FLUORINATED CARBOHYDRATES.

PART XIV[1]. 3-DEOXY-3-FLUORO-L-IDOSE; THE USE OF ^{19}F RESONANCE DATA TO PROBE A MUTAROTATIONAL EQUILIBRIUM AND THE CONFORMATION OF THE COMPONENTS THEREOF

A. B. FOSTER, R. HEMS, AND J. H. WESTWOOD

Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, Fulham Road, London SW3 6JB (Great Britain)

AND J. S. BRIMACOMBE

Chemistry Department, The University, Dundee (Great Britain)

(Received May 19th, 1972; accepted July 31st, 1972)

ABSTRACT

Mild treatment of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose with acid gave 3-deoxy-3-fluoro-L-idose (**2–3**) as a syrup. Under more vigorous acid conditions, **2–3** was converted into crystalline 1,6-anhydro-3-deoxy-3-fluoro-β-L-idopyranose, the structure of which was confirmed by the n.m.r. data on the 2,4-diacetate. A solution of 3-deoxy-3-fluoro-L-idose in H_2O or D_2O at equilibrium showed four ^{19}F resonances, which were assigned to the α- and β-pyranose and furanose forms, and the proportions of which correspond closely to those observed for D-idose. From the F-H splittings of the appropriate ^{19}F resonances, the conformation of each pyranose form was deduced.

INTRODUCTION

The configuration and conformation of fluorinated carbohydrates can be investigated by ^{19}F n.m.r. spectroscopy under conditions (*e. g.* aqueous solutions) where detailed study of ^{1}H resonances may be more difficult. In addition to vicinal F-H coupling, long-range (^{4}J and ^{5}J) couplings[2] may occur and be particularly informative. Thus, significant coupling between F/H-1 occurs only in the α-anomers of 3-deoxy-3-fluoro-D-glucopyranose (^{4}J) and the 4-fluoro analogue (^{5}J), so that signal intensities and splitting patterns of ^{19}F resonances can be used[3] to study mutarotation, and the anomeric composition of these fluoro sugars in aqueous solution at equilibrium. The anomeric equilibrium of D-glucose in aqueous solution is not markedly affected[3] by the presence of a fluorine substituent severally at positions 2, 3, 4, and 6, and only the α- and β-pyranose forms are significant contributors to the mutarotational equilibria of these compounds; the 4-fluoro compound cannot form furanoid structures.

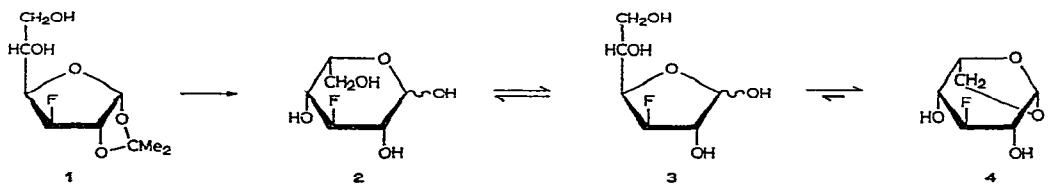
We have now extended this study to 3-deoxy-3-fluoro-L-idose, an aqueous solution of which at mutarotational equilibrium contains furanose and pyranose forms.

