Note

Fluorinated carbohydrates
Part XV[1]. 2,3,6-Tri-*O*-acetyl-4-deoxy-4-fluoro-α- and β-D-galactopyranosyl fluoride: observations on ^5J ^{19}F–^{19}F coupling

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The conformation of pyranoid carbohydrates can be defined with reasonable precision on the basis of ^1H–^1H coupling constants obtained by n.m.r. spectroscopy[2]. It therefore follows that, for fluorinated derivatives, the steric relationship of a secondary fluorine substituent to most if not all of the protons and to other fluorine substituents in the same molecule can also be defined. Thus, fluorinated carbohydrates are of particular value in studying the sign and configurational dependence of long-range (^4J and ^5J), ^1H–^{19}F and ^{19}F–^{19}F couplings. Data on vicinal[3] and ^4J ^{19}F–^{19}F couplings[4] for certain fluoro sugar derivatives have been recorded, and we now report on ^5J couplings.

The four possibilities for ^5J F–F coupling in the hexopyranose series involve derivatives having two fluorine substituents attached to the pairs of carbon atoms 1–4, 1–6, 2–5, and 3–6. Only the first two categories have been exemplified (2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α- and β-D-glucopyranosyl fluoride[5] and 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α and β-D-glucopyranosyl fluoride[6]). Of particular interest are the 1,4-difluorides as, in appropriate examples, the two fluorine substituents can be attached to a conformationally homogeneous pyranoid ring and permit the study of the geometrical dependence of ^5J couplings. Pyranoid 1,6-difluorides are of limited value, as the F–F couplings are averaged values resulting from a mixed rotamer population about the C-5–C-6 bond. Pyranoid 3,6-difluorides, which are presently unknown, would be subject to the same limitations and the 2,5-difluorides, also unknown, are synthetically inaccessible.

We now report on 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α- (**1**) and β-D-galacto-pyranosyl fluoride (**2**) which, together with the *gluco* analogues described recently[5], comprise a complete set of *ax* and *eq* variations of two fluorine substituents attached to positions 1 and 4 in conformationally homogeneous pyranoid derivatives.

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Treatment of 4-deoxy-4-fluoro-D-galactose[7] with pyridine–acetic anhydride at room temperature gave the $\alpha\beta$-tetra-acetate from which the β-anomer crystallised. Reaction of the $\alpha\beta$-tetra-acetate with hydrogen fluoride at $-10°$ gave the α-fluoride **1**. When the $\alpha\beta$-tetra-acetate was treated in sequence with hydrogen bromide–acetic acid and silver fluoride–acetonitrile the β-fluoride **2** was obtained.

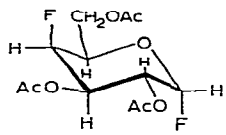
The vicinal H–H and F–H coupling constants recorded in Table I for **1** and **2** are consistent[9,10] with the $^4C_1$(D) chair conformations depicted in the formulae.

TABLE I

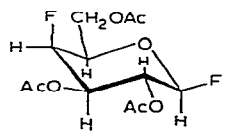
VICINAL[a] H–H AND F–H COUPLING CONSTANTS IN HZ FOR 2,3,6-TRI-*O*-ACETYL-4-DEOXY-4-FLUORO-α (**1**) AND β-D-GALACTOPYRANOSYL FLUORIDE (**2**)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$[b]	$J_{F-1,2}$[c]	$J_{F-4,3}$	$J_{F-4,5}$
1	+2.3	9.9	+2.5	<0.5	+24	+25.4	28±1
2	+6.7	10.5	+2.5	1.0	+9.6	+25.6	25.2

