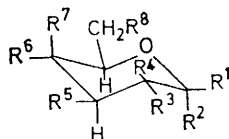# The Carbon-13 Nuclear Magnetic Resonance Spectra of the Deoxyfluoro-D-glucoses, 2-Deoxy-2-fluoro-D-mannose, and 4-Deoxy-4-fluoro-D-galactose. Orientational and Substituent Effects upon $^nJ_{FC}$

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A detailed study has been made of the ^{13}C n.m.r. spectra of the anomeric pairs of the deoxyfluoro-D-glucopyranoses, 2-deoxy-2-fluoro-D-mannopyranose, and 4-deoxy-4-fluoro-D-galactose. The variation in $^1J_{FC}$ with the electronegativity of α-substituents is rationalised by consideration of literature data and by the use of a procedure used previously to rationalise ^{19}F chemical shifts. $^2J_{FC}$ is less dependent upon the electronegativity of substituents attached to the coupled fragment but it shows a marked dependency upon the orientation of substituents bonded to the coupled carbon. $^3J_{FC}$ and $^4J_{FC}$ show marked dependencies upon the orientation of the coupled nuclei, and in the former the orientation of substituents upon the coupled fragment is important. INDO MO calculations reproduce the trends in both $^3J_{FC}$ and $^4J_{FC}$, and rationalise the long-range J_{FH} data obtained previously for these systems. ^{13}C Shifts are discussed briefly.

NUCLEAR magnetic resonance studies have given valuable information about the conformation and configuration of carbohydrates in solution, and the rigid

		R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
(I)	β	F	H	OH	H	OH	OH	H	OH
(II)	α	H	OH	F	H	OH	OH	H	OH
	β	OH	H	F	H	OH	OH	H	OH
(III)	α	H	OH	OH	H	F	OH	H	OH
	β	OH	H	OH	H	F	OH	H	OH
(IV)	α	H	OH	OH	H	OH	F	H	OH
	β	OH	H	OH	H	OH	F	H	OH
(V)	α	H	OH	OH	H	OH	OH	H	F
	β	OH	H	OH	H	OH	OH	H	F
(VI)	α	H	OH	H	F	OH	OH	H	OH
	β	OH	H	H	F	OH	OH	H	OH
(VII)	α	H	OH	OH	H	OH	H	F	OH
	β	OH	H	OH	H	OH	H	F	OH

nature of the heterocyclic ring has proved a useful framework for the study of the orientational dependence of substituent effects. In particular the extensive studies of Hall and his co-workers [1] of the pyranosyl and

furanosyl fluorides provided important information about the angular dependence of J_{FH} and J_{FF} values. Similarly our earlier work [2,3] on the ^{19}F n.m.r. of the deoxyfluoro-D-glucopyranoses showed the importance of substituent orientation and electronegativity upon J_{FH} values and ^{19}F chemical shifts.

The poor understanding of the effects of substituents upon J_{FC} values and the sparsity of data for rigid systems suggested that a ^{13}C n.m.r. study of the fluorocarbohydrates was needed. We report here a ^{13}C n.m.r. study of 1-deoxy-1-fluoro-D-glucose, (I), and of the anomeric pairs of 2-deoxy-2-fluoro-, (II), 3-deoxy-3-fluoro-, (III), 4-deoxy-4-fluoro-, (IV), and 6-deoxy-6-fluoro-D-glucose, (V), 2-deoxy-2-fluoro-D-mannose, (VI), and 4-deoxy-4-fluoro-D-galactose, (VII).

EXPERIMENTAL

Spectra were recorded on both a Varian XL-100-12 spectrometer and a Varian CFT-20 spectrometer, both operating in the Fourier transform mode at 25.16 and 20.0 MHz respectively. Each instrument was locked to the deuterium resonance of the D_2O solvent and controlled with Varian 620-L computers. Parameters were chosen to give 12 K transforms for sweep widths of 5 000 Hz (XL-100) and 8 K transforms for sweep widths of 4 000 Hz

[1] L. D. Hall, P. R. Steiner, and C. Pedersen, *Canad. J. Chem.*, 1970, **48**, 1155, and previous papers.

[2] L. Phillips and V. Wray, *J. Chem. Soc. (B)*, 1971, 1618.

[3] L. Phillips and V. Wray, *J.C.S. Perkin II*, 1974, 928.

(CFT-20), which gave a resolution of better than 0.3 and 0.4 Hz respectively by the use of centroid interpolation routines.[4]

Samples of each carbohydrate (100—200 mg/2 ml) were dissolved in D_2O and allowed to come to anomeric equilibrium. Noise-decoupled and single-frequence off-resonance proton decoupled spectra (SFORD) were obtained at 36 ± 2 °C in 10-mm sample tubes with external $SiMe_4$ as reference. Triple-irradiation experiments were performed on the XL-100 by the introduction of a selective ^{19}F frequency into the decoupling coils during the observation of $^{13}C\{^{1}H\}$ spectra. The corresponding signals were generated with a Schomandl ND 100 M frequency synthesizer and amplified with an ENI 310L RF power amplifier.

