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CONFIGURATIONAL DEPENDENCIES OF ^{19}F-SHIFTS IN FLUOROMONOSACCHARIDES*

P. W. KENT, R. A. DWEK and N. F. TAYLOR

Dept. of Biochemistry. Oxford University, U.K. and Biochemistry Group. University of Bath, U.K.

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Abstract—Examination of a series of fluoromonosaccharides indicates that the ^{19}F-chemical shifts (with reference to $CFCl_3$) show some structural dependencies. Values ($\pm$2 ppm) were F(1) + 152 to +156 ppm; F(2) = 211 to +215; F(6) + 229 to +230 and OCF_3(1) +60 to +61. F(3) in pyranoses show two sets of resonances +194 and +200 to +202, attributed to the β & α-anomers respectively.

INTRODUCTION

IN RECENT years, there has been considerable explorations of the ^{19}F-nuclear magnetic resonance properties of a variety of fluorinated compounds (reviewed by Mooney[2,3]). In general ^{19}F-chemical shifts ($\varnothing_c$) are at least an order of magnitude greater than the corresponding proton ones. This is assumed to result from the paramagnetic terms in the expression for nuclear shielding which are significant in the case of ^{19}F, but are negligible for protons because of the much larger excitation energies required. Superconducting solenoids are currently under development to explore further the intricacies of complex proton spectra from consequently enhanced chemical shifts and from improved signal-to-noise ratio at these higher magnetic fields (>50KG). Such techniques will also allow more detailed ^{19}F-measurements to be made, chiefly through strengthened signal response.

With existing techniques however, useful information regarding the extent of configurational dependence of $\varnothing_c$ can be undertaken, with a view to exploring new fluorine-containing probes of biological structure. Fluorocarbohydrates and their derivatives offer an attractive field for such investigations. In principle, each hydroxyl group may be replacable by fluorine on account of their similar size and with minimal disturbance of the stereochemistry of the molecule. Such compounds can be expected to be convenient magnetic resonance probes for structure determination, since ^{19}F-parameters are considerably more sensitive to environment than those of protons. Using ^{19}F-NMR techniques, evidence of specific binding of N-fluoroacetyl-α-D-glucosamine to lysozyme has already been obtained.[4]

Preliminary communications[5] have been made of $\varnothing_c$ for F(1) and F(2) for a number of fluorocarbohydrates. Here we have slightly revised some of the earlier values and have extended the investigation to F(3) in the pyranose and furanose series as well as to F(6) of the pyranose series. Several ^{19}F-coupling constants are also reported.

DISCUSSION

Inspection of the available results (Table 1) suggests that, while it would be premature to draw far-reaching conclusions, ^{19}F-chemical shifts show some consistencies

* Fluorocarbohydrates.[1] Part XXIII.

TABLE 1. VALUES FOR ^{19}F-CHEMICAL SHIFTS ($\emptyset_c$) IN DIFFERENT RING POSITIONS OF FLUOROMONOSACCHARIDES AT 33°† (ppm, with reference to $CFCl_3$)

Compound	Solvent	$\emptyset_c$F(1)	$\emptyset_c$F(2)	$\emptyset_c$F(3)	$\emptyset_c$F(6)	$\emptyset_c(OCF_3(1))$
I	C	153	212	—	—	—
II	C	—	211	—	—	60
III	C	156	215	—	—	—
IV	C	—	214	—	—	61
V	C	156	212	—	—	—
VI	C	—	212	—	—	60
VII	C	152	212	—	—	—
VIII	C	—	214	—	—	61
IX	D	—	—	197*	—	—
X	W	—	—	194, 200	—	—
XI	W	—	—	194, 200	—	—
XII	W	—	—	197·5, 202	—	—
XIII	C	—	—	188	—	—
XIV	C	—	—	203	—	—
XV	W	—	—	—	230	—
XVI	C	—	—	—	229	—
XVII	W	—	—	195, 199	—	—
XVIII	C	—	—	194	—	—
XIX	D	—	—	194	—	—
XX	C	—	—	194	—	—
XXI	C	—	—	205	—	—
XXII	R	—	—	209·8	[F(5) 231·5]	

* (±2 ppm)

