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Acyloxonium ions in the high-yielding synthesis of oxolanes from alditols, hexoses, and hexonolactones catalysed by carboxylic acids in anhydrous hydrogen fluoride*†

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ABSTRACT

Treatment of D-glucono-1,5- or D-mannono-1,4-lactone with anhydrous hydrogen fluoride catalysed by formic or acetic acid yields 3,6-anhydro-D-glucono- and -D-mannono-1,4-lactone, respectively. Similarly, D-mannitol is converted into 1,4-anhydro-D-mannitol and subsequently into the 1,4:3,6-dianhydride, whereas D-glucitol forms exclusively the 3,6-anhydride and, on further reaction, 1,4:3,6-dianhydro-D-glucitol. D-Glucose and 2-acetamido-2-deoxy-D-glucose are also converted into the corresponding 3,6-anhydrides by reaction with hydrogen fluoride and formic acid. ^{13}C-N.m.r. spectroscopy indicates that the reactions involve intermediate dioxolanylium ions.

INTRODUCTION

The acid-catalyzed formation of anhydrides from alditols usually requires treatment with strong aqueous acid or acidic ion-exchange resins at rather high temperatures[2,3]. Alditols may be converted into dianhydrides by heating with acetic acid and hydrogen chloride[4]. In connection with studies of the reactions of carbohydrates with anhydrous hydrogen fluoride[5,6], it has been observed that treatment of aldonic acids, alditols, or reducing sugars with formic or acetic acid in anhydrous hydrogen fluoride may cause rapid formation of tetrahydrofuran derivatives at room temperature. A related reaction is provided by the behaviour of D-*glycero*-D-*gulo*-heptonolactone towards hydrogen bromide–acetic acid[7].

RESULTS AND DISCUSSION

When a mixture of D-glucono-1,5-lactone (**1**), formic acid (1 equiv.), and anhydrous hydrogen fluoride (HF, 5 parts) was kept for 8 h at 20°, anhydride formation

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‡ Equipe CNRS, SDI 5509.

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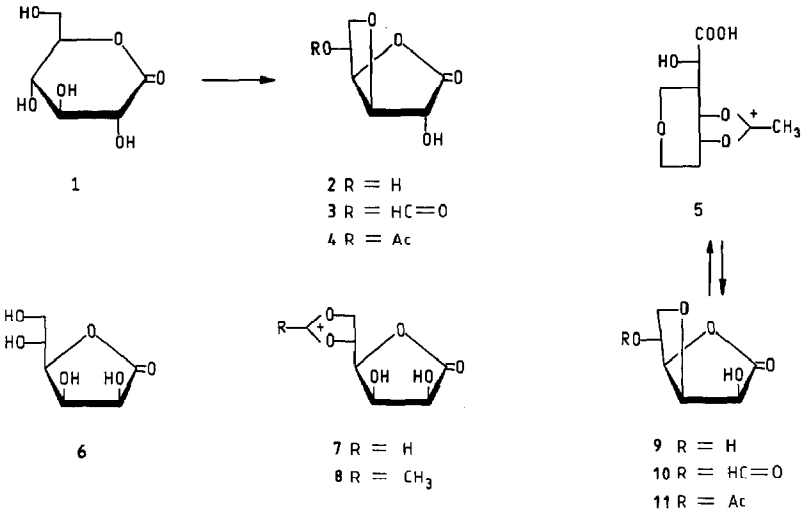


1

2 R = H
3 R = HC=O
4 R = Ac

5

6

7 R = H
8 R = CH_3

9 R = H
10 R = HC=O
11 R = Ac

took place as shown by ^{13}C-n.m.r. spectroscopy. Subsequent evaporation of the HF left a partially formylated product (**3**), treatment of which with water gave 3,6-anhydro-D-glucono-1,4-lactone (**2**, 87%). The same product was obtained when acetic acid was used instead of formic acid, but the reaction required ~15 h at 20° for completion. Furthermore, the resulting partially acetylated product (**4**) was more difficult to hydrolyse than **3**. Therefore, formic acid is preferred for this reaction. Similarly, treatment of D-mannono-1,4-lactone (**6**) with formic acid in HF for ~3 h followed by hydrolysis gave only 3,6-anhydro-D-mannono-1,4-lactone (**9**), as seen from a ^{13}C-n.m.r. spectrum, and crystallisation gave 60% of **9**.