RESULTS AND DISCUSSION

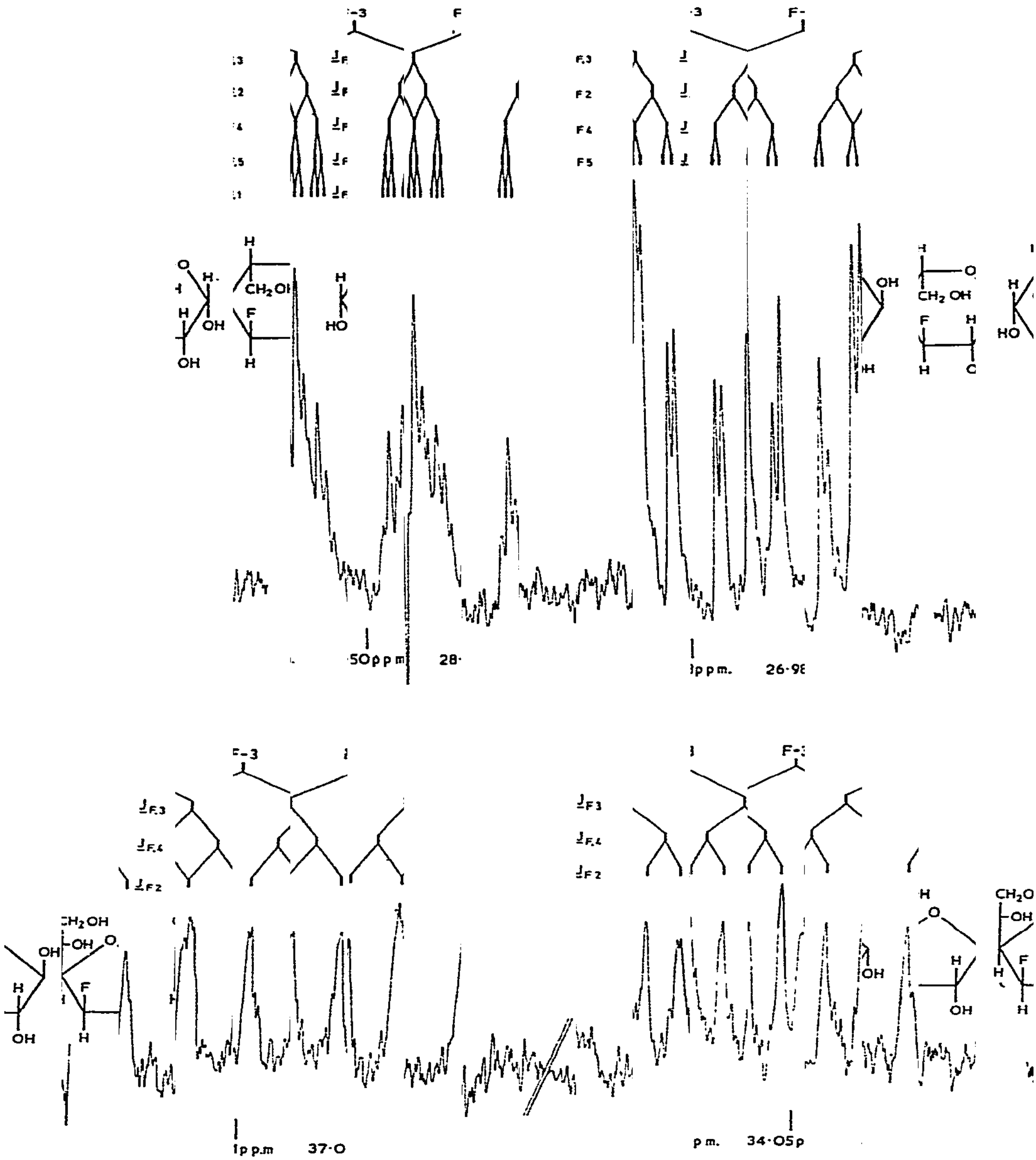
3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose, a suitable precursor of 3-deoxy-3-fluoro-L-idose, has been synthesised[4] from 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose by a sequence involving two inversions of configuration at C-3. Recently, a more convenient synthesis of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (**1**) by inversion of configuration at C-5 in 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[5] was devised[6], making 3-deoxy-3-fluoro-L-idose reasonably accessible.

When an aqueous solution of **1** containing a suspended cation-exchange resin (H^+ form) was maintained at 100°, monitoring by t.l.c. revealed the sequential formation of 3-deoxy-3-fluoro-L-idose (**2–3**) and its 1,6-anhydride **4**. By the appropriate adjustment of conditions, >80% of **2–3** or **4** could be obtained. When 3-deoxy-3-fluoro-L-idose was equilibrated with the 1,6-anhydride **4** under similar acidic conditions at 100°, acetylation of the product mixture followed by chromatography gave 2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-3-fluoro-β-L-idopyranose and a mixture of tetra-acetates of 3-deoxy-3-fluoro-L-idose in the molar ratio 100: ~7. Although the starting material was not accounted for quantitatively, it is probable that a greater proportion of 1,6-anhydride is formed than from L-idose[7] under similar conditions (molar ratio 100: ~22; 80.5% of 1,6-anhydride).

3-Deoxy-3-fluoro-L-idose was not obtained crystalline, but the structure expected by the route of synthesis was confirmed by the following n.m.r. data for the 2,4-di-acetate of the 1,6-anhydride **4**; $J_{1,2}$ 2, $J_{2,3}$ 8, $J_{3,4}$ 8, $J_{4,5}$ 4.5 $J_{5,6endo}$ ~0, $J_{5,6exo}$ 4.5, $J_{6endo,6exo}$ 8, $J_{F,1}$ 4.5, $J_{F,2}$ 16, $J_{F,3}$ 50, $J_{F,4}$ 16.5, $J_{F,6}$ 4.5 Hz. The values of $J_{2,3}$ and $J_{3,4}$ are indicative[8] of *trans* diaxial H-H coupling and those of $J_{F,2}$ and $J_{F,4}$ are maximal[9] for *gauche* F-H couplings. The long-range couplings for F/H-1 and F/H-5 are similar in magnitude to that (~4 Hz) regarded as typical[2,10] of the planar W arrangement of the coupling pathway F–C–C–C–H.