† TFA—$CFCl_3$ = 78 ppm (All values positive). Solvents: C, chloroform; W, water; D, D_2O; R, CCl_4

in relation to the different positions of F-substitution. Thus, axial fluorine at position 1 gives values for $\emptyset_c$ in the range 152–158 ppm, F(2 equatorial) 212–215 ppm, F(6) 228–230 ppm and —OCF_3, as an aglycone 60 ppm, with no coupling to ring positions. Further measurements are required to establish whether these shifts are uniformly characteristic of each given ring position environment, before the technique may be used diagnostically. Potentially the method offers a powerful means of specific stereochemical determination. Hitherto, the only chemical shifts reported[15,20] for F(3) gave a value of +208 ppm (*cf* +205 ppm, 33 in the present investigation) for 3-deoxy-3-fluoro-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (XXI, in $CHCl_3$) and 209·8 ppm for 3,5-dideoxy-3,5-fluoro-1,2-*O*-isopropylidene-D-xylose (XXII, in CCl_4). With pyranose sugars (X, XI, XII), chemical shifts for F(3) pose a problem in that two resonances are observed (Table 1). This may be accounted for in a number of ways, including pyranose-furanose equilibrium and/or the equilibrium between β- and α forms, each anomer having a distinctive influence on fluorine at position 3. The relative areas of the resonance peaks indicates that about 50% of each "form" is present, and each resonance gives similar coupling constants with protons on adjacent positions (X, Table 2).

In the 3F-hexopyranose derivatives (XIX, XX) only one set of resonances at lower field are observed in the region +194 to +195 ppm, and these are provisionally

TABLE 2. SOME TYPICAL VALUES FOR ^{19}F—^{1}H COUPLING CONSTANTS (Hz)

Compound I		Compound II		Compound III	
F(2e)-H(2a) = 47	F(1a)-H(1e) = 53	F(2e)-H(2a) = 47		F(2e)-H(2a) = 47	F(1a)-H(1e) = 53
F(2e)-F(1a) = 20	F(1a)-F(2e) = 20	F(2e)-H(3a) = 11·3		F(2e)-F(1a) = 19	F(1a)-F(2e) = 19
F(2e)-H(3e) = 12	F(1a)-H(2a) = 23	F(2e)-H(1e) = 0·5		F(2e)-H(3e) 4	F(1a)-H(2a) = 25

Compound IV	Compound VI	Compound XIII	Compound X ($\varnothing_c$194)	Compound X ($\varnothing_c$200)
F(2e)-H(2a) = 46	F(2e)-H(2a) = 46	F(3)-H(3) = 46	F(3e)-H(3a) = 55	F(3e)-H(3a) = 57
F(2e)-H(1e) = 6	F(2e)-H(1e) = 6	F(3)-H = 7	F(3e)-H(2) = 13	F(3e)-H(2a) = 13·6
F(2e)-H(3e) = 0	F(2e)-H(3a) = 8	F(3)-H = 10	F(3e)-H(4) = 13	F(3e)-H(4a) = 12·6

Compound XIV	Compound XV	Compound XVIII
F(3)-H(3) = 56	F(6)-H(6) = 54	F(3e)-H(3a) = 57·5 ± 3
F(3)-H(4) = 24	F(6)-H(5a) = 19	F(3e)-H(2a) = 15 ± 3
F(3)-H(2) = 15		F(3e)-H(4a) = 15 ± 3

ascribed to the β-anomeric form. Nevertheless the 3F-α-guloside (IX) has value of $\varnothing_c$ +197 (±2 ppm). Further studies are in progress to detect signals resulting from pyranose-furanose equilibria.

In the furanoside series, $\varnothing_c$ for F(3) in 3F-di-isopropylidene-α-D-glucose[15] is +205 ppm and is reported as +209·8 ppm in 3,5-dideoxy-3,5-difluoro-1,2-isopropylidene-α-D-xylofuranose.[20] In the latter, $\varnothing_c$ for the extracyclic position F(5) is +231·5 in close agreement with $\varnothing_c$ for the corresponding fluorine F(6) in hexopyranoses. However in the substituted 3F-β-xylofuranoside (XIV), $\varnothing_c$ is at +203 and with the 3-F-α-arabofuranoside $\varnothing_c$ is at substantially lower field. Further investigations are required before it is possible to draw conclusions from these observations. Available evidence from detailed NMR studies of 5-deoxy-5-iodo[16]- and 5-deoxy-5-fluoro-D-xylose[17] indicates considerable possibility of ring deformation in these compounds.

Under high resolution examination of 2F-glycosyl fluorides, the resonances of F(2) were found to be much broader than F(1), possibly owing to the additional spin–spin couplings to F(2) of a long-range nature. There is as yet however no adequate theory for the interpretation of such postulated effects. Alternatively, the spin–spin relaxation times of F(2) may be much shorter than those for F(1) owing to greater environmental constraints at the former position. Fig 1 illustrates this observation for the 2F-lyxosyl-β-D-fluoride (III). Similarly, it has been noted that the resonances at higher field in F(3) sugars are markedly broader than these at the lower field.