D-Mannitol and D-glucitol were each treated with formic or acetic acid in HF under various conditions (Tables I and II). With 1 equiv. of formic acid and 5 parts of HF, D-mannitol (**12**) was converted into the formate of **24** in 10 h at 20°, which, after hydrolysis and distillation gave the 1,4:3,6-dianhydride **24** in a yield of 67%. A ^{13}C-n.m.r. spectrum of the crude product revealed ~90% of **24** and ~8% of a 2,5-anhydro-hexitol. The latter compound was the main product when **12** was heated with strong aqueous sulphuric acid[3]. When **12** was treated with formic acid–HF for a few min or with acetic acid–HF for 1–2 days, 1,4-anhydro-D-mannitol (**22**) was obtained (Table I). The conversion of D-glucitol (**26**) into 1,4:3,6-dianhydro-D-glucitol (**36**) required treatment with HF for 12 h in the presence of 1 equiv. of formic acid. A ^{13}C-n.m.r. spectrum of the crude product revealed **36** (95%) and ~5% of a 2,5-anhydro-hexitol. When the reaction was interrupted after ~7 min, **26** was no longer present and the main product was 3,6-anhydro-D-glucitol (**30**) together with 10% of **36** (Table II). This result shows that the 3,6-anhydride is formed rapidly and that its conversion into the dianhydride **36** is slower. The other possible intermediate, 1,4-anhydro-D-glucitol, was not observed. When D-glucitol was converted into the dianhydride **36** by treatment with aqueous acid, the 1,4-anhydride was the main intermediate and only ~3% of the 3,6-anhydride **30** was observed[3].

TABLE I

Products[a] obtained by reaction of D-mannitol with HF and formic or acetic acid at 20°

Formic acid (equiv.)	*HF (mL/g of mannitol)*	*Reaction time*	*1,4-Anhydride (22)*	*Dianhydride (24)*	*2,5-Anhydro-D-glucitol*[b]
1	2	23 h	0	96 (70)	4
1	5	8 h	5	93	2
1	5	30 min	50 (41)	41	9
1	5	8 min	68 (62)	23	7
Acetic acid					
1	2	6 days		90	
1	2	48 h	32 (20)	64	4
1	2	23 h	47 (27)	47	6
1	4	24 h	65 (47)	35	4
1	8	36 h	58 (50)	32	
2	4	45 h	53 (35)	47	
2	6	45 h	93 (69)	5	2

[a] Product compositions were estimated from the ^{13}C-n.m.r. spectra of the crude products obtained after evaporation of the HF and hydrolysis of the esters. Yields in parentheses are for products isolated by crystallisation or distillation. [b] Identified only by the ^{13}C-n.m.r. spectrum.