Signal Assignments.—In solution, the deoxyfluoropyranoses exist in anomeric equilibria,[2] hence at first it is necessary to distinguish the ^{13}C signals for each anomer.

25.2 and 20.0 MHz allowed J_{FG} values to be measured and hence shifts could be determined unambiguously.

The ^{13}C chemical shifts and J_{FG} values for compounds (I) to (VII) are given in Tables 1 and 2, respectively. The chemical shifts of D-glucose (VIII), D-mannose (IX), and D-galactose (X) are included for comparison purposes, and their assignments were taken from the literature.[5-9] Solvent effects upon the shifts were tested with (VIII). The results for this compound in 2.2M-solution and at infinite dilution (Table 1) indicate that only small changes of <0.17 p.p.m. occur on going to infinite dilution.

The assignment of the signals for the individual anomers is given below. In each case C-6 was distinguished by its multiplicity in the SFORD experiment while carbon bonded to fluorine was distinguished by the large $^{1}J_{FG}$ and its characteristic low-field shift. Carbon β to the fluorine-bearing carbon were distinguished by the characteristic magnitude of their couplings.[1,11]

TABLE 1

^{13}C Chemical shifts of fluoropyranoses (I)—(VII) and pyranoses (VIII)—(X) in D_2O (p.p.m.). Referenced to external $SiMe_4$

*Compound	α-Anomer 1	2	3	4	5	Carbon 6	β-Anomer 1	2	3	4	5	6
(I) a							110.48	74.38	76.05	70.30	77.30	61.69
b							106.28	71.29	71.87	67.55	72.14	61.86 ‡
(II)	90.86	91.47	72.37	70.41	72.49	61.61	94.74	94.14	75.27	70.53	77.26	61.80
(III)	93.45	71.20	96.23	69.14	72.00	61.41	96.41	73.84	97.75	69.14	65.81	61.58
(IV)	93.18	72.24	72.27 §	90.47	70.14 §	61.22	97.14	74.94	75.02 §	90.29	72.27 §	61.37
(V)	93.47	72.63	73.86	69.81	71.54	83.65	97.28	75.26	76.81	69.68	75.63	83.47
(VI)	92.54	91.63	70.68	68.12	73.55	61.84	93.57	92.58	73.09	67.88	77.34	62.00
(VII)	93.58	69.59	69.20 §	91.73	70.48 §	61.30	97.42	73.08	72.82	90.81	74.77	61.13
(VIII)†	93.31	72.71 §	73.99	70.89	72.67 §	61.84	97.14	75.37	76.99 §	70.84	77.16 §	61.99 (i)
	93.43	72.82 §	74.13	71.01	72.76 §	62.01	97.23	75.49	77.10 §	70.96	77.23 §	62.15 (ii)
(IX)	95.26	71.93	71.48	68.10	73.64	62.21	94.90	72.45	74.29	67.86	77.38	62.21
(X)	93.52	70.40 §	69.59	70.55 §	71.70	62.40	97.70	73.13	74.05	69.98	76.36	62.21

* Compounds are: 1-deoxy-1-fluoro-, (I), 2-deoxy-2-fluoro-, (II), 3-deoxy-3-fluoro-, (III), 4-deoxy-4-fluoro-, (IV), and 6-deoxy-6-fluoro-D-glucose, (V), 2-deoxy-2-fluoro-D-mannose, (VI), 4-deoxy-4-fluoro-D-galactose, (VII), D-glucose, (VIII), D-mannose, (IX), and D-galactose, (X). † (i) Shifts extrapolated to infinite dilution; (ii) shifts in 2.2M-solution. ‡ Tetra-acetate in $CDCl_3$ with internal $SiMe_4$; CH_3 resonances at 20.65 and 20.53 p.p.m. in the ratio 1 to 3, and CO resonances at 170.53, 170.01, 169.29, and 169.11 p.p.m. § Resonances in horizontal line are not unambiguously assigned.

In the present work, triple-irradiation experiments were carried out for compounds (III) and (IV), in which the third irradiating frequency was positioned at the β-anomer and α-anomer fluorine frequencies respectively. This caused the collapse of the fluorine splittings for these signals and hence distinction could be made between the signals for the two anomers. This technique is only applicable when the fluorine shifts are sufficiently far apart, and thus it could not be used for compounds (II) and (V). For these compounds and for (VI) and (VII) the difference in the anomer proportions at equilibrium[2] made the identification of their signals possible by careful measurement of peak intensities.

Secondly the coupling of the fluorine to most of the carbons and the similarity of their chemical shifts makes the identification of their J values and hence shifts extremely difficult when spectra at only one field strength are observed. In the present investigation comparison of spectra at

Assignments.—*Compounds* (Ia) *and* (Ib). Only C-3, C-4, and C-5 of (Ia) and (Ib) remain to be assigned. Comparison with C-4 in glucose and β-D-glucose penta-acetate,[12] respectively, identified C-4, while C-3 was assigned the larger of the two $^{3}J_{FG}$ values by comparison with the other $^{3}J_{FGCG}$ values (see below). The shifts of these two compounds have been assigned previously by Bock and Pedersen,[13] whose shifts and couplings differ significantly from those found in the present work. Careful comparison with this work indicated that their use of results at only one field strength led them to choose the wrong peaks for the coupled carbons. Rearrangement of the reported values for β-D-glucosyl fluoride tetra-acetate gave figures in agreement with the present work. Some of the apparent inconsistencies in the values of the $^{3}J_{FG}$ values must arise from this fact and emphasises the danger of using only one field strength for the identification of fluorine-coupled nuclei with similar ^{13}C chemical shifts.

