Reactions with and in anhydrous hydrogen fluoride. Part 6. Reactions of peracetylated long-chain 3-*O*-(n-alkyl)- and 4,6-*O*-(n-alkylidene)-D-glucosyl fluorides in anhydrous hydrogen fluoride systems

R. Miethchen*, D. Peters

University of Rostock, Department of Chemistry, Buchbinderstrasse 9, D-2500 Rostock (Germany)

and C. Pedersen

The Technical University of Denmark, Institute of Organic Chemistry, DK-2800 Lyngby (Denmark)

(Received June 3, 1991; accepted August 29, 1991)

Abstract

The 2,4,6-tri-*O*-acetyl-3-*O*-alkyl-D-glucopyranosyl fluorides (**1–5**) undergo rearrangement in anhydrous hydrogen fluoride to give the 1,2:5,6-diacetoxonium ions (**11–15**). On further reaction, the latter (except the methyl derivative **5**) are dealkylated and further rearrange to give the 2,3:5,6-diacetoxonium ion of the D-mannofuranosyl fluoride **19**. The 2,3-di-*O*-acetyl-4,6-*O*-alkylidene-D-glucopyranosyl fluorides (**22** and **23**) were prepared from the corresponding 1-*O*-acetates by treatment with hydrogen fluoride in nitromethane.

Introduction

Peracetylated 3-*O*-(n-alkyl)-D-glucopyranoses, or -pyranosyl fluorides [1, 2], having C_{12}–C_{16} alkyl groups, form micelles in anhydrous hydrogen fluoride [3, 4]. When measuring the critical micelle concentration (c.m.c.) it is important to know whether the micelle-forming compounds are stable during the measurements (~6 h at 0 °C). We have therefore studied the behaviour of the 3-*O*-alkyl-2,4,6-tri-*O*-acetyl-D-glucopyranosyl fluorides (**1–4**) (Scheme 1) in anhydrous hydrogen fluoride (HF) solution at concentrations both below and above the c.m.c. values. The reactions of compounds **1–4**, and of the corresponding 3-*O*-methyl derivative (**5**), were studied by NMR spectroscopy. Compounds **1–5** all form 3-*O*-alkyl-1,2:5,6-diacetoxonium ions (**11–15**) in HF solution. Whereas the 3-*O*-methyl ion (**15**) is stable, the ions **11–14**, having higher alkyl chains, subsequently lose the alkyl groups and undergo further rearrangement.

The reactivity of 4,6-*O*-alkylidene-D-glucopyranose derivatives in HF–nitromethane mixtures was also studied. For the synthesis of the anomeric

*Author to whom correspondence should be addressed.

0022-1139/92/$5.00

TABLE 1

^{1}H NMR spectra (250 MHz) of the compounds **1–5**, **11–16** and **19** in HF–DF[a]

	Compounds					
	1–4[b]	**5**	**11–14**[b]	**15**	**16**	**19**
H-1	5.45dd	5.43dd	6.99d	6.97d	7.00d	5.91d
$J_{1,2}$	2.5	2.5	4.8	4.8	4.8	~0
$J_{1,F}$	52.3	52.5				53.5
H-2	4.72ddd	4.71ddd	5.53d	5.58d	5.49d	5.96dd
$J_{2,3}$	10.0	10.0	~0	~0		
$J_{2,F}$	24.3	24.5				
H-3	3.76m	3.76m	4.27d	4.20d	4.67d	6.14dd
$J_{3,4}$	10.0	10.0	4.6	4.2		
H-4	5.04dd	5.05dd	4.95d	4.88d	4.87d	5.75dd
$J_{4,5}$	10.0	10.0	~0	~0		$J_{4,F}$=6.0
H-5	3.94m	3.94m	5.65dd	5.66dd	5.70dd	
$J_{5,6}$	4.4	4.5	9.2	9.0		
$J_{5,6'}$	2.5	2.5	9.2	9.0		
H-6	4.12dd	4.10dd	5.00m	4.96m	5.02m	
$J_{6,6'}$	12.5	12.0				
H-6'	4.31dd	4.29dd	5.00m	4.96m	5.02m	
α-CH_2/α'-CH_2	3.56m		3.38m/3.21m			
β-CH_2	1.26m		1.26m			
$(CH_2)_n$[c]	0.94m		0.93m			
CH_3	0.50t	3.42s	0.52t	3.16s		
$H_3C-C=O$	1.92s	1.92s				
H_3C-C^+			2.44s	2.46s	2.45s	
			2.40s	2.40s	2.40s	

[a] δ values in ppm; J values in Hz.
[b] Differences between compounds of this group: $\delta = \pm 0.01$ ppm; $J = \pm 0.5$ Hz.
[c] All other CH_2 groups.

glycosyl fluorides, a similar influence of the temperature, time and reagent composition was found as described for the use of HF–pyridine mixtures [5, 6].