A ~10% solution of 3-deoxy-3-fluoro-L-idose in D_2O at ~37° showed four ^{19}F resonances (Fig. 1) the chemical shifts and splittings of which are given in Table I. Unfortunately, no useful data could be obtained[11] from the ^1H spectrum even at 220 MHz, nor could any crystalline or homogenous derivative be obtained following acetylation of 3-deoxy-3-fluoro-L-idose. Since $J_{H,F-gauche}$ in deoxyfluoropyranoses is usually ≯ ~16 Hz and values >25 Hz have been recorded[10] for the furanose analogues, the resonances at +34.05 and +37.01 p.p.m. are assigned to the furanose forms. 3-Deoxy-3-fluoro-D-glucofuranose and 3-deoxy-3-fluoro-L-idofuranose differ



re ifts aical shChemD_2O. (e in D-idosaoro-ıy-3-fli-deoxı of 3lutio)% soa ~1(s for aance reso1. ^{19}F Fig. C_6F_6.l for (signalf the ield on. upf p.p.n

of airs cve ppectie resor thngs fse riıranohe fuhat t so t C-5,on atırationfigthe cc in tl only
e ›y thted hdopons amationforıe ccs. Tluentıbstilof sıays ıl arenticay idε carrners anoı
o fluoıcy-3-deoıhe 3 nd tose aıranucofı-D-glne-α-ylideprop-O-iso1,2-(s in ringnose fura
:s /alue(5). Vion ormaconfc$^3T_2$ (the te toximapprond ar[10] amilaely si close arevativ deri'

7 17–22)72) 225 (1Res., hyd. Carbo

TABLE I

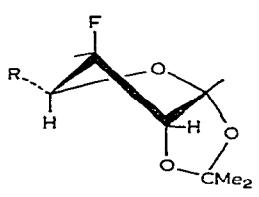
^{19}F RESONANCES FOR A SOLUTION OF 3-DEOXY-3-FLUORO-L-IDOSE IN D_2O

^{19}F resonance[a] (p.p.m.)	Integrated intensity (%)	Observed splittings			Assignment
		gem	vic	^4J	
+26.98	39 (37.5)[b]	51	14,14	3	α-pyranose (8 ⇌ 9)
+28.50	28 (31)	46	9,9	3,3	β-pyranose (10 ⇌ 11)
+34.05	19 (18.5)	50	28,14		β-furanose (6)
+37.01	14 (13.5)	52	20,20[c]		α-furanose (7)

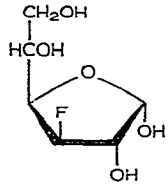
[a]Relative to external C_6F_6; addition of 162.3 p.p.m. will give values relative to CCl_3F. [b]Figures in parentheses are for L-idose inferred from the data given by Angyal and Pickles[19] for an aqueous solution of the D-isomer at 44°; at 31° the percentages were α-pyranose 38.5, β-pyranose 36, α-furanose 11.5, β-furanose 14. [c]±1 Hz.

of $J_{F,2}$ 10.5 and $J_{F,4}$ 28.8 Hz (for a solution in $CDCl_3$) have been reported[10] for **5** and were provisionally associated with dihedral angles of ~30° and ~150°, respectively. These J values are not significantly changed by variation of the substituents at C-5. Thus, by analogy, the vicinal F-H couplings of 14 and 28 Hz associated with the ^{19}F resonance at +34.05 p.p.m. may be assigned to $J_{F,2}$ and $J_{F,4}$ of 3-deoxy-3-fluoro-β-L-idofuranose (**6**). The differences in magnitude of $J_{F,2}$ and $J_{F,4}$ for **5** and **6** are probably due, at least in part, to the presence of the 1,2-*O*-isopropylidene ring in **5** and to solvent effects ($CDCl_3$ for **5**, D_2O for **6**).

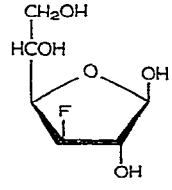
The extent of distortion from the planar form of the furanose ring in **6** will be determined mainly by the non-bonded interactions O-1/O-2 and F-3/C-5. As the former interaction is absent from the α-L-furanose **7**, distortion should be less than in the β-isomer. This being so, it follows that the dihedral angles F/H-2 and F/H-4 in **7**, if changed at all, should be smaller than the corresponding angles in the β-anomer **6**. Since the Karplus curve for vicinal F-H couplings has a profile[12] similar to that well established for H-H couplings then, for the α-furanose **7**, the values of $J_{F,2}$ and



5



6(β-L)



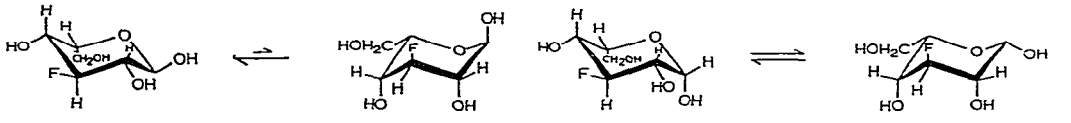
7(α-L)

$J_{F,4}$ should be ⩾14 and ⩽28 Hz, respectively; the observed values are both ~20 Hz. Thus, the ^{19}F resonance at +37.01 p.p.m. is assigned to the α-L-furanose form **7**.