Compounds (II), (III), (IV), *and* (V). The remaining

[4] L. Ernst and D. N. Lincoln, *J. Magnetic Resonance*, 1974, **16**, 190, 1975, **17**, 272.

[5] L. D. Hall and L. F. Johnson, *Chem. Comm.*, 1969, 509.

[6] D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, 1970, **92**, 1355.

[7] A. S. Perlin, B. Casu, and H. J. Koch, *Canad. J. Chem.*, 1970, **48**, 2596.

[8] W. Voelter, V. Bilik, and E. Breitmaier, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2054.

[9] P. A. J. Gorin, *Canad. J. Chem.*, 1974, **52**, 458.

[10] J. B. Stothers, ' Carbon-13 NMR Spectroscopy,' Academic Press, London, 1972.

[11] J. B. Grutzner, M. Jautel, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1970, **92**, 7107.

[12] D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 4463.

[13] K. Bock and C. Pedersen, *Acta Chem. Scand.*, 1975, **B29**, 682.

resonances of (II) (C-4 and C-5), (III) (C-2, C-4, and C-5), and (V) (C-2, C-3, and C-4) were assigned by comparison with D-glucose. For compound (IV) the resonance of C-2 in the α- and β-anomers of (IV) has been assigned to give a consistent β-effect although not unambiguously.

Compounds (VI) *and* (VII). The remaining resonances of (VI) (C-4 and C-5) and (VII) (C-2, C-3, and C-5) were assigned by comparison with D-mannose and D-galactose respectively.

RESULTS AND DISCUSSION

Our earlier ^{1}H and ^{19}F n.m.r. investigation[2] suggested that all the structures studied here have the $^{4}C_{1}$(D) conformation of the pyranose ring in deuterium oxide. This was not unexpected as Lemieux[14] has shown that

3.6] with those of the glycopyranosyl fluorides[13] (13 compounds; $^{1}J_{FC}^{av}$ 224.6 ± 3.8) and 6-deoxyfluoro-glucoses [(Vα) and (Vβ); $^{1}J_{FC}^{av}$ 167.4 ± 0.3] indicates an increase in the magnitude of J with an increase in the electronegativity of the atoms attached to the coupled carbon. This is further verified by comparison with $^{1}J_{FC}$ in $CF_{2}CH_{2}OH$[18] where a further increase in electro-negativity causes an increase of $^{1}J_{FC}$ to 241 Hz. This result is in marked contrast to the observations in the work of Muller and Carr[19] where for the system $CF_{3}X$ an increase in the electronegativity of X causes a decrease in J_{FC}. There is no explanation from their work of the reversal in the effect of substituent electronegativity found here. However, we found a similar reversal in
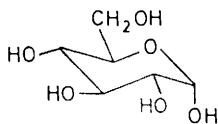
TABLE 2

J_{FC} Values of fluoropyranoses (I)—(VII) (Hz)

| Compound | α-Anomer (Carbon) | | | | | | β-Anomer (Carbon) | | | | | |
	1	2	3	4	5	6	1	2	3	4	5	6
(I) a							210.6	21.6	11.7	0	4.7	0
b							219.4	29.3	8.8	0	4.4	0
(II)	21.4	185.9	17.5	8.0	1.3	0	23.0	183.1	17.3	8.2	1.2	0
(III)	10.9	16.8	178.6	17.6	7.3	1.5	12.4	17.2	180.5	17.6	8.2	1.9
(IV)	1.4	8.3	17.6 §	179.9	23.9 §	0	1.4	8.8	18.0 §	180.0	24.5 §	0
(V)	0	0	0.7	6.6	17.2	167.2	0	0	0	6.9	18.7	167.6
(VI)	29.6	172.2	17.5	1.4	0	0	15.8	180.0	17.6	1.5	0	0
(VII)	0	2.2	17.6 §	177.0	17.6 §	5.5	0	1.1	18.0	177.7	17.3	5.5

Footnote: see Table 1.

strong proton-accepting solvents favour an equatorial disposition of hydroxy-groups. The $^{4}C_{1}$(D) structure is shown for α-D-glucose below.

CH₂OH / HO / HO / HO / OH

^{19}F–^{13}C *Spin–Spin Coupling Constants.*—The magnitudes of the J_{FC} values are given in Table 2. The complexity of the spectra made it impossible to determine the signs of the couplings. However, $^{1}J_{FC}$ has been shown, both experimentally[15] and theoretically,[16] to be absolutely negative, while $^{2}J_{FC}$ was found to be of opposite sign[17] to $^{1}J_{FC}$ in $CFCl_{2}CFCl_{2}$. The similarity of the $^{2}J_{FC}$ values in σ-bonded systems[5] suggests that all the $^{2}J_{FC}$ values here are positive. There is no evidence in the literature for the sign of the longer range J values.