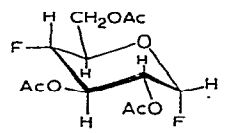
[a]The following long-range couplings were also observed: **1** $J_{F-4,2}$, 2.8; $J_{F-4,6}$, <1; $J_{F-4,6'}$, <1; $J_{F,F}$, −3.7 Hz; **2** $J_{F-1,4}$, −2.5; $J_{F-4,1}$, 0.8; $J_{F-4,2}$, 1.3; $J_{F-4,6} = J_{F-4,6'} = 1.0$; $J_{F,F}$, −1.3 Hz. [b]The low values of $J_{4,5}$ are typical of galactopyranose derivatives[8]. [c]*cf.* $J_{F,2}$ 22.2 and 10.0 Hz, respectively, for solutions of 2,3,4,6-tetra-*O*-acetyl-α and β-D-galactopyranosyl fluoride[9] in $CDCl_3$.



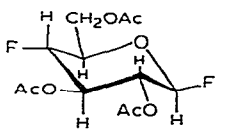
1 ($J_{F,F}$ −3.7 Hz)



2 (−1.3 Hz)



3 (−0.6 Hz)



4 (+3.1 Hz)

2,3,6-Tri-*O*-acetyl-4-deoxy-4-fluoro-α (**3**) and β-D-glucopyranosyl fluoride (**4**) have also been shown[5] to exist in the $^4C_1$ (D) conformation. Thus, compounds **1–4** comprise a complete set of *ax* and *eq* variations with respect to the two fluorine substituents, and show $^5J_{F,F}$ couplings as follows: **1** (F-1/F-4, *ax,ax*), −3.7; **2** (*eq,ax*), −1.3; **3** (*ax,eq*) −0.6; and **4** (*eq,eq*), +3.1 Hz.

Because of the large distance separating the two fluorine substituents in compounds **1–4**, the ^5J coupling is probably manifest through the intervening bonds with a minimal through-space contribution. A through-space contribution may be possible in $^4J_{F,F}$ couplings when the fluorine substituents are in *syn*-axial positions, where the distance of separation is near to the sum of the van der Waals radii (*cf.* ref. 11). For a series of 3-deoxy-3-fluoropyranosyl fluorides[4] the following $^4J_{F,F}$ values have been reported: *ax,ax*, +10.4; F-1*ax*, F-3*eq*, +1.0; and *eq,eq*, −3.0 Hz. Whereas maximal ^4J H–H and F–H couplings apparently are associated with a planar, W-arrangement of the intervening bonds, this is clearly not true for F–F coupling, and the unusually large *ax,ax* coupling may be due to a through-space effect.

The factors that determine the magnitude and sign of $^5J_{F,F}$ couplings are largely unknown. Most literature examples[12] of $^5J_{F,F}$ coupling involve a pathway containing a π-bond, whereas only σ-bond pathways (F–C–C–C–C–F and F–C–C–O–C–F) are available for $^5J_{F,F}$ coupling in the 1,4-difluorides **1–4**. The effect of introducing an oxygen atom into a ^5J coupling pathway has not been determined. The magnitude of the $^4J_{H,H}$ coupling is increased in this way[13] and probably $^4J_{F,H}$ coupling[14] but, as far as we are aware, no example of $^4J_{F,F}$ coupling has been reported involving a planar, W-arrangement of the bonds F–C–O–C–F. Data on the σ-bond pathway F–C–C–C–C–F should be obtainable from 1,4-difluoro-1,4-dideoxyinositols, a class of compound not yet exemplified.

An extension of the planar, W-arrangement of the intervening bonds associated with maximal through-bond ^4J couplings is not essential for maximal $^5J_{F,F}$ coupling. Although the two C-F bonds in each of the 1,4-difluorides **1–4** lie approximately in the same plane, the intervening bonds lie outside this plane. Maximal $^5J_{F,H}$ coupling is probably associated with a *trans*-coplanar relationship of the coupled nuclei to the bond that is the mid-point of the coupling pathway[13]. A situation apparently more complex is associated with $^5J_{F,F}$ couplings, as magnitudes can be similar (*e.g.* for **1** and **4**), but the signs opposite. Thus, for the β-D-*gluco*-1,4-difluoride **4** ($J_{F,F}$ +3.1 Hz) each fluorine substituent is *trans* to the mid-point bonds (C-5–O-5, C-2–C-3), whereas for the α-D-*galacto*-1,4-difluoride **1** ($J_{F,F}$ −3.7 Hz) the orientations are *gauche*. The remaining 1,4-difluorides, **2** and **3**, each have one *trans* and one *gauche* arrangement.

