An Anomalous Conformation in a Deoxyfluoro-sugar Nucleoside

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Summary The conformation of the carbohydrate portion in the nucleoside 4-methoxy-1-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-2′-fluoro-β-D-glucopyranosyl)-2(1H)-pyrimidone is the expected $^4C_1$ but that in the α-anomer is intermediate between $^1C_4$ chair and $^{2,4}B$ or $B_{2,5}$ boat conformations.

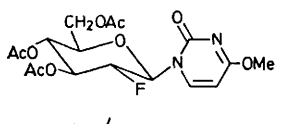
FLUORINATED carbohydrates are now relatively accessible[1] and in continuing work on fluorinated nucleosides[2] the condensation of a fluorosugar with a nitrogenous base has been investigated. Hitherto, fluorosugar nucleosides have been obtained by modification of intact nucleosides,[1] an approach which limits structural variation of the carbohydrate portion.

When 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide[3] was treated with 2,4-dimethoxypyrimidine[4] in boiling acetonitrile in the presence of a molecular sieve (BDH, Type 4A XW) for 5 days a mixture of the β- (**1**) and α-(**2**) anomers of 4-methoxy-1-(3′,4′,6′-tri-*O*- acetyl-2′-deoxy 2′-fluoro-D-glucopyranosyl)-2(1H)-pyrimidone was formed in the ratio 1 : 5 [isolation by chromatography on silica gel (Merck 7734) using ether–ethyl acetate (4 : 1)]. The carbohydrate portion of the β-anomer in solution in deuteriochloroform had the expected $^4C_1$ conformation, that in the α-anomer was a distorted $^1C_4$ conformation.

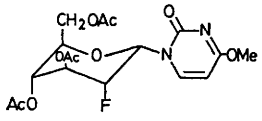
Compound (**1**) had m.p. 219° (ethyl acetate–ethanol), $[\alpha]_D$ +20° (*c* 0·35, $CHCl_3$), and (**2**) had an ill-defined m.p. (75—85°) (ethyl acetate–ethanol), $[\alpha]_D$ −8° (*c* 0·8, $CHCl_3$).† The mass spectra of (**1**) and (**2**) each contained a peak for the molecular ion, *m/e* 416, and the fragmentation patterns were closely similar.

† Compounds (**1**) and (**2**) gave satisfactory elemental analyses.

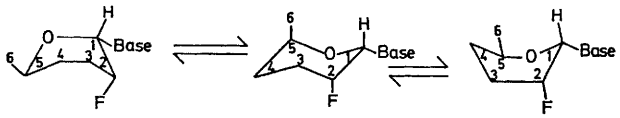
Assignments of the structures (**1**) and (**2**) were made on the basis of ^1H and ^{19}F n.m.r. spectroscopy of *ca.* 10% solutions in $CDCl_3$. The spectrum of (**1**), interpreted on a first-order basis, contained the coupling constants: $J_{5,6}$ 7·5, $J_{1',2'}$ 9, $J_{2',3'}$ 9, $J_{3',4'}$ 9·5, $J_{4',5'}$ 9·5, $J_{F,1'}$ 2·5, $J_{F,2}$ 50·5, and $J_{F,3'}$ 13 Hz. The fluorine resonance was centred at 3557 Hz above that for C_6F_6. The large vicinal $J_{H,H}$ values for the sugar portion in (**1**) establish both the *β-gluco* configuration and the $^4C_1$ conformation. The value (13 Hz) of $J_{F,3'}$ is that expected[5] for an H, F_{gauche} orientation.



(1) ($^4C_1$)



(2) ($^1C_4$)



(3) ($B_{2,5}$) (4) ($^1C_4$) (5) ($^{1,4}B$)

The spectrum of (**2**), also interpreted on a first-order basis, contained the coupling constants: $J_{5,6}$ 7·5, $J_{1',2'}$ 1·5, $J_{2',3'}$ 3·5, $J_{3',4'}$ 3·5, $J_{4',5'}$ 4·5, $J_{F,1'}$ 27, $J_{F,2'}$ 46 and $J_{F,3'}$ 11·5 Hz. The fluorine resonance was centred at 3877 Hz above that of C_6F_6. The large value (27 Hz) of $J_{F,1'}$ unequivocally establishes[5] a *trans*-diaxial arrangement between the two nuclei. In addition, the vicinal couplings for the ring protons of the carbohydrate portion and the value (11·5 Hz) of $J_{F,3'}$ establish the *α-gluco* configuration for (**2**) and are consistent with a conformation within the range reflected by the equilibrium $B_{2,5}$ (**3**) ⇌ $^1C_4$ (**4**) ⇌ $^{1,4}B$ (**5**). The value expected for $J_{F,3'}$ in the $^1C_4$ conformation is difficult to predict precisely, owing to the paucity of relevant data. However, using the parameters described by Phillips and Wray[6] for calculation of vicinal $J_{H,F-gauche}$ and assuming O to be replaceable by N, the calculated value for $J_{F,3'}$ is 8·5 Hz. The observed value of 11·5 Hz is compatible with a decrease in the F, H-3 dihedral angle, a consequence of the contributions from the boat conformations, particularly the $^{1,4}B$ form (**5**).

The high value of $J_{F,1'}$ for (**2**) requires that H-1 and F-2 in the sugar portion be essentially *trans* coplanar. Lemieux and Saluja[7] have shown that 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 4-methylpyridinium bromide adopts a $B_{2,5}$ conformation (**3**) in both the crystalline state and in solution.

The tendency of the α-anomer (**2**) to adopt an anomalous conformation may reflect the operation of a reverse anomeric effect.[8] However, previous examples[9] of this effect have involved *N*-glycosides or related compounds in which the nitrogen atom was positively charged; N-1 in (**2**) does not carry a formal positive charge.

In an attempt to evaluate the role of F-2 of the α-anomer (**2**) in determining the conformation, a comparison with the corresponding acetoxy derivative [4-methoxy-1-2(2',3'-4', 6'-tetra-*O*-acetyl-α-D-glucopyranosyl)-2(1H)-pyrimidone was considered. However, condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with 2,4-dimethoxypyrimidine gave only the β-anomer (*cf.* ref. 10).

Other nucleosides containing hexoses, halogenated at the 2'-position, are being investigated.

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