$^{1}J_{FC}$.—An inspection of the values of $^{1}J_{FC}$ in Table 2 indicates that this J depends upon both the electro-negativity of the attached atoms on the coupled carbon and the orientation, with respect to the coupled fluorine, of substituents on adjacent carbons. A comparison of the average values of $^{1}J_{FC}$ for the 2-, 3-, and 4-deoxy-fluoropyranoses [(IIα), (IIβ), (IIIα), (IIIβ), (IVα), (IVβ), (VIα), (VIβ), (VIIα), and (VIIβ); J_{FC}^{av} 179.5 ±

the effect of substituent electronegativity upon the fluorine chemical-shifts in comparable systems.[20] This latter effect has been rationalised and quantified by the use of a simple perturbational approach to the calculation of these shifts which gives an equation involving only the electronegativities of the surrounding atoms.[20] The attempt of a similar approach here is, therefore, justified.

For the molecule $C_{ab}FX$ the variation in $^{1}J_{FC}$ for a change in the electronegativity of the substituent X, for the situation in which a and b are held constant, can be deduced from the limited amount of data in the literature;[4] this is shown in Table 3. From this Table it can be seen that the sensitivity of $^{1}J_{FC}$ to the change in the electronegativity of X is critically dependent upon the nature of a and b. A plot of the change in $^{1}J_{FC}$,ΔJ, per unit of change of the electronegativity of X against the sum of the electronegativities of a and b is shown in Figure 1.

It is seen that the carbohydrate data fit in well with the other data; a reversal is to be expected in the substituent effects at the sum of the electronegativities of a and b smaller than *ca.* 6. This cross-over point coincides with the corresponding point of 5.8 found for the reversal in the effect of substituent electronegativity changes upon fluorine chemical-shifts in similar molecules.[20]

The restricted amount of information precludes any

[14] R. U. Lemieux and A. A. Pavia, *Canad. J. Chem.*, 1969, **47**, 4441.
[15] R. A. Bernheim and B. J. Lavery, *J. Amer. Chem. Soc.*, 1967, **89**, 1279.
[16] G. E. Maciel, J. W. McIver, N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 11.

[17] G. V. D. Tiers, *J. Phys. Chem.*, 1963, **67**, 928.
[18] G. P. Van der Kelen and Z. Eeckhaut, *J. Mol. Spectroscopy*, 1963, **10**, 141.
[19] N. Muller and D. T. Carr, *J. Phys. Chem.*, 1963, **67**, 112.
[20] L. Phillips and V. Wray, *J. Chem. Soc.* (B), 1971, 2067.

quantitative evaluation of the data. Still, it is worth noting that the fluoromethane data ($\times$ in Figure 1) do not fit on to the same line as the other data. Again this is to be expected if comparison is made with the fluorine chemical-shift correlations.

TABLE 3

The variation of $^1J_{FO}$ (Hz) with substituent electronegativity,[a] E, for the molecule CabFX

Compound[b] and $^1J_{FC}$				$E_a + E_b$	$\dfrac{\Delta J}{\Delta E_x}$[c]
CF$_4$ 257	CF$_3$Cl 299	CF$_3$Br 324	CF$_3$I 344	7.80	−70.9
CF$_3$Cl 299	CF$_2$Cl$_2$ 325			7.05	−30.6
CF$_3$Br 324	CF$_2$Br$_2$ 358			6.85	−35.8
CF$_3$CH$_3$ 271	CF$_2$ClCH$_3$ 288			6.50	−22.7
CF$_2$Cl$_2$ 325	CFCl$_3$ 337			6.30	−14.1
CF$_2$Br$_2$ 358	CFBr$_3$ 372			5.90	−14.7
CF$_2$HCH$_2$OH 244	C–CFH–O 224.6	C–CFH–C 179.5	C–CFH$_2$ 167.4	4.80	+47.6

[a] Huggins electronegativity (M. L. Huggins, *J. Amer. Chem. Soc.*, 1953, **75**, 4123). [b] Data from ref. 4, except for the last entries which are from the present work (C–CFH–C and C–CFH$_2$) and from ref. 14 (C–CFH–O). [c] The slope of the line of $^1J_{FC}$ against E_x in Hz per unit of Huggins electronegativity.

chemical-shift correlations. The differences in geminal interaction constants involving hydrogen and those for other atoms [20] are to be expected, and this would lead to the divergence from the line shown. Indeed an approach to the problem by Malinowski,[21] in which $^1J_{FO}$ values are calculated from constants involving
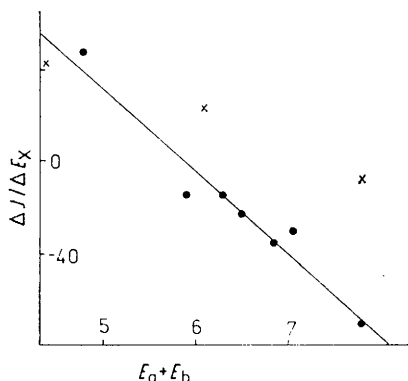

FIGURE 1 Plot of $\Delta J/\Delta E_x$ against $E_a + E_b$ for $^1J_{FC}$ in CabFx: $\times$ = points for CF_nH$_{4-n}$

pairwise interaction between substituents, does indicate that interactions involving hydrogen are quite different from those involving other atoms.