Experimental

NMR spectra for HF–DF solutions were obtained on a Bruker AC-250 MHz instrument. The solutions were prepared at −70 °C and transferred to a polyethylene tube which was evacuated and sealed. This tube fitted inside a 5 mm glass NMR tube. The spectra were measured at −10 °C. The acetyl groups were used as the internal reference; for ^{1}H spectra the methyl group was placed at 2.0 ppm and at 20 ppm for ^{13}C spectra. The following concentrations of compounds were used: **1** (18,59 and 213 mM); **2** (29, 43,

TABLE 2

^{13}C NMR spectra (62.9 MHz) of the compounds **1–5**, **11–16** and **19** in HF–DF[a]

	Compounds					
	1–4	**5**	**11–14**[b]	**15**	**16**	**19**
C-1	104.5d	104.5d	119.4	119.5	119.2	111.1d
$J_{C-1,F}$	230.6	226.4				234.0
$J_{C-2,F}$						47.5
C-2	74.9d	74.5d	91.2	90.8	94.5	95.1d
C-3	78.7	80.0	80.2	81.6	73.3	92.9
C-4	69.2	68.7	83.5	83.5	83.4	80.4
C-5	70.1	69.9	88.2	88.2	88.2	84.4
C-6	62.9	62.7	76.9	77.1	76.9	78.1
α-CH_2	71.2		73.9			
$(CH_2)_m$[c]	20.2–33.8		20.2–33.6			
CH_3	14.5	61.0	14.1	59.4		
$CH_3C{=}O$	181.7	181.8				
	181.3	181.5				
	181.0	181.0				
CH_3C^+			15.5	15.8	15.4	15.4
			14.8	15.0	14.7	14.8
CH_3C^+			195.5	195.2	195.4	195.3
			194.4	194.2	194.4	194.4

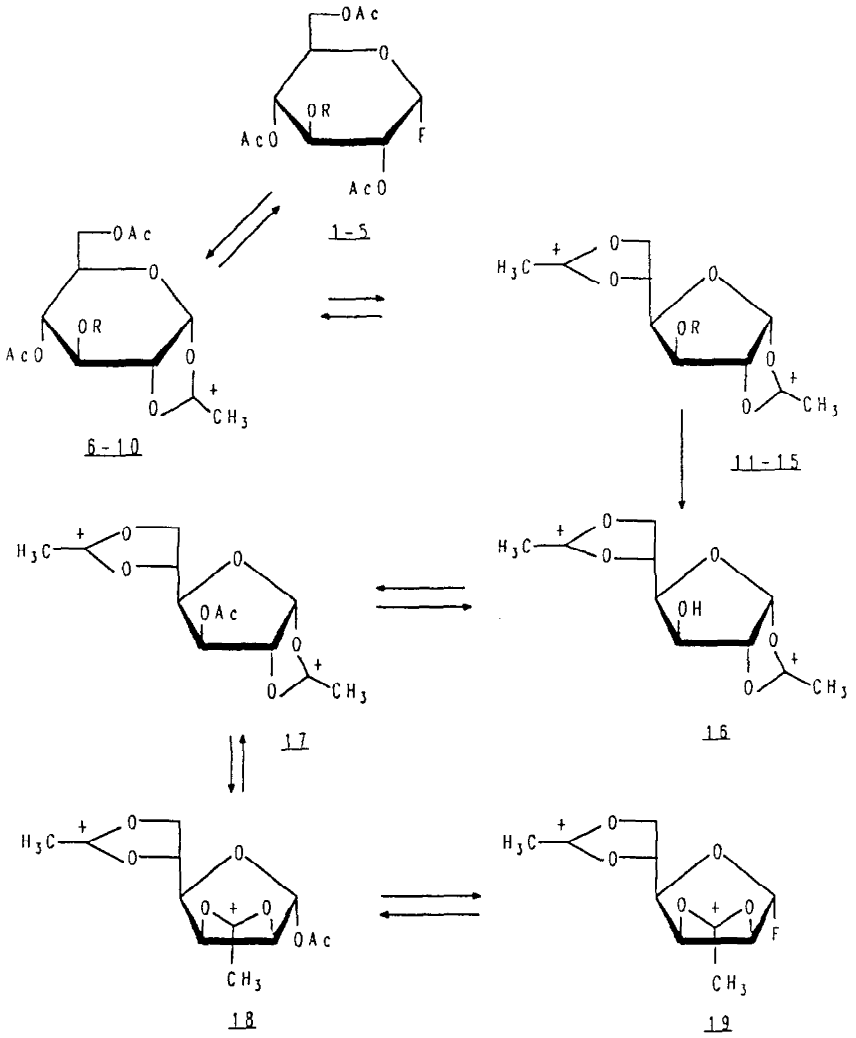
[a] δ values in ppm; J values in Hz.
[b] Differences between compounds of this group: $\delta = \pm 0.1$ ppm; $J = \pm 0.2$ Hz.
[c] All other CH_2 groups.