It follows that the two remaining ^{19}F resonances (Table I) are associated with pyranose forms. Interpretation of these resonances is more complex and, to some extent, speculative. The splittings observed for the ^{19}F resonance at +26.98 p.p.m.

are assigned as follows: geminal 51, vicinal (F/H-2, F/H-4) 14 and 14, long-range (^4J) 3 Hz. Smaller geminal (46 Hz) and vicinal (9 and 9 Hz) splittings are associated with the ^{19}F resonance at +28.50 p.p.m. and there are two ^4J splittings (each 3 Hz). The geminal couplings are typical of sp^3-hybridized carbon, and the vicinal couplings are not grossly different from the values (each 12 Hz) of $J_{F,H-gauche}$ (*i.e.* F/H-2 and F/H-4) for 3-deoxy-3-fluoro-β-D-glucopyranose in aqueous solution[9].

The 3-Hz splittings are clearly long-range; both ^4J (F/H-1, F/H-5) and ^5J (F/H-6,6′) couplings are possible in 3-deoxy-3-fluoro-L-idopyranose. Although ^5J F-H couplings of 3–3.3 Hz have been recorded for certain fluoro sugar derivatives [*e.g.* between F/H-1 (*eq,eq*-orientation) in derivatives of 4-deoxy-4-fluoro-α-D-glucopyranose[3] ($CDCl_3$ solution)], it would be difficult to explain coupling of this type with H-6 (or H-6′) in one anomer and with both H-6 and H-6′ in the other; ^5J coupling (1.5 Hz) has been observed[2] between F and one of the protons on C-6 in 3-deoxy-3-fluoro-β-D-glucopyranose tetra-acetate ($CDCl_3$ solution). It is more reasonable to assign the 3-Hz F–H splittings to $^4J_{eq,eq}$ couplings. Several examples (~4 Hz) of ^4J F_{eq}–H_{eq} coupling have been observed namely, F/H-1 in the tetra-acetates of 3-deoxy-3-fluoro-α-D-glucopyranose[10] and the *galacto* analogue[13] and F/H-5_{eq} in the tri-acetate of 3-deoxy-3-fluoro-β-D-xylopyranose[10]. In contrast, it should also be noted that the ^4J F_{eq}–H_{ax} couplings observed[10,13] in derivatives of 3-deoxy-3-fluoro-D-glucopyranose and the *galacto* analogue and in 4-deoxy-4-fluoro-D-glucopyranose[3] are ≯1.1 Hz. Moreover, in derivatives of 2-deoxy-2-fluoro-D-mannopyranose[14] and 4-deoxy-4-fluoro-D-galactopyranose[1] where ^4J F_{ax}–H_{ax} coupling is possible, the observed couplings were ~0 Hz. However, for 2,4-di-*O*-acetyl-3-deoxy-3-fluoro-β-D-xylopyranosyl fluoride[15] which, because of the large anomeric effect associated with F-1, exists preponderantly in the *1C* (D) conformation having all substituents *ax*, ^4J F_{ax}–H_{ax} couplings of +2.4 (F-3/H-5*ax*) and 0.5 Hz (F-1/H-5*ax*) have been observed. Although not determined, the signs of the 3 Hz F-H couplings are not likely to be informative as both $^4J_{eq,eq}$ (ref. 2) and $^5J_{eq.eq}$ F–H couplings (ref. 3) are absolutely positive in sign.



8 (*C1*, α-L) 9 (*1C*, α-L) 10 (*C1*, β-L) 11 (*1C*, β-L)

[H-substituents shown are those expected to couple to F-3]

If the 3 Hz F-H couplings are assigned to the $^4J_{eq,eq}$ category, then not only anomeric configuration but also conformation preference can be based thereon. Thus, the ^{19}F resonance at +26.98 p.p.m. can be associated with the α-pyranose form and the single 3 Hz long-range splitting assigned to F/H-5 coupling in the *C1* (L) conformation **8**; no such coupling is possible in the *1C* (L) form **9**. Assessment of the extent to which the *C1* form **8** contributes to the conformational equilibrium

will depend on at least two factors, which are difficult to assess precisely. First, the degree of deformation from the ideal-chair conformation **8** as a consequence of the non-bonded interactions associated with the *ax* CH_2OH group. Such deformation could distort F/H-5 from the planar W arrangement and thereby reduce the magnitude of the ^4J value from ~4 Hz which, based on the examples just cited, can be regarded as typical. Second, the magnitude of $J_{F,5}$ for contributors, other than the *C1* (L) form **8**, to the conformational equilibrium. On the assumption that $J_{F,5}$ for these contributors is zero, then the contribution of the distorted *C1* (L) form **8** can be assessed as 66–75%.