The effect of the orientation of β- and longer-range substituents upon $^1J_{FO}$, for situations in which the electronegativity of the α-atoms are held constant, can be seen from the results for the 2-, 3-, and 4-deoxyfluoro-pyranoses [(IIα), (IIβ), (VIα), (VIβ), (IIIα), (IIIβ), (IVα), (IVβ), (VIIα), and (VIIβ)] in Table 2, where $^1J_{FO}$ covers the range 172.2 to 185.9 Hz. Only certain orientational effects can be discerned from these data. If the orientation of the fluorine is changed from a

gauche-orientation (with respect to the ring oxygen) to a *trans*-orientation, the magnitude of $^1J_{FO}$ increases by 2.8 ± 0.3 Hz [(VIβ) to (IIβ), (VIIα) to (IVα), and (VIIβ) to (IVβ)], while just the opposite effect occurs when only the orientation of a β-hydroxy-group is changed from a *gauche*- to a *trans*-orientation with respect to the fluorine; here a decrease in the magnitude of $^1J_{FO}$ by 7.8 Hz occurs [(VIβ) to (VIα)]. Thus a simple orientational dependence of $^1J_{FO}$ upon β-substituents is not apparent because of the possibly complex nature of the mutual interactions between the polar functions in the molecule.

$^2J_{FO}$.—There is not such a pronounced dependency of $^2J_{FO}$ upon the electronegativity of the atoms attached to the coupled fragment as there was for $^1J_{FO}$; although there is a much greater effect upon J of the orientation of groups with respect to the coupled fluorine. Thus J for the fragment C–CHF·CHOH–O (i) has values between 15.8 and 29.6 Hz, which overlaps the ranges of the other fragments C–CHF·CHOH–C (ii) and CFH$_2$·CH(C)–O (iii). For (ii) there are 14 J values in Table 2, where the oxygen function on the coupled carbon is *gauche* to the coupled fluorine and their magnitudes are constant at 17.5 ± 0.3 Hz. The change to a *trans*-orientation of the oxygen function, for (ii), causes an increase in magnitude to 24.2 ± 0.4 Hz. For (i) a similar trend is observed on going from the *gauche* orientation of 2-deoxyfluoro-β-mannose [(VIIβ) 15.8 Hz] to 2-deoxyfluoro-β-glucose [(IIβ) 23.0 Hz], while a *trans*-hydroxy-group has a larger effect than the *trans*-ring oxygen, as is clear from the value of $^2J_{FO}$ for 2-deoxy-2-fluoro-α-mannose [(VIIα) 29.6 Hz]. A similar orientational dependency is apparent in the fluoropyranosyl acetates [13] for the fragment O–CHF·CHO·COCH$_3$–C where the $^2J_{FO}$ in β-glucopyranosyl fluoride of 29.3 increases to 39.7 Hz in α-mannopyranosyl fluoride.

Thus in summary the following effects of electronegative substituents upon $^2J_{FO}$ have been observed. (a) The general effects of changing the electronegativity of substituents upon the coupling fragment appear to be smaller than for $^1J_{FO}$ and are masked by the following effect. (b) For a particular fragment, $^2J_{FO}$ increases with the change of an electronegative substituent bonded to the coupled carbon from a *gauche* to a *trans*-orientation with respect to the fluorine involved in the coupling.

$^3J_{FO}$ and $^4J_{FO}$.—The effects of substituent changes and orientation upon $^3J_{FO}$ and $^4J_{FO}$ are shown in Table 4 and Figure 2 respectively. At least three effects are indicated from the values of $^3J_{FO}$. An increase in the electronegativity of the substituents upon the coupled carbon or carbon attached to the fluorine causes a small increase in $^3J_{FO}$ [cf. (ia) with (iv) and (ii)]. A much larger effect is observed, however, for a change in the orientation of the coupled nuclei, thus a change from a *trans*-orientation to a *gauche* one results in a large decrease in the magnitude of the coupling [(ia) ⟶ (ib)

[21] E. R. Malinowski and T. Vladimiroff, *J. Amer. Chem. Soc.*, 1964, **86**, 3575.

and (ii) ⟶ (iii)]. An effect of a similar magnitude is observed if the relative position of the coupled nuclei are held constant but the orientation of an oxygen substituent attached to the middle carbon of the coupling

used to calculate these long-range J values by the approach developed by Blizzard and Santry.[22] Standard geometries [23] have been used, except for the C–O bond distance (1.54 Å) in the pyran and ether calculations,

TABLE 4

Orientational dependence of $^3J_{FC}$

	Orientation	$^3J_{FC}$ Values	$^3J_{FC}^{av.}$
(i)	(a) F-*trans*-C	8.2, 8.0, 7.3 8.2, 8.3, 8.8	8.1
	(b) F-*gauche*-C	1.5, 1.4, 1.1 2.2	1.6
(ii)	F-*trans*-C	12.4, 10.9	11.7
(iii)	F-*gauche*-C (a) F-*trans*-O ring (b) F-*gauche*-O ring	0, 0 5.5, 5.5	0 5.5
(iv)	F-*trans*-C	11.7	
(v) FCH₂·CHOᵣ·CHOH.C		6.9, 6.6	6.8

