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ACID-CATALYZED EPIMERIZATION OF 2-DEOXY-2-FLUORO-D-HEXOSES

Terushi Haradahira, Minoru Maeda, Yoko Kanazawa, Yuko Momozono,
and Masaharu Kojima*

Faculty of Pharmaceutical Sciences, Kyushu University,
Fukuoka 812, Japan

Interconversion of 2-deoxy-2-fluoro-D-glucose (FDG) and 2-deoxy-2-fluoro-D-mannose (FDM) catalyzed by acid has been detected by ^{19}F -NMR method. Although FDG and FDM were stable towards 1 N hydrochloric acid, in stronger acidic media the two hexoses underwent epimerization at C-2.

KEYWORDS ——— epimerization; acid-catalysis; 2-deoxy-2-fluoro-D-glucose; 2-deoxy-2-fluoro-D-mannose; ^{19}F -NMR

^{19}F -Nuclear magnetic resonance (^{19}F -NMR) is a useful tool for the structural analysis of fluorinated carbohydrates,^{1,2)} and the isomer analysis of radiolabeled 2-deoxy-2-fluoro-D-glucose (FDG) by ^{19}F -NMR has recently been reported.³⁾ We have developed methods for synthesizing FDG and 2-deoxy-2-fluoro-D-mannose (FDM) by fluoride ion displacement.^{4,5)} ^{19}F -NMR spectra of FDG and FDM obtained by this process showed the presence of impurities. In the course of our investigation of the origin of the impurities, we have found, using ^{19}F -NMR spectroscopy, that the epimerization between FDG and FDM is caused by the action of acids.

Fluorination of methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(trifluoromethanesulfonyl)- β -D-mannopyranoside with tetraethylammonium fluoride, after purification by chromatography, gave pure methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-fluoro- β -D-glucopyranoside (1)⁴⁾ as determined by ^{19}F -NMR. The ^{19}F -NMR spectrum of FDG obtained by hydrolysis of 1 with 8 N methanesulfonic acid revealed the presence of 2% FDM. Similarly, although the ^{19}F -NMR spectrum of methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-fluoro- β -D-mannopyranoside (2) obtained by nucleophilic displacement reaction of the corresponding 2-O-(trifluoromethanesulfonyl)- β -D-glucopyranoside with tetraethylammonium fluoride⁵⁾ showed it to be epimerically pure, the FDM obtained by hydrolysis of 2 with 5 N methanesulfonic acid contained 6% FDG as determined by ^{19}F -NMR. These results indicated the possibility of a partial epimerization at the C₂-fluorine atom at the stage of the acid deblocking process. Thus we investigated the reactivities of epimerically pure FDG and FDM towards acid.

Epimerically pure FDG was prepared by hydrolysis of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-D-glucopyranose⁶⁾ with 1 N hydrochloric acid, followed by recrystallization from methanol-ethyl acetate after column chromatography on dry silica gel. Pure FDM was also prepared by the same procedure, using 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-D-mannopyranose.⁶⁾ The pure FDG or FDM (30-40 mg) was

heated with the acid at various concentrations (1 ml) at $110 \pm 2^\circ\text{C}$ for 30 min. After exact neutralization with 2 N NaOH, the solution was evaporated to dryness and the residue was chromatographed on dry silica gel with ethyl acetate. The recovery of the 2-deoxy-2-fluoro-D-hexose fraction was in the range of 49 to 87% depending on the concentration of acid used. The ^{19}F -NMR spectra of the samples (0.2 mol in D_2O) thus obtained were recorded on a JEOL FX-100 standard FT spectrometer at 93.7 MHz at ambient temperature ($22\text{--}23^\circ\text{C}$) (Fig. 1). The ^{19}F -chemical shifts of the two epimers were observed at δ : 32.38 ppm for the β -anomer of FDG, 32.53 ppm for the α -anomer of FDG, 37.85 ppm for the α -anomer of FDM, and 56.26 ppm for the β -anomer of FDM,²⁾ upfield from hexafluorobenzene (HFB) used as an external reference. As shown in Table I, both FDG and FDM were stable under mildly acidic conditions such as 1 N hydrochloric acid. As expected, in stronger acidic media the two 2-deoxy-2-fluoro-D-hexoses underwent epimerization at C-2, with slight formation of the 1,6-anhydro compounds.

Table I. The 2-Deoxy-2-fluoro-D-hexoses Ratio Determined by ^{19}F -NMR on the Treatment with Acids^{a)}

Compound	Acid	Percentages of 2-Deoxy-2-fluoro-D-hexoses ^{b)}	
		FDG ($\alpha+\beta$)	FDM ($\alpha+\beta$)
FDG	1N HCl	100	0
	3N HCl	98	2
	5N HCl	100	0
	8N HCl	95	5
	1N MeSO_3H	98	2
	3N MeSO_3H	77	23
	5N MeSO_3H	70	30
	8N MeSO_3H	56	44
FDM	1N HCl	0	100
	3N HCl	2	98
	5N HCl	21	79
	8N HCl	27	73
	1N MeSO_3H	11	89
	3N MeSO_3H	15	85
	8N MeSO_3H	19	81

a) Heated at $110 \pm 2^\circ\text{C}$ for 30 min in acidic media.

b) Relative ratios were calculated from the integrated peak areas obtained by the Fourier-transform technique.

The epimerization of aldoses and aldose-ketose isomerization by acids, bases, or enzymes are well known as the Lobry de Bruyn-Alberda van Ekenstein transformation.⁷⁾

Fig. 1. A ^{19}F -NMR Spectrum of FDG Treated with 8N MeSO_3H
 a, b and c: high-resolution spectra of the observed peaks.

There are some precedents in the literature for epimerization in fluorinated carbohydrates. These include the conversion of 2-deoxy-2-fluoro-D-altrose into 2-deoxy-2-fluoro-D-allose catalyzed by trimethylamine,⁸⁾ the C-1 anomerization of 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro- β -D-mannopyranosyl fluoride by hydrogen fluoride,⁹⁾ and the biological interconversion of FDG and FDM in yeast and chick-embryo cells.¹⁰⁾ The present result provides the first example of interconversion of FDG and FDM by the action of strong acids. Probably this occurs via an enolization type of mechanism such as the base-catalyzed isomerization of free sugars.⁷⁾ The synthesis of

FDG and FDM or their ^{18}F -labeled analogs, which requires the use of acids to remove the protecting groups of the 2-deoxy-2-fluoro intermediates leading to the formation of free sugars, should be handled with extreme caution with regard to epimeric purity.

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