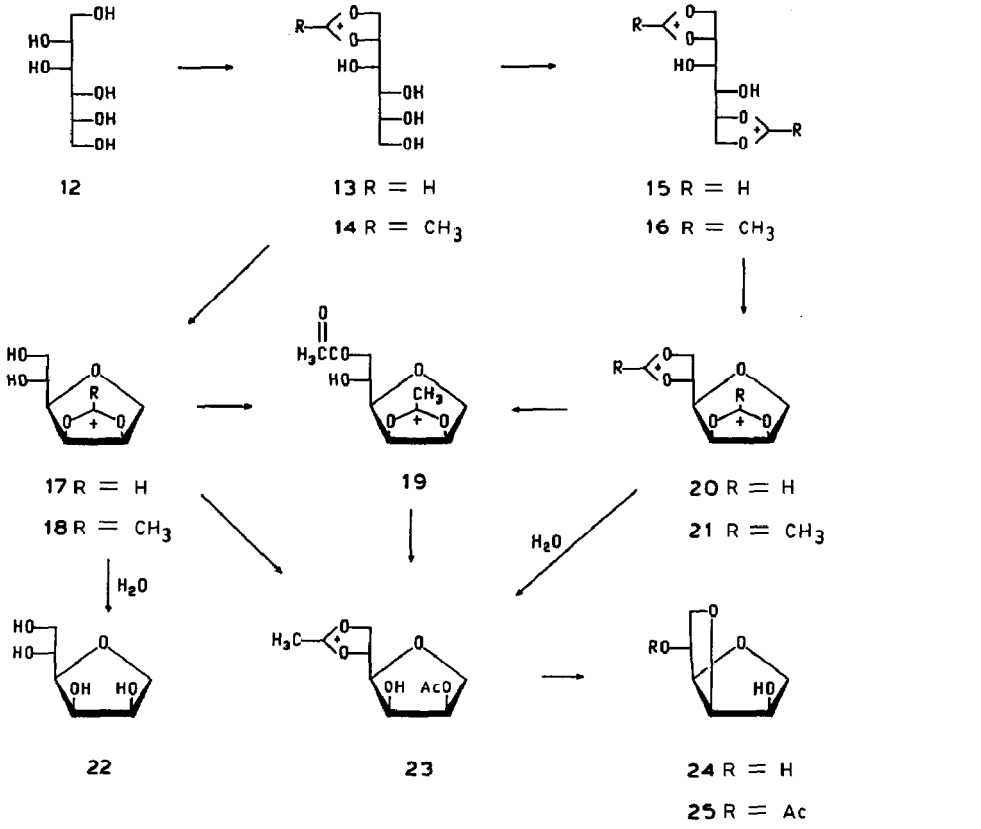
TABLE II

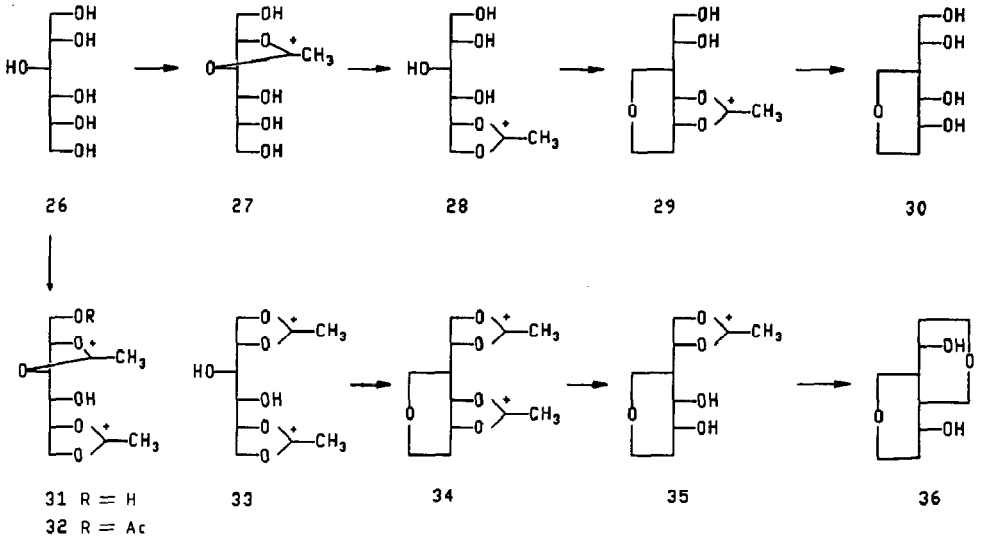
Products obtained by reaction of D-glucitol with HF and formic or acetic acid under various conditions[a]

