays little part in determining the conformation about C-5–C-6 in the tetra-acetate.

For solutions in Me_2SO, substitution of OH by F at C-6 (→ 6FGlc) leaves the distribution of rotamer populations unchanged. Since neither Me_2SO nor the CH_2F moiety are hydrogen-bond donors, intermolecular solvent–solute hydrogen bonding can play no part in determining the conformation about the C-5–C-6 bond in 6FGlc or methyl α-D-glucopyranoside.

The rotamer gt is more favourable than tg for 6FGal (76% *versus* 5% in H_2O, 74% *versus* 11% in Me_2SO) presumably because of a favourable interaction of F and O-5. For the $CH(OH)CH_2F$ moiety of 2-fluoro-1-(4-bromophenyl)ethanol in a solution in acetone[20], we found 66% gt, 24% gg, and 10% tg, where the gt rotamer has the F *gauche* to OH. This finding reinforces the notion of a favourable interaction of the C–F and C-5–O bonds in 6FGal, the so-called *gauche*-effect[21]. The overall attractive interaction of small electronegative atoms, particularly F and O, in cyclic and acyclic compounds has been observed in many compounds[22]. The fact that substitution of HO-6 by fluorine leaves the distribution of rotamers unchanged in D-glucopyranose, and the value of P_{gg} remains small for D-galactopyranose, is consistent with the notion that there is a 1,3-*syn*-diaxial interaction of HO-4 and F-6. Since the fluorine atom has approximately the same steric volume as hydrogen, this repulsion is probably dipole oriented.

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