By similar reasoning, the ^{19}F resonance at +28.5 p.p.m. may be assigned to the β-pyranose form and the two 3-Hz long-range splittings associated with F/H-1 and F/H-5 couplings ($^4J_{eq,eq}$) in the *C1* (L) conformation **10**. The non-bonded interaction between the CH_2OH group and HO-1, which are *syn*-axial in **10**, could distort both F/H-1 and F/H-5 from the planar W-arrangement shown in the ideal chair form **10**, with a consequent reduction in the magnitude of the corresponding *J* values. If $J_{F,1}$ and $J_{F,5}$ are each zero in the other contributor(s) to the conformational equilibrium. then a somewhat distorted *C1* (L) form **10** must preponderate to an extent of 66–75%.

At this point it is pertinent to consider the splittings of the pyranose ^{19}F resonances assigned to vicinal F-H couplings. From a study of a wide range of deoxyfluorohexopyranoses, mainly of the D-*gluco* configuration, Phillips and Wray[9] showed that the magnitude of $^3J_{H,F-gauche}$ is usually less than the unperturbed[9] value of 16 Hz (as in fluoroethane) and is influenced by (*a*) the number of substituent oxygen atoms on the carbon atoms of the coupling fragment (*i.e.* HC–CF), (*b*) the presence of any oxygen atom *trans* to the fluorine substituent *via* the coupling pathway, and (*c*) the presence of a hydroxyl group *trans* to the C-C bond of the coupling pathway. The relevant incremental contributions (Hz) to the value of $J_{H,F-gauche}$ were assigned as follows: (*a*) −2.5 per oxygen substituent, (*b*) −7 (possible for a secondary fluorine substituent only when axial), (*c*) −2 if H,F are *cis* and +2 if H,F are *trans*-diequatorial. The approximate nature of the incremental contributions and the possible existence of other parameters was clearly recognized, so that the calculated *J* values in Table II must also be regarded as approximate.

The magnitudes of the incremental contributions were selected to give good correspondence, in the main, between the calculated and observed values of $J_{H,F-gauche}$ for a variety of fluoro sugars having the *gluco* and *manno* configurations. All of the derivatives studied were conformationally homogeneous, the *C1* (D) conformation favoured. The availability of 3-deoxy-3-fluoro-L-idose provided an opportunity to apply these calculations to a sugar derivative the pyranose forms of which were expected to be conformationally inhomogeneous.

The ideal *C1* (L) and *1C* (L) chair conformations of 3-deoxy-3-fluoro-α- and β-L-idopyranose are depicted in formulae **8–11**, and the calculated values of $J_{F,2}$ and $J_{F,4}$ are shown in Table II. Because of the deformation arising out of non-bonded interactions associated with axial and *syn*-axial groups, the extremes of the conforma-

tional equilibria for the α and β-pyranose forms are unlikely to be the ideal-chair conformations **8–11**, so that the calculated J values probably require some adjustment by an amount that is difficult to assess. The vicinal couplings ($J_{F,2} = J_{F,4} = 14$ Hz) observed for the α-pyranose are much closer to, and in fact slightly exceed, those (11.5, 13.5 Hz) calculated for the *C1* (L) conformation **8**, thereby indicating a more

TABLE II

CALCULATED $J_{F,H-gauche}$ VALUES FOR THE *C1* AND *1C* CONFORMATIONS OF 3-DEOXY-3-FLUORO-α AND β-L-IDOPYRANOSE

Conformation	*Vicinal coupling*	*Incremental parameters*[a]			16-($a+b+c$) (*Hz*)	eq, eq $^4J_{F,H}$ *coupling* (*Hz*)	*Observed couplings* (*Hz*)
		(*a*)	(*b*)	(*c*)			
C1 (α-L) (**8**)	F/H-2	−2.5	0	+2, −2	13.5	F/H-5	14, 14, 3
	F/H-4	−2.5	0	−2	11.5		
1C (α-L) (**9**)	F/H-2	−2.5	−7	0	6.5		
	F/H-4	−2.5	−7	0	6.5		
C1 (β-L) (**10**)	F/H-2	−2.5	0	−2	11.5	F/H-1, F/H-5	9, 9, 3, 3
	F/H-4	−2.5	0	−2	11.5		
1C (β-L) (**11**)	F/H-2	−2.5	−7	−2	4.5		
	F/H-4	−2.5	−7	0	6.5		

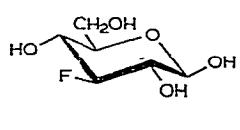
[a]See Discussion for explanation.

preponderant contribution of **8** to the conformational equilibrium than is indicated by the long-range coupling data. On the other hand, the vicinal couplings ($J_{F,2} = J_{F,4} = 9$ Hz) observed for the β-pyranose lie between those calculated for the *C1* (L) (**10**, $J_{F,2} = J_{F,4} = 11.5$ Hz) and the *1C* (L) forms (**11**, $J_{F,2}$ 4.5, $J_{F,4}$ 6.5 Hz), and indicate conformational inhomogeneity with no significant preponderance of the *C1* (L) or *1C* (L) forms. A slight preponderance of the *C1* (L) form was tentatively inferred from the long-range coupling data.