Formic acid (equiv.)	*HF (mL/g of glucitol)*	*Reaction time*	*3,6-Anhydride (30)*	*Dianhydride (36)*	*2,5-Anhydro-hexitol*[b]
5	4	5 days	10	88	4
1	4	12 h		95 (57)	5
1	5	4 h	26	69	4
1	5	1 h	51	44	6
1	5	15 min	73	20	6
1	10	7 min	85	10	5
Acetic acid					
1	2	24 h	68 (24)	28	4
1	4	24 h	81	15	4
2	3	6 days	5	85	3
2	4	45 h	88 (47)	13	traces
2	6	45 h	82 (56)	13	traces

[a] For further details, see Table I. [b] Identified only by the ^{13}C-n.m.r. spectrum.

Treatment of D-glucose (**37**) with formic acid–HF gave a complex mixture of products. However, ^{13}C-n.m.r. spectroscopy of the mixture showed that all signals were below 70 p.p.m. and there were no signals at 60–65 p.p.m. where C-6 of hexoses resonate[8]. This result indicated that the anhydride **38** was formed but was converted into reversion products similar to those obtained[5] by treatment of glucose with pure HF[4]. In

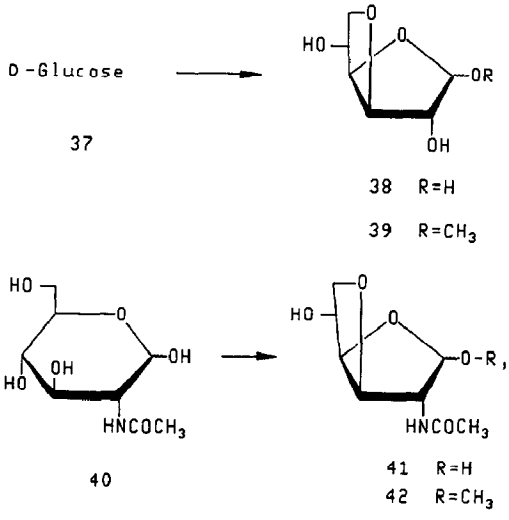

12
13 R = H
14 R = CH3
15 R = H
16 R = CH3
17 R = H
18 R = CH3
19
20 R = H
21 R = CH3
H2O
22
23
24 R = H
25 R = Ac


26
27
28
29
30
31 R = H
32 R = Ac
33
34
35
36

order to avoid the formation of reversion products, the mixture of products from glucose, formic acid, and HF was diluted with methanol and work-up then gave almost exclusively a mixture (**39**) of the anomeric methyl 3,6-anhydro-α- and -β-D-glucofuranosides.

Treatment of 2-acetamido-2-deoxy-D-glucose (**40**) with formic acid–HF gave the crystalline 3,6-anhydride **41**, which did not form reversion products[1]. Following treatment with methanol, the methyl β-D-furanoside β-**42** was obtained. The same products could be obtained from chitin after preliminary degradation in HF.

Formic acid or acetic acid, or probably other carboxylic acids, are necessary for the ready formation of the anhydrides described above. Thus, D-glucono-1,5-lactone and D-mannitol were unaffected on treatment with HF for several days. D-Glucitol reacted slowly with HF and gave mainly the 1,4-anhydride and subsequently the dianhydride, but >2 weeks at 20° were required to complete the reaction. Prolonged reaction of D-glucose with HF produced small amounts of 3,6-anhydro-D-glucose[9]. Since carboxylic acids react readily with di- or poly-valent alcohols in HF to yield esters and subsequently dioxolenium ions[10], it is probable that a similar reaction takes place during the formation of the anhydrides. Thus, D-mannono-1,4-lactone (**6**) could react with a carboxylic acid in HF to give an ester, probably preferentially at O-6, and then the dioxolenium ion **7** or **8**. Meerwein *et al.*[11] showed that dioxolenium ions react with ethanol to give ethers with opening of the ionic ring. Furthermore, tetrahydrofuran derivatives are formed by treatment of acylated polyols with HF, presumably *via* acetoxonium ions[12]. The formation of the 2,5-dibenzoate of dianhydro-D-glucitol by heating 1,6-di-*O*-benzoyl-D-glucitol with *p*-toluenesulfonic acid[13] may involve intermediate benzoxonium ions[14]. Dioxolanylium ions are probably intermediates when dianhydrides are prepared from glucitol or mannitol by treatment with hydrogen chloride and a carboxylic acid[4], or from glucitol by treatment with an acidic ion-exchange resin in the presence of ethyl acetate[15]. Hence, the ions **7** or **8** might also be expected to form an acylated 3,6-anhydride (**10** or **11**). In order to confirm this mechanism, some of the reactions described above were monitored by ^{13}C-n.m.r. spectroscopy.