Table 2 gives values of some of the measured spin–spin coupling constants. It is noticeable that, in the pyranose series the *gem* coupling constants J(F(a)—H(e)) are greater (*J* 53 Hz) than the values J(F(e)—H(a)) (*J* 46 Hz) when F is equatorically disposed. Otherwise, the coupling constants have expected values, noting that the

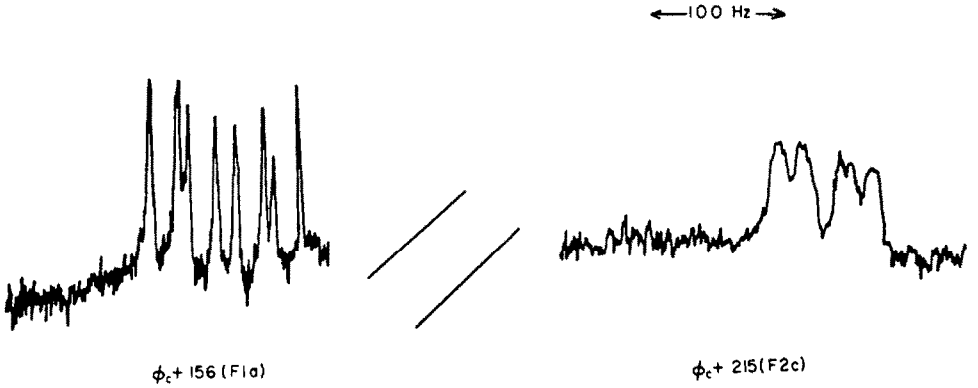

FIG 1. [^{19}F] NMR resonances at 94·05 MHz shown by 3,4-di-O-acetyl 2-deoxy-2-fluoro-β-D-lyxosyl fluoride ($CHCl_3$). Signals at low field ($\varnothing_c$ +156) ascribed to F(1) and at $\varnothing_c$ 215 to F(2)

magnitude of the coupling constants of F to adjacent protons is generally in the order *trans* diaxial > axial-equatorial > equatorial-equatorial. Though this is the order predicted by the Karplus equation it should not be assumed axiomatically that this equation is directly applicable to F—H coupling constants.[18]

Although it is not appropriate to apply the terms axial and equatorial to substituent groups in the furanose series, nevertheless the *gem* coupling constants indicate that in the 3F-arabinofuranoside (XIII), the fluorine environment approximates to axial, and to equatorial in the 3F-xylofuranoside (XIV).

Other coupling constants have not been fully assigned and it is planned to investigate proton spectra at 350 MHz to obtain further information.

EXPERIMENTAL

NMR *measurements.* ^{19}F-measurements were made on a JEOL (Model JNM-4H-100) spectrometer operating at 94 MHz and 33°C. Chemical shifts were measured relative to trifluoroacetic acid (TFA) as external standard, using a field sweep with a range of 90 ppm. The technique entailed putting concentrically, a thin capillary containing TFA into the normal 5 mm (external diameter) NMR tube. The tubes could be spun if required. Spectra including side bands were recorded using a 4 KHz modulation and shifts were measured from the *upper* side band of TFA to the respective resonances all at higher field, at an estimated error of ±2 ppm. ^{19}F-coupling constants were measured with a frequency sweep over a range of 9 ppm. In these cases samples were spun. Values are subject to an error of ±2 Hz. This relatively large error arises from a low signal to noise ratio and to inherent drift in the spectrometer.

Gas-liquid chromatography. Retention times (Tm) were determined using a Pye 104 Chromatograph Model 24 with an 8′ column of Diatoport-S-80-100 mesh (Hewlett-Packard) with 3%-SE30 (Applied Sciences Inc.), and an argon flow of 40 cm^3/min. The starting temperature and temperature gradient are given in each case. Acetylated or benzoylated sugars were analysed as such non-acetylated derivatives were converted to trimethyl-silyl ethers before analysis.

3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-2-*fluoro*-α-D-*galactosyl fluoride* (I).[5–7] m.p. 68–70°, $[\alpha]^{20}$ +130 (*c* 1, $CHCl_3$); Tm 13·5 min (140°, gradient 2°/min).

Trifluoromethyl 3,4,6-*tri*-O-*acetyl*-2-*deoxy*-2-*fluoro*-α-D-*galactoside* (II).[5–7] m.p. 53–55°. $[\alpha]_D^{25}$ +147° (*c* 0·5 $CHCl_3$) Tm 11·3 min (140° : 2°/min).

3,4-*Di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-β-D-*lyxosylfluoride* (III).[5,6] m.p. 109–111°; $[\alpha]_D^{25}$ −114 (*c* 0·5, $CHCl_3$) Tm 16·5 min (110° ; 2°/min).