Oᵣ refers to the ring oxygen.

pathway changes with respect to the coupled fluorine. Thus a change of 5.5 Hz occurs between the J values of the fluorine to C-6 in the 4-deoxy-4-fluoroglucoses and 4-deoxy-4-fluorogalactoses [(iiia) and (iiib)].
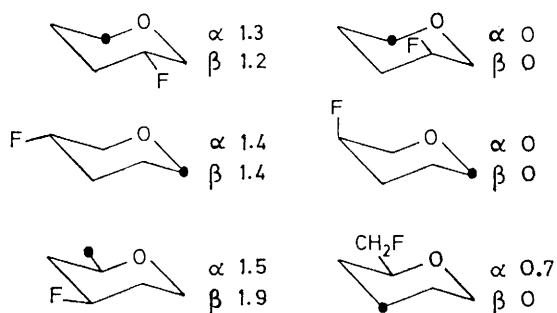
α 1.3 β 1.2

α 0 β 0

α 1.4 β 1.4

α 0 β 0

α 1.5 β 1.9

α 0.7 β 0

FIGURE 2 $^4J_{FC}$ in compounds (II), (III), (IV), (V), and (VII)

The $^4J_{FC}$ values depend markedly on orientation. Thus equatorial fluorines in all positions except at C-1 show observable J values while their axial isomers do not.

In order to clarify these effects SCF perturbation theory at the INDO level of approximation has been

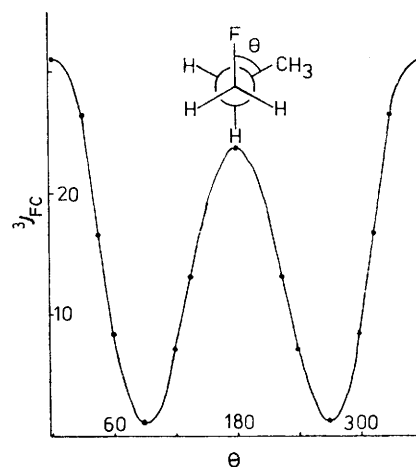which was used in order to maintain a standard chair conformation.

FIGURE 3   Angular dependence of $^3J_{FC}$ in FCH₂·CH₂·CH₃

The results for model compounds that describe $^3J_{FC}$ are given in Table 5 and Figures 3 and 4. 1-Fluoropropane was used to simulate the angular dependence of

[22] A. C. Blizzard and D. P. Santry, *J. Chem. Phys.*, 1971, **55**, 950.

[23] J. A. Pople and M. S. Gordon, *J. Amer. Chem. Soc.*, 1967, **89**, 4253.

$^3J_{FC}$ and the results for the Fermi-contact term are plotted in Figure 3. The J is predicted to be positive (of opposite sign to $^1J_{FC}$), to be dominated by the contact term and to show an angular dependence similar to that found for $^3J_{HH}$ and $^3J_{FH}$. These calculations

$^3J_{FC}$ values of *exo*-2-fluoronorbornane [12] of 2.3 (C-4), 9.3 (C-6), and 1 Hz (C-7) with dihedral angles of 242°, 191°, and 84° respectively lend further support to the form of the curve.

The orientational effects of an oxygen substituent

TABLE 5

INDO MO calculations of $^3J_{FC}$ and $^4J_{FH}$ for model systems related to the glucopyranose system

(i) Angular dependence of $^3J_{FC}$ in 1-fluoropropane

		Contributions to J/Hz			
θ°	Fermi-contact	Orbital	Dipolar	Exp.§	
0	31.00	0.12	0.26		
30	26.41	−1.74	−0.09		
45	16.58	−0.24	0.00		
60	8.38	−0.14	−0.02	1.6, 0, 5.5	
90	0.89	0.07	−0.02		
120	7.17	0.05	−0.11		
135	13.02	−0.02	0.00		
150	18.53	−0.10	0.24		
180	23.71	−0.19	0.59	8.1, 11.7, 11.7	
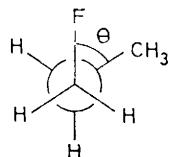
(ii) Dependence of $^3J_{FC}$ upon the orientation of the β-hydroxy-group in 1-fluoro-2-hydroxypropane

0	3.17	0.06	−0.09	
30	1.00	0.06	−0.01	
60	9.56	−0.15	−0.02	5.5
90	23.74	−0.19	0.09	
120	27.28	0.11	0.22	
150	19.89	−0.16	0.06	
180	5.72	−0.07	−0.01	
210	1.54	0.10	−0.03	0
240	9.26	0.06	−0.11	
270	18.53	−0.09	0.25	
300	19.31	−0.17	0.54	
330	11.56	−0.09	0.19	
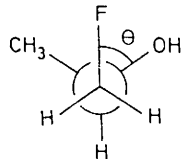
(iii) $^3J_{FC}$ and $^4J_{FH}$ in 3-fluoro-1-hydroxypyran and 1-fluoropyran