When a mixture of D-mannono-1,4-lactone (**6**), acetic acid (1 equiv.), and HF (4 parts) was kept at 20°, ^{13}C-n.m.r. spectroscopy after 10 min showed that the solution contained virtually only the 5,6-acetoxonium ion **8** as seen from the signals at 15.1 and 193.7 p.p.m.[16] (Table III); only traces of acetic acid or acetoxy groups were indicated by the signals at 20 p.p.m.. After 24 h, some **8** remained, but it had disappeared after 45 h and the main product was the ion **5** together with a smaller quantity of the partially acetylated anhydride **11**. The structure of **5** was deduced from the fact that work-up at this stage gave 3,6-anhydro-D-mannonolactone. The signals at 15.1 and 194.3 p.p.m. (Table III) showed that an acetoxonium ion was present and the two signals at 95.7 and 93.9 p.p.m. indicated that this ion was fused to a five-membered ring, since secondary carbon atoms in simple acetoxonium ions resonate at ~89 p.p.m.[16].

When D-mannono-1,4-lactone was treated with 1 equiv. of formic acid in HF at −10°, the 5,6-formoxonium ion **7** was the main product after 20 min (Table III). The temperature was then raised to 20° and a spectrum obtained after 45 min showed that a complete conversion into a mixture of two 3,6-anhydrolactones, probably formylated at O-5 (**10**) or O-2, had taken place. No formoxonium ion was present, as seen from the disappearance of the signal of **7** at 181.4 p.p.m. and the appearance of a signal at 167.9 p.p.m. that corresponded to esters of formic acid. Thus, the 3,6-anhydride was formed more rapidly with formic acid than with acetic acid. Apparently, the 5,6-ions **7** and **8** are

TABLE III

^{13}C-N.m.r. data [−10°, 22.6 or 62.9 MHz, internal acetone-d_6 (29.8 p.p.m.)] for solutions in hydrogen fluoride

Dioxolanylium ion	*Chemical shifts (p.p.m.)*							
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	$-\overset{+}{C}\!<^{O-}_{O-}$	$H_3C-\overset{+}{C}\!<^{O-}_{O-}$
7	179.9	72.4[a]	70.1[a]	80.9	89.5	76.9	181.4	
8	180.6	72.5[a]	70.6[a]	81.8	88.9	76.8	193.7	15.1
5	176.5	71.7[a]	73.2[a]	95.7[b]	93.9[b]	73.2	194.3	15.1
13	72.9	92.1	68.9[a]	70.3[a]	71.0[a]	64.6	178.9	
17	72.9[a]	96.5[b]	94.8[b]	81.1	73.2[a]	65.1	179.3	
14	72.9	89.7	69.8[a]	70.2[a]	71.3[a]	63.7	194.1	15.0
16	77.4	91.4	70.2	70.2	91.4	77.4	193.9	15.1
18	73.3	94.5[a]	95.9[a]	81.4	70.5	65.3	194.3	15.0
19	73.3	94.5[a]	95.9[a]	81.4	68.8	68.1	193.3	15.0
21	73.2	93.5[a]	96.2[a]	80.1	84.9	77.6	194.3	15.0, 15.1
27	64.7	92.2[a]	90.1[a]	72.4[b]	70.4[b]	62.0	[d]	14.9
X	63.9[a]	77.0[b]	89.6[c]	91.2[c]	78.4[b]	64.0[a]	[d]	[d]
33	78.4[a]	89.9[b]	70.2[c]	71.2[c]	89.7[b]	77.4[a]	[d]	[d]
31	61.9	91.4[a]	93.0	68.6	89.2[a]	77.2	[d]	15.0
32	64.2	88.7[a]	89.6[a]	68.1	89.7[a]	76.6	[d]	15.0
29	65.7	71.1[a]	81.7	94.3[b]	96.2[b]	72.8[a]	[d]	15.0
34	79.1[a]	85.7	80.3[a]	93.2[b]	96.4[b]	72.9	[d]	15.0, 15.1