It is clear that n.m.r. data on a much wider range of examples will be needed before the stereospecificity of ^5J couplings can be defined.

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were obtained for ~1% solutions in chloroform by using a Perkin–Elmer 141 polarimeter. N.m.r. data were determined for solutions in $CDCl_3$–CCl_3F–Me_4Si (16:3:1, v/v) by using a modified Varian HA-100 spectrometer operating in the locked frequency-sweep mode at 94 MHz for ^{19}F resonances and at 100 MHz for ^1H resonances. Conventional decoupling and spin-tickling techniques were used to establish the origin and signs of couplings.

*1,2,3,6-Tetra-*O*-acetyl-4-deoxy-4-fluoro-β-*D*-galactopyranose.* — Conventional treatment of 4-deoxy-4-fluoro-D-galactose[4] (1.42 g) with pyridine–acetic anhydride at room temperature gave the syrupy $\alpha\beta$-tetra-acetate (2.37 g). Crystallization from ethanol–light petroleum (b.p. 60–80°) gave the β-anomer, m.p. 119–121°, $[\alpha]_D$ +28° (Found: C, 48.3; H, 5.4; F, 5.8. $C_{14}H_{19}FO_9$ calc.: C, 48.0; H, 5.5; F, 5.4%).

N.m.r. data: ϕ_c 217.4 p.p.m., $J_{1,2}$ 8.0, $J_{2,3}$ 10.0, $J_{3,4}$ +2.5, $J_{4,5}$ <1.0, $J_{F,1}$ 0.8, $J_{F,3}$ +26.5, $J_{F,5}$ 25.0, $J_{F,6}$ 1.0, $J_{F,6'}$ 1.0 Hz. These data establish the β-configuration and are consistent with the $^4C_1$ (D) conformation.

*2,3,6-Tri-*O*-acetyl-4-deoxy-4-fluoro-α* (**1**) *and β-*D*-galactopyranosyl fluoride* (**2**). — (*a*) The foregoing $\alpha\beta$-tetra-acetate (0.88 g) was treated[5] with anhydrous hydrogen

fluoride (10 ml) for 20 min at −10°. After a further 15 min at room temperature the mixture was poured into water (50 ml). Extraction with chloroform and neutralization in the usual manner gave a syrupy product (0.61 g) that crystallized from ether–light petroleum (b.p. 60–80°) to give **1**, m.p. 92–93°, $[\alpha]_D$ +112° (Found: C, 46.7; H, 4.9; F, 12.2. $C_{10}H_{14}F_2O_6$ calc.: C, 46.4; H, 5.2; F, 12.3%).

(*b*) A solution of the foregoing αβ-tetra-acetate (1.03 g) in a 45% solution (5 ml) of hydrogen bromide in acetic acid was stored for 2 h at room temperature. Concentration of the reaction mixture at 30°/0.5 mmHg gave the syrupy α-glycosyl bromide, a solution of which in acetonitrile (10 ml) was stirred with silver fluoride (15 g) for 1 h at room temperature. The filtered mixture was concentrated and the residue was eluted from Kieselgel (Merck, 7734) with 1:1 ether–light petroleum (b.p. 60–80°). Concentration of the appropriate fractions and crystallisation of the resulting syrup (0.48 g) from the foregoing solvent mixture gave **2**, m.p. 88–89°, $[\alpha]_D$ +11° (Found; C, 46.1; H, 5.3; F, 12.6%).

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