$^3J_{FC(1)}$	20.22	0.06	0.62	11.7
$^3J_{FC(5)}$	19.65	−0.05	0.60	8.1
$^4J_{FH(5eq)}$	4.30			3.9
$^4J_{FH(5ax)}$	−1.70			0.5
$^3J_{FC(3)}$	18.48	0.01	0.57	11.7
$^3J_{FC(5)}$	5.49	−0.10	0.74	4.7
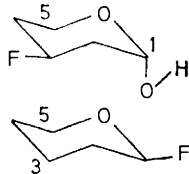
Footnotes to Tables 5 and 6: § See text for discussion and clarification. Only the magnitudes of the couplings are known; see ref. 2 for $^4J_{FH}$ and $^5J_{FH}$.

clearly rationalise qualitatively the results observed here; thus the *trans* $^3J_{FC}$ value is calculated to be considerably larger than the *gauche* $^3J_{FC}$ one. The
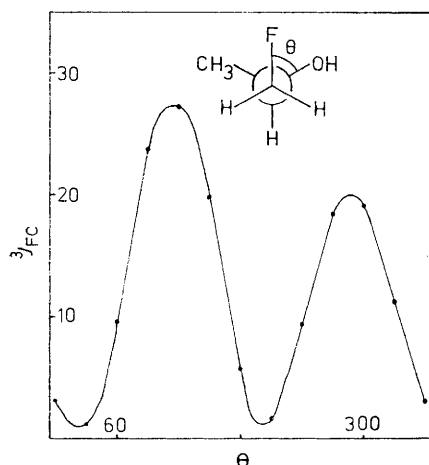

FIGURE 4 Angular dependence of $^3J_{FC}$ in $FCH_2 \cdot CHOH \cdot CH_3$

attached to the β carbon were simulated with 1-fluoro-2-hydroxypropane, in which the OH bond was *trans* to the C(1)–C(2) bond; the results are shown in Figure 4. Again the observed effect is calculated correctly, although the calculated magnitude of the difference in the J values between (iiia) and (iiib) (60° and 180° in Figure 4) is critically dependent upon small deviations from the idealised geometry. The apparent * decrease in $^3J_{FC}$ found for the coupling across the ring oxygen in β-glucopyranosyl fluoride compared to the coupling to C-3 is reproduced by the INDO calculations on 1-fluoropyran.

The calculations for 3-fluoro-1-hydroxypyran in the conformation shown (Table 5) exhibit only a small difference in $^3J_{FC}$ values which underestimates the effect of an increase in the electronegativity of substituents on the coupled carbon, although the J values are in the correct order.
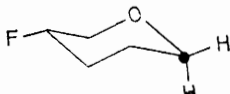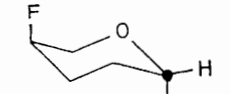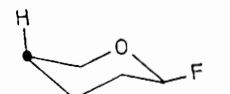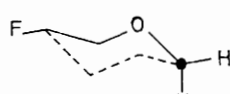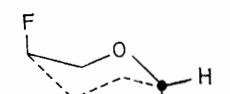
* These observations rely upon the correct assignment of C-3 and C-5 in β-glucopyranosyl fluoride. The similarity of the *trans*-vicinal couplings across the carbon framework for the other compounds justified this assignment.

The relevant compounds used in the calculation of $^4J_{FC}$ are shown in Table 6. The orientational dependence is clearly reproduced, with an equatorial fluorine showing a much larger J value than its axial counterpart. The reduction in $^4J_{FC}$ for β-glucopyranosyl fluoride is predicted, although the decrease is too small. These same calculations also reproduce the trends found in our earlier work on $^4J_{FH}$ and $^5J_{FH}$ values in these systems.[2] Thus the difference in $^4J_{FH}$ for the α- and β-anomers of 3-deoxy-3-fluoroglucose of 3.9 and 0.5

'through' oxygen pathway is there a significant $^5J_{FH}$ and $^4J_{FC}$ that reproduces the experimental trend. Thus the presence of the oxygen is necessary not only to increase the magnitude of the J but also to reproduce its orientational dependence.

In most of the calculations above the magnitudes of the calculated J values are approximately a factor of two too large. These depend upon the numerical value of the nuclear shell s-electron densities [$s^2(0)$] for the Fermi-contact term and upon the expectation value of