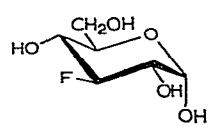
A consideration of ^{19}F chemical-shift data also supports the foregoing conclusions. Phillips and Wray[9] recognized that several structural parameters in fluorinated sugars affect the shielding (and therefore the chemical shift) of fluorine substituents; some of the parameters were designated. Thus, it is possible to deduce approximate values of the chemical shifts of the fluorine substituents in the conformations **8–11**; F-3 is *eq* in the *C1* (L) forms **8** and **10** and *ax* in the *1C* (L) forms **9** and **11**.

The number of known fluorinated sugars that are considered conformationally homogeneous and have an *ax* fluorine substituent is relatively small. In this category are 4-deoxy-4-fluoro-α and β-D-galactopyranose[16] for which the chemical shifts are ~51 and ~53 p.p.m., respectively. The difference in chemical shifts may reflect a relatively small long-range shielding or de-shielding effect of HO-1 (*cf.* ref. 9), so that the average value of 52 p.p.m. is taken for F_{ax} with two *gauche* oxygens atoms. The presence of a hydroxyl group *trans* to F_{ax} deshields to the extent of ~18.5 p.p.m. If, as seems reasonable, the effect of two hydroxyl groups *trans* to F_{ax} is additive, then the F chemical shift in the *1C* (L) conformation **9** is +15 p.p.m. less an amount

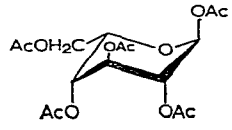
(probably small) due to *syn*-axial deshielding by HO-1. By similar reasoning, the F chemical shift in the *1C* (L) conformation **11** should be $\sim +15$ p.p.m.



12



13

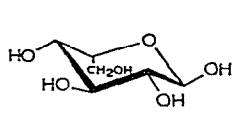


14 (*1C*)

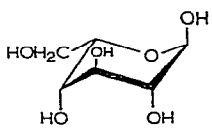
The F chemical shift of $\sim +28$ p.p.m. observed[10] for 3-deoxy-3-fluoro-β-D-glucopyranose (**12**) may also be assumed for F-3 in the *C1* (L) conformation **8** as the immediate environments of F-3 in each structure are closely similar. Likewise, the value $\sim +33$ p.p.m. observed[10] for the α-D-*gluco* compound (**13**) can also be associated with F-3 in the *C1* (L) conformation **10**. If the *C1* (L) conformations **8** and **10** preponderate, as inferred from the coupling constant data, then the predicted F chemical shifts for the 3-deoxy-3-fluoro-α and β-L-idopyranose should be somewhat smaller than the values +28 and +33 p.p.m., respectively, calculated for **8** and **10** by an amount that reflects the contribution of other conformations. The observed values of +26.98 and +28.5 p.p.m. accord with a greater preponderance, in the respective conformational equilibria, of the *C1* (L) form (**8**) of the α-anomer than of the *C1* (L) form (**10**) of the β-anomer.

It is of interest to compare the foregoing inferences regarding the conformational equilibrium of the pyranose forms of 3-deoxy-3-fluoro-α-and β-L-idose with observations and predictions for D-idopyranose and its α-tetra-acetate. In order to facilitate comparisons, the relevant literature data have been transposed to the L-series.

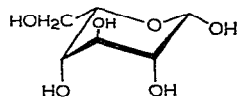
The n.m.r. data reported by Bhacca *et al.*[17] indicate that, in $CDCl_3$, α-L-idopyranose penta-acetate exists almost exclusively in the 1*C* (L) form **14** (*eq* acetoxymethyl group, four *ax* acetoxy groups). In contrast, and from a computation of total interaction energies, Angyal[18] predicted that, in aqueous solution, α-L-idopyranose would be conformationally inhomogeneous, *i.e.* *C1* (L) (**15**) ⇌ *1C* (L) (**16**) and that



15 (*C1*,α-L)



16 (*1C*,α-L)



17 (*1C*,β-L)

the *C1* (L) form should at least be marginally favoured [*1C* (L) 4.35, *C1* (L) 3.85 kcal/mole]. On the basis of n.m.r. data (magnitude of $J_{1,2}$), it was inferred[19] that the *C1* (L) form **15** contributed 60–70% to the conformational equilibrium on the assumption that the other contributor was the *1C* (L) form (**16**). The prediction[18] that the *1C* (L) form (**17**) of β-L-idopyranose should be the principal contributor to the conformational equilibrium was also supported by the n.m.r. data[19].