58, 78, 83, 144 and 200 mM); **3** (68, 87, 228 and 240 mM); **4** (249 mM); and **5** (330 mM).

2,4,6-Tri-*O*-acetyl-3-*O*-alkyl-D-glucopyranosyl fluorides (**1–5**) were prepared as described in [1, 3]. 2,3-Di-*O*-acetyl-4,6-*O*-(alkylidene)-D-glucopyranosyl fluorides (**22a**, **22b**, **23a** and **23b**) were prepared using method B described in ref. 2 and under the reaction conditions specified in Table 3. The products were rather unstable syrups which decomposed after a few days at room temperature.

Results and discussion

The 3-*O*-alkyl-D-glucose derivatives (**1–5**) were dissolved in HF which contained ~30% deuterium fluoride in order to obtain field-frequency stabilisation of the NMR instrument. The solutions were prepared at −70 °C and were allowed to reach 0 °C over the course of 24 h. The ^1H and ^{13}C NMR spectra measured at this stage showed that the HF–DF solutions mainly contained the glucopyranosyl fluorides **1–5** in equilibrium with the 1,2-acetoxonium ions **6–10** [7, 8]. A similar, temperature-dependent equilibrium has been observed for tetra-*O*-acetyl-α-D-glucopyranosyl fluoride [9]. From

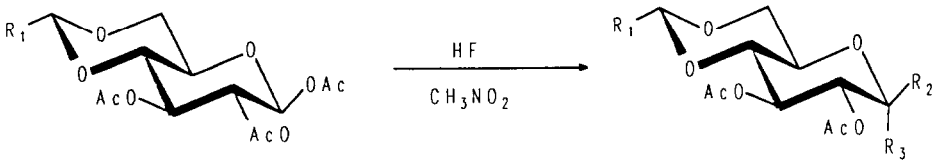


R=n-$C_{16}H_{33}$ **1, 6, 11** R=n-$C_{12}H_{25}$ **3, 8, 13**
R=CH_3 **5, 10, 15** R=n-$C_{14}H_{29}$ **2, 7, 12**
R=n-$C_{10}H_{21}$ **4, 9, 14**

Scheme 1. Reactions of acetylated 3-*O*-alkyl-D-glucopyranosyl fluorides **1–5** in hydrogen fluoride.

these results it must be concluded that the previously measured [3] c.m.c. data for **1–3**, obtained over 6 h at 0 °C, actually represent data for a mixture of **1–3** and **6–8**.

When solutions of **1–5** in HF–DF were kept successively for 20 h at −25 °C, 20 h at 5 °C and 5 h at 20 °C, the fluorides **1–5** and the 1,2-acetoxonium ions **6–10** were completely converted into the diacetoxonium ions **11–15** as seen from the ^1H and ^{13}C NMR spectra (Tables 1 and 2). The proton spectra were assigned through decoupling experiments.



20 $R_1 = n\text{-}C_3H_7$

21 $R_1 = n\text{-}C_{11}H_{23}$

22a $R_1 = n\text{-}C_3H_7$, $R_2 = F$, $R_3 = H$
22b $R_1 = n\text{-}C_3H_7$, $R_2 = H$, $R_3 = F$
23a $R_1 = n\text{-}C_{11}H_{23}$, $R_2 = F$, $R_3 = H$
23b $R_1 = n\text{-}C_{11}H_{23}$, $R_2 = H$, $R_3 = F$

Scheme 2. Preparation of 4,6-*O*-(n-alkylidene)-2,3-di-*O*-acetyl-D-glucopyranosyl fluorides.