Trifluoromethyl 3,4-*di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-β-D-*lyxoside* (IV).[5–7] Not cryst., chromatographically homogeneous $[\alpha]_D^{29}$ −120° (*c* 0·5, $CHCl_3$) Tm 15·2 min (110° ; 2°/min).

3,4-*Di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-β-D-*arabinosyl fluoride* (V).[8] Not cryst., chromatographically homogeneous $[\alpha]_D^{23}$ −176° (*c* 0·4, $CHCl_3$) Tm 13·5 min (120°; 2°/min).

Trifluoromethyl 3,4-*di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-β-D *arabinoside* (VI).[8] Not cryst., chromatographically homogeneous. $[\alpha]_D^{26}$ −226° (*c*. 1·03, $CHCl_3$); Tm 12·0 min (120°; 2°/min).

3,4-*Di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-α-D-*xylopyranosylfluoride* (VII).[5] Not cryst., Tm 14·0 min (110°; 2° min).

Trifluoromethyl 3,4-*di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-α-D-*xyloside* (VIII).[5] m.p. 150°; $[\alpha]_D^{24}$ +130° (*c* $CHCl_3$) Tm 13·0 min (110°; 2°/min).

Methyl 3-*deoxy*-3-*fluoro*-α-D-*guloside* (IX). This was synthesized[9] (Mr A. S. Harrison) from methyl 3,4-anhydro-2,6-di-*O*-benzyl-D-galactoside by the action of KHF_2 in MeCN. mp. 123°, $[\alpha]_D^{28}$ +146 (*c* 0·3, MeOH).

3-*Deoxy*-3-*fluoro*-α-D-*xylose* (*X*).[10] m.p. 126–128°; $[\alpha]_D^{25}$ +25·7 (*c* 1·7, H_2O), Tm 5·8 min.

3-*Deoxy*-3-*fluoro*-αβ-D-*glucose* (XI).[1, 11] m.p. 108°; $[\alpha]_D^{22}$ +64, (*c*, 1, H_2O) Tm 14·2; 16·9 min.

3-*Deoxy*-3-*fluoro*-β-D-*arabinose* (XII).[10, 12] 120° $[\alpha]_D^{20}$ −105° (equilib. c 1, H_2O) Tm, 5·95; 6·40 min.

Methyl 2,5-*di*-O-*benzoyl*-3-*deoxy*-3-*fluoro*-α-D-*arabinofuranoside* (XII).[12] m.p. 81°, Tm 40 min (120°, 2°/min).

Methyl 2,5-*di*-O-*benzoyl*-3-*deoxy*-3-*fluoro*-β-D *xylofuranoside* (XIV).[12] m.p. 68; $[\alpha]_D^{22}$ (*c* 1, EtOH) Tm 4·9 min (120°; 2°/min).

Methyl 6-*deoxy*-6-*fluoro*-α-D-*galactoside* (XV).[13] m.p. 139°; $[\alpha]_D^{20}$ +194 (*c*, 0·1 H_2O).

Methyl 2,3,4-*tri*-O-*acetyl*-6-*deoxy*-6-*fluoro*-α-D-*galactoside* (XVI).[14] m.p. 74°, $[\alpha]_D^{20}$ +152 (*c* 1, $CHCl_3$).

Methyl 3-*deoxy*-3-*fluoro*-αβ-D-*glucosides* (XVII). Obtained by treatment of XI with methanolic HCl.

Benzyl 2,4,6-*tri*-O-*acetyl* 3-*deoxy*-3-*fluoro*-β-D-*glucopyranoside* (XVIII).[1] m.p. 104°, $[\alpha]_D^{19}$ −62° (*c*, 1 $CHCl_3$).

Benzyl 3-*deoxy*-3-*fluoro*-β-D-*glucopyranoside* (XIX).[1] m.p. 93° $[\alpha]_D^{20}$ −50° (*c* 1, EtOH).

Tetra-O-*acetyl*-3-*deoxy*-3-*fluoro*-β-D-*glucose* (XX).[19] m.p. 119° $[\alpha]_D^{20}$ −12° (*c* 1·9, $CHCl_3$).

1,2:5,6-*Di*-O-*isopropylidene*-3-*deoxy*-3-*fluoro*-α-D-*glucofuranose* (XXI).[15] b.p. 65–70°/0·03 mm, $[\alpha]_D^{25}$ −20° (*c* 1, $CHCl_3$).

3,5-*Dideoxy*-3,5-*difluoro*-1,2-*isopropylidene*-α-D-*xylofuranose* (XXII).[20] b.p. 112–114°/10 mm, $[\alpha]_D^{20}$ −23° (*c* 2, $CHCl_3$).

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