TABLE 6

INDO MO calculations of $^4J_{FC}$ and $^5J_{FH}$ for model systems related to the glucopyranose system

| | | Contributions to J/Hz | | | |
		Fermi-contact	Orbital	Dipolar	Exp.§
	$^4J_{FC}$	−3.55	0.01	0.03	1,4, 1.4
					1.2, 1.3
	$^5J_{FH(eq)}$	6.00			3.5
	$^5J_{FH(ax)}$	0.71			0
	$^4J_{FC}$	−0.96	−0.04	0.01	0, 0
					0, 0
	$^5J_{FH(eq)}$	0.59			0
	$^5J_{FH(ax)}$	0.06			0
	$^4J_{FC}$	−2.09	−0.01	−0.04	0
	$^5J_{FH(ax)}$	0.79			0
	$^4J_{FC}$	−0.31	−0.02	0.00	§
	$^5J_{FH(eq)}$	0.47			
	$^5J_{FH(ax)}$	0.44			
	$^4J_{FC}$	−0.46	0.01	0.01	§
	$^5J_{FH(eq)}$	0.23			
	$^5J_{FH(ax)}$	0.06			
	$^4J_{FC}$	−1.77	0.04	0.04	§
	$^5J_{FH(eq)}$	1.32			
	$^5J_{FH(ax)}$	0.13			
	$^4J_{FC}$	−0.66	0.00	0.00	§
	$^5J_{FH(eq)}$	0.35			
	$^5J_{FH(ax)}$	0.15			

Hz respectively, and the decrease of $^5J_{F(4)H'(1)}$ in 4-deoxy-4-fluoro-α-glucose of 3.5 to 0 Hz in 4-deoxy-4-fluoro-β-glucose are reproduced by these calculations. In our earlier work we suggested that the inclusion of the ring oxygen into one of the two possible pathways connecting the F and H for $^5J_{FH}$ could account for the significant size of this J. This appears to be substantiated by the calculations for 1-fluorobutane and 1-fluoroethyl methyl ether in conformations similar to those of a pyranose; the former reproduces the all-carbon pathway while the latter reproduces the 'through' oxygen pathway.

Comparison of the results shows that only for the

r^{-3} for the valence shell p-orbitals ($\langle r^{-3} \rangle$) for the orbital and dipolar terms. A decrease in $s^2(0)$ for fluorine by one half would give a better numerical fit with the present results.

Thus, in summary, the significant angular dependence of $^3J_{FC}$ and $^4J_{FC}$ and their dependence on the angular disposition of electronegative substituents is well reproduced by INDO MO calculations.

^{13}C *Chemical Shifts.*—The ^{13}C chemical shifts are listed in Table 1. Substituent chemical shifts (SCS), defined as the difference between the shift of a particular carbon in the deoxyfluoropyranose and the shift of the

same carbon in the parent pyranose, are given in Table 7. An analysis of these shifts in terms similar to those found for the J values was not possible, and only certain trends could be detected. The magnitudes of the

For compounds with the fluorine in a *trans*-arrangement with one of the β-oxygen functions (ring oxygen or hydroxy-group), the SCS was 19.08 ± 0.39 p.p.m. while for the *gauche*-arrangement the SCS was 21.02 ± 0.88
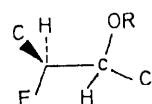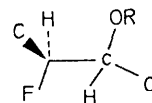
TABLE 7

Substituent chemical shifts in compounds (I)—(VII) (p.p.m.)

| Compound | α-Anomer | | | | | | Carbon | | β-Anomer | | | |
	1	2	2	4	5	6	1	2	3	4	5	6
(I)							13.34	−0.99	−0.94	−0.54	0.14	−0.30
(II)	−2.45	18.76	−1.62	−0.48	−0.18	−0.23	−2.40	18.77	−1.72	−0.31	0.10	−0.19
(III)	0.14	−1.51	22.24	−1.75	−0.67	−0.43	−0.73	−1.53	20.76	−1.70	−1.35	−0.41
(IV)	−0.13	−0.47	−1.72	19.58	−2.53	−0.62	0.00	−0.43	−1.97	19.45	−4.89	−0.62
(V)	0.16	−0.18	−0.13	−1.08	−1.13	21.81	0.14	−0.11	−0.18	−1.18	−1.53	21.48
(VI)	−2.72	18.91	−0.80	0.02	−0.09	−0.37	−1.33	20.13	−1.20	0.02	−0.04	−0.21
(VII)	0.06	−0.81	−0.39	21.18	−1.22	−1.10	−0.28	−0.05	−1.23	20.83	−1.59	−1.08

SCS's were similar to those found in the 6β-substituteds 5α-cholestane-3β,5-diols.[24] For the directly bonded carbon the lowest SCS was shown by C(1) of compound

TABLE 8

Dependence of the two-bond SCS's upon the orientation of oxygen substituents attached to the shifted carbon. (The number of values available are given in parentheses)

Fragment	Orientation of oxygen substituent	
	trans OR	*gauche* OR
	SCS (p.p.m.)	
	−3.73 ± 1.68 (2)	−1.43 ± 0.43 (14)
	−2.53 ± 0.17 (3)	−1.33 (1)

(I), the carbon with α-substituents of highest electronegativity. For the carbons with the same α-substituents two distinct groups of SCS's were apparent.

p.p.m. An orientational effect was also apparent for the two-bond SCS's and is shown in Table 8. For the longer range SCS's the small magnitude and variation in the SCS precludes any determination of the factors affecting the SCS.

Thus, in summary, the orientational dependence of substituent effects upon J_{FC} can be observed and rationalised over a large number of bonds. Although ^{13}C substituent chemical shifts were observed for all carbons the complexity of the factors affecting these precludes any detailed discussion.

[24] J. W. Blunt, *Austral. J. Chem.*, 1975, **28**, 1017.