TABLE 3

Influence of reaction conditions on the conversion of **20** and **21** to **22a/22b** and **23a/23b**, respectively, in HF–nitromethane

Compounds[a]	HF: CH_3NO_2 (ml/ml)	Time (min)	Temp. (°C)	Yield (%)	**22a:22b** (NMR)	**23a:23b** (NMR)
20	2:10	5	−20	71	100:0	–
	2:10	7	−20	70	100:0	–
	2:10	12	−20	79	100:0	–
	2:10	20	−20	57	85:15	–
	2:10	30	−20	63	85:15	–
	2:10	60	−20	61	85:15	–
	2:10	7	−10	51	80:20	–
	4:10	5	0	55	75:25	–
	4:10	7	0	44	20:80	–
	4:10	10	0	49	0:100	–
21	4:10	7	0	58	–	20:80

[a]1 g per 12 ml reagent solution.

The diacetoxonium ions **11–14** would probably have higher c.m.c. values than those found for **1–4**, and the determination of these values would require rather long measuring times. It was therefore of interest to study the stability of the ions **11–15** in HF solution. When **1–4** were kept in HF solution for 3 d at 20 °C, the diacetoxonium ions **11–14** were still present. However, a second diacetoxonium ion was formed as well, and from the NMR spectra (Tables 1 and 2) it appeared to be the 1,2:5,6-diacetoxonium ion **16**. After 10 d at 20 °C, **16** was the dominating species present. However, on further standing (3 weeks), a new set of signals appeared in the spectra which showed that this final product **19** was identical with the previously described 2,3:5,6-diacetoxonium ion derived from D-mannofuranosyl fluoride [10]. The 3-*O*-methyl diacetoxonium ion **15** obtained from **5** was completely stable in HF solution for *ca.* 3 weeks.

Scheme 1 depicts the probable course of the reactions described above, based on similar reactions described previously [10]. The conversion of **11–14** into **16** must take place by protonation of the ether oxygen and

TABLE 4

^{1}H NMR spectra (200 MHz) of the 4,6-*O*-(n-alkylidene)-D-glucopyranosyl fluorides **22a/22b**, **23a/23b** in $CDCl_3$ with TMS as the external standard[a]

	Compound			
	22a	**22b**	**23a**	**23b**
H-1	5.38dd	5.70dd	5.37dd	5.69dd
$J_{1,2}$	6.0	2.8	5.7	2.9
$J_{1,F}$	52.5	52.5	52.5	52.5
H-2	5.05ddd	4.91ddd	5.05ddd	4.91ddd
$J_{2,3}$	6.0	10.0	6.0	10.0
$J_{2,F}$	10.5	24.8	10.5	24.8
H-3	5.16dd	5.48dd	5.16dd	5.49dd
$J_{3,4}$	7.9	9.8	7.9	9.8
H-4	3.66m	3.89m	3.66m	3.90m
H-5, H-6	3.57m	3.51m	3.57m	3.52m
$J_{6,6'}$		10.5		10.5
H-6'	4.24dd	4.18dd	4.24dd	4.19dd
H-7[b]	4.55t	4.53t	4.53t	4.52t
α-CH_2	1.57m	1.58m	1.59m	1.59m
$(CH_2)_n$[c]	1.43m (2H)	1.38m (2H)	1.26m (18H)	1.26m (18H)
CH_3	0.95t	0.86t	0.88t	0.88t
CH_3CO	2.11s	2.10s	2.11s	2.11s
	2.10s	2.07s	2.06s	2.06s

[a] δ values in ppm; J values in Hz.
[b] Acetal proton.
[c] All other CH_2 groups.

subsequent cleavage of the oxygen–alkyl bond to give a primary carbenium ion, which undergoes polymerisation. The further conversion of **16** must involve acetylation to give **17** and the rearrangement to **18** [10]. Qualitatively, the ether cleavage seemed to be slower in HF solutions having concentrations above the c.m.c. values than in those with submicellar concentrations.

Preparation of 4,6-*O*-(n-alkylidene)-2,3-di-*O*-acetyl-D-glucopyranosyl fluorides by treatment of the corresponding 1-*O*-acetates with HF is not possible, even at −20 °C, without cleavage of the alkylidene groups [11]. It was, however, possible to isolate the fluorides **22** and **23** after treatment of **20** and **21**, respectively, with HF in nitromethane [2] (Scheme 2). Table 3 lists the results from a series of experiments in which the reaction conditions were varied. Treatment of the 1-acetate **20** with HF–nitromethane (1:5) for a few minutes at −20 °C gave the kinetically favoured β-fluoride **22a** exclusively. A small amount of unreacted **20** could easily be separated by chromatography. On longer reaction times, **20** reacts completely, but, at the same time, partial anomerisation to the α-fluoride **22b** takes place. At 0 °C, using a higher proportion of HF, the α-fluoride is formed exclusively but in

TABLE 5

^{13}C NMR spectra (50.3 MHz) of the 4.6-*O*-(n-alkylidene)-D-glucopyranosyl fluorides **22a/22b**, **23a/23b** in $CDCl_3$ with TMS as the external standard[a]

	Compounds			
	22a	**22b**	**23a**	**23b**
C-1	106.3d	104.1d	106.4d	104.1d
$J_{C-1,F}$	218.5	229.4	218.6	230.0
C-2	71.9d	70.5d	72.1d	70.5d
$J_{C-2,F}$	29.4	24.6	29.4	24.8
C-3	71.4	68.2	71.5	68.9
C-4	76.8	77.3	76.9	77.7
C-5	65.8d	64.4d	65.9d	64.7d
$J_{C-5,F}$	7.1	3.5	6.7	3.8
C-6	67.9	67.4	68.0	67.8
C-7[b]	102.1	102.3	102.9	102.9
α-CH_2	35.8	35.5	33.9	33.9
$(CH_2)_n$[c]	17.1	17.0	22.6–31.8	22.6–31.8
CH_3	13.6	13.4	14.0	14.0
CH_3CO	20.4	20.2	20.4	20.5
CH_3CO	169.7	169.8	170.1	170.1
	169.1	169.4	169.5	169.5

[a] δ values in ppm; J values in Hz.
[b] Acetal carbon.
[c] All other CH_2 groups.

lower yields because of cleavage of the acetal group (Table 3), and after 30-min reaction under these conditions the acetal group is completely cleaved.

The anomeric structures of **22** and **23** were determined from C,H-correlated NMR spectra. The α-anomers **22b** and **23b** show H-1 as a double doublet at 5.70 ppm with small coupling constants of 2.8–2.9 Hz, while C-1 gives a doublet at 104.1 ppm with $^1J_{C-1,F}=230$ Hz. The β-anomers **22a** and **23a** have H-1 at 5.37–5.38 ppm and C-1 at 106.3–106.4 ppm. They have larger $J_{H-1,H-2}$ values (5.7–6.0 Hz) and smaller $^1J_{C-1,F}$ values (216.6–218.5 Hz) than those of the α-anomers [12–14]. Further NMR data for **22** and **23** are shown in Tables 4 and 5. In our communication [2] there are mistakes in the NMR data given for H-1 and C-1 in the compounds **22b** and **23b**. The correct data are shown in Tables 4 and 5. The data for H-1 of 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-α-D-glucopyranosyl fluoride [2] are δ 5.65 ppm ($J_{1,F}=53.1$ Hz, $J_{1,2}=3.0$ Hz).

Acknowledgement

R.M. and D.P. wish to thank the Deutsche Forschungsgemeinschaft for financial assistance.

References

1 Part 5: R. Miethchen, T. Gabriel, D. Peters, J. Holz and M. Michalik, *Carbohydr. Res. 214* (1991) 331.
2 R. Miethchen, G. Kolp, D. Peters and J. Holz, *Z. Chem., 30* (1990) 56.
3 R. Miethchen, J. Holz and D. Peters, *Z. Chem., 29* (1989) 420.
4 D. Peters, J. Holz and R. Miethchen, *J. Fluorine Chem., 50* (1990) 217.
5 M. Hayashi, S. Hashimoto and R. Noyori, *Chem. Lett.*, (1984) 1747.
6 W. A. Szarek, G. Grynkiewicz, B. Doboszewski and G. W. Hay, *Chem. Lett.*, (1984) 1751
7 H. Paulsen, *Pure Appl. Chem., 41* (1975) 69.
8 R. Miethchen, *Z. Chem., 29* (1989) 425.
9 K. Bock and C. Pedersen, *Acta Chem. Scand., 27* (1973) 2701.
10 K. Bock and C. Pedersen, *Acta Chem. Scand., 26* (1972) 2360.
11 J. Defaye, A. Gadelle and C. Pedersen, *Carbohydr. Res., 174* (1988) 323.
12 K. Bock and C. Pedersen, *Acta Chem. Scand., B29* (1975) 682.
13 K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem., 41* (1983) 27.
14 R. Csuk and B. I. Glaenzer, *Adv. Carbohydr. Chem. Biochem., 46* (1988) 73.