These findings for D-idose (transposed to the L series) contrast with the foregoing tentative conclusions for 3-deoxy-3-fluoro-α and β-L-idopyranose in that the *C1* (L) conformations are more favoured in the latter compounds. An effect that might, at least in part, account for this difference has been observed in derivatives of the type $CH_2X.CH_2Y$, where X and Y are small, electronegative substituents such as oxygen and fluorine. The *gauche* rotamers of $CH_2OH.CH_2OH$ and $CH_2OH.CH_2F$ are unusually stabilised to the extent of ~1 kcal/mole[20,21], for which hydrogen bonding is not responsible as the effect is observed in the acetates[22]. The stabilisation is greater by at least 0.1 kcal/mole in the 2-fluoroethanol series[23]. The *C1* (L) conformations **8** and **10** of 3-deoxy-3-fluoro-α and β-L-idopyranose, respectively, but not the corresponding *1C* (L) forms, contain two *gauche* F-OH pairs and this could result in enhanced stability. Likewise, this effect may be invoked to explain the more extensive acid-catalysed conversion already noted of 3-deoxy-3-fluoro-L-idose into the 1,6-anhydropyranose derivative than for L-idose.

Although the data and arguments presented in this paper are reasonably self consistent, the conclusions drawn therefrom about the favoured conformations of 3-deoxy-3-fluoro-α- and β-L-idopyranose in aqueous solution must be regarded as tentative. Consolidation of the approach[9] of Phillips and Wray to conformationally inhomogeneous deoxyfluoropyranoses requires a study of other examples. In this connection it may be noted that the pyranose forms in aqueous solutions of lyxose, ribose, and altrose display conformational inhomogeneity[18], and an n.m.r. study of their fluorinated derivatives is merited; 2-deoxy-2-fluoro-D-ribose[24] and 2-deoxy-2-fluoro-D-altrose[25] are known.

If the assignments of ^{19}F resonances in Table I are correct, then there is a close correspondence in the percentage of α and β pyranose and furanose forms for L-idose (at 44°) and the 3-deoxy-3-fluoro derivatives (at ~37°) present at mutarotational equilibrium in aqueous solution. Thus, for the hexose series, the lack of any significant effect on the mutarotational equilibria by appropriate replacement of OH by F is further illustrated.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were obtained for 0.5–1% solutions by using a Perkin–Elmer 141 polarimeter. T.l.c. was performed on Kieselgel (Merck, 7731) and detection was effected with conc. sulphuric acid. Column chromatography was effected on Kieselgel 7734.

N.m.r. spectra (kindly determined by Dr. V. Wray) were obtained conventionally with a Varian HA-100 instrument at 100 MHz for ^1H resonances and at 94.1 MHz for ^{19}F resonances on ~10% solutions in D_2O (external C_6F_6) for free sugars and in $CDCl_3$ (internal Me_4Si) for acetates. The ^{19}F resonance spectra for solutions in D_2O and H_2O were closely similar.

Hydrolysis of 3-deoxy-3-fluoro-1,2-O-isopropylidene-β-L-idopyranose (**1**). — (*a*) A solution of **1** (50 mg) in water (2 ml) was stirred with Amberlite IR-120 (H^+) resin

(1 ml) for 17 h at 100°, after which no starting material remained (t.l.c., ethyl acetate–ethanol, 9:1) and two products (R_F ~0.8, ~0.4) were detected in the ratio ~4:1. The filtered hydrolysate was concentrated in the presence of Kieselgel (1 g) and the residue was placed on a dry column of Kieselgel (9 g). Elution with ethyl acetate–ethanol (9:1) gave 1,6-anhydro-3-deoxy-3-fluoro-β-L-idopyranose (**4**, 30 mg, 81%), m.p. 106–109°, $[\alpha]_D^{26}$ +106° (acetone) (Found: C, 43.7; H, 5.5; F, 12.1. $C_6H_9FO_4$ calc.: C, 43.9; H, 5.5; F, 11.6%). N.m.r. datum (D_2O): ^{19}F +35.3 p.p.m.

Further elution gave syrupy 3-deoxy-3-fluoro-L-idose (7 mg, 17%). (*b*) A solution of **1** (600 mg) in water (24 ml) was stirred with Amberlite IR-120 (H^+) resin (12 ml) at 60° and the reaction was monitored by t.l.c. (ethyl acetate–ethanol, 9:1). After 5 h, no starting material remained and only one product (R_F ~0.4) was detected. The filtered hydrolysate was concentrated in the presence of Kieselgel (5 g). The residue was added to a column of dry Kieselgel (30 g) and elution effected with ethyl acetate–ethanol (9:1) gave syrupy 3-deoxy-3-fluoro-L-idose (488 mg, 99%), $[\alpha]_D$ −21° (equil., water), R_G 1.46 (butanol–acetic acid–water, 5:2:3) M_G 1.35 (borate buffer[27], pH 9).