[a-c] Assignments may be reversed. [d] Not assigned.

formed rapidly, but the subsequent formation of anhydride takes place more rapidly from the formoxonium ion **7**, probably because the latter is less stable than the acetoxonium ion **8** (ref. 17). The higher stability of acetoxonium ions may also explain why **5** is formed in equilibrium with **11**.

When a mixture of D-mannitol (**12**), acetic acid (1 equiv.), and HF (4 parts) was kept for 15 min at 20°, a mixture of the 1,2-acetoxonium ion **14** and the 1,2:5,6-diacetoxonium ion **16** (Table III) together with **12** was present. With 2 equiv. of acetic acid, **16** was almost the only species present after 20 min (Fig. 1). A proton-coupled ^{13}C-n.m.r. spectrum of **16** confirmed the assignment (Table III) and showed the signal for C-1,6 as a triplet. When the mixture was kept at 20°, the ions **14** and **16** reacted slowly and, after 20 h, they were replaced by the 1,4-anhydro-acetoxonium ions **18** and **21**, respectively (Table III). With 1 equiv. of acetic acid, **18** preponderated but some **21** and the dianhydride **25** were present. With 2 equiv. of acetic acid, the diacetoxonium ion **21** was the main product (Fig. 1) and there was a small proportion of the 6-acetylated ion **19**. When the HF solutions were kept at 20°, **18** slowly gave the dianhydride **25**. The diacetoxonium ion **21** was almost unchanged after 6 days. The conversion of **18** and **21** into the dianhydride **25** must take place *via* **23**, involving hydrolysis of the 2,3-ion and, for **18**, the formation of a 5,6-acetoxonium ion after acetylation at C-6. Water is formed during the reactions and the consequent hydrolysis of the 2,3-acyloxonium ions in **18** and **21** will depend on the amount of HF used. Thus, when 6–8 parts of HF were used, the monoanhydride **22** may be obtained in rather good yield (Table I) because its conversion into the dianhydride is slow.

When the reaction of D-mannitol with formic acid in HF was monitored by ^{13}C-n.m.r. spectroscopy, the formoxonium ions **13** and **17** were observed as intermediates at $-10°$, but they disappeared rapidly and, after a few h at 20°, the only product was the formylated dianhydride **24**. The reaction may be carried out with only 0.2 equiv. of formic acid and the formation of the dianhydride is complete in a few h. This result shows that the formyl group of **24** is transferred to mannitol in order to complete the reaction.

The treatment of D-glucitol (**26**) with acetic acid in HF solution gave initially complex mixtures of acetoxonium ions as seen from ^{13}C-n.m.r. spectra (Table IV). With 1 equiv. of acetic acid, the preponderant species was a monoacetoxonium ion that contained two secondary carbon atoms (90.1 and 92.2 p.p.m.) and two primary hydroxyl groups (62.0 and 64.7 p.p.m.) (Table III), and was assumed tentatively to be the 2,3-acyloxonium ion **27**. A second