Equilibration of 3-deoxy-3-fluoro-L-idose and its 1,6-anhydride. — A solution of 3-deoxy-3-fluoro-L-idose (220 mg) in water (8 ml) was stirred for 20 h at ~100° with Amberlite IR-120 (H^+) resin (4 ml). T.l.c. (ethyl acetate–ethanol, 9:1) then revealed only traces of starting material. The filtered solution was concentrated and the residue was acetylated with pyridine (2 ml) and acetic anhydride (1 ml). The crude product (~220 mg), isolated in the usual manner, was eluted from Kieselgel with 1:1 ether–light petroleum (b.p. 40–60°). The fractionation was monitored by t.l.c. and combination of the appropriate fractions gave 2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-3-fluoro-β-L-idopyranose (200 mg), m.p. 83–84° (from ether–light petroleum), $[\alpha]_D$ +80.5° (chloroform) (Found: C, 48.5; H, 5.35; F, 7.3. $C_{10}H_{13}FO_6$ calc.: C, 48.4; H, 5.2; F, 7.7%). N.m.r. datum ($CDCl_3$): ^{19}F +39.2 p.p.m.

Combination of the later fractions gave a mixture (20 mg) of tetra-acetates of 3-deoxy-3-fluoro-L-idose.

ACKNOWLEDGMENTS

This investigation was supported by grants to the Chester Beatty Research Institute (Institute of Cancer Research:Royal Cancer Hospital) from the Medical Research Council and the Cancer Research Campaign. The authors thank Drs. L. Phillips and V. Wray for helpful discussions, and Professor S. J. Angyal for a manuscript copy of the paper cited in ref. 19.

REFERENCES

1 Part XIII. J. ADAMSON AND D. M. MARCUS, *Carbohyd. Res.*, 22 (1972) 37.
2 A. B. FOSTER, R. HEMS, L. D. HALL, AND J. F. MANVILLE, *Chem. Commun.*, (1968) 158.
3 A. D. BARFORD, A. B. FOSTER, J. H. WESTWOOD, L. D. HALL, AND R. N. JOHNSON, *Carbohyd. Res.*, 19 (1971) 49.

4 J. S. BRIMACOMBE, P. A. GENT, AND J. H. WESTWOOD, *Carbohyd. Res.*, 12 (1970) 475; *J. Chem. Soc. (C)*, (1970) 1632.
5 A. B. FOSTER, R. HEMS, AND J. M. WEBBER, *Carbohyd. Res.*, 5 (1967) 292.
6 J. S. BRIMACOMBE, A. M. MOFTI, AND J. H. WESTWOOD, *Carbohyd. Res.*, 21 (1972) 297.
7 E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL, AND G. A. MORRISON, *Conformational Analysis*, Wiley, New York 1965, p. 417.
8 L. D. HALL, *Advan. Carbohyd. Chem.*, 19 (1964) 51.
9 L. PHILLIPS AND V. WRAY, *J. Chem. Soc.*, (B) (1971) 1618.
10 A. B. FOSTER, R. HEMS, AND L. D. HALL, *Can. J. Chem.*, 48 (1970) 3937.
11 L. PHILLIPS, personal communication.
12 K. L. WILLIAMSON, YUAN-FANG LI, F. H. HALL, AND S. SWAGER, *J. Amer. Chem. Soc.* 88 (1966) 5678.
13 J. S. BRIMACOMBE, A. B. FOSTER, R. HEMS, J. H. WESTWOOD, AND L. D. HALL, *Can. J. Chem.*, 48 (1970) 3946.
14 J. ADAMSON, A. B. FOSTER, L. D. HALL, R. N. JOHNSON, AND R. H. HESSE, *Carbohyd. Res.*, 15 (1970) 351.
15 L. D. HALL, R. N. JOHNSON, A. B. FOSTER, AND J. H. WESTWOOD, *Can. J. Chem.*, 49 (1971) 236.
16 D. M. MARCUS AND J. H. WESTWOOD, *Carbohyd. Res.*, 17 (1971) 269.
17 N. S. BHACCA, D. HORTON, AND H. PAULSEN, *J. Org. Chem.*, 33 (1968) 2484.
18 S. J. ANGYAL, *Angew. Chem. Int. Ed. Engl.*, 8 (1969) 157.
19 S. J. ANGYAL AND V. A. PICKLES, *Austral. J. Chem.*, 25 (1972) 1695.
20 P. BUCKLEY AND P. A. GIGNERE, *Can. J. Chem.*, 45 (1967) 397.
21 R. J. ABRAHAM AND K. PARRY, *J. Chem. Soc.* (B), (1970) 539 and references cited therein.
22 R. J. ABRAHAM AND K. G. R. PACHLER, *Molec. Phys.*, 7 (1963) 165.
23 L. PHILLIPS, unpublished data.
24 J. F. CODDINGTON, I. DOERR, AND J. J. FOX, *Carbohyd. Res.*, 1 (1965) 455.
25 I. JOHANSSON AND B. LINDBERG, *Carbohyd. Res.*, 1 (1965) 467.
26 A. B. FOSTER, *Advan. Carbohyd. Chem.*, 12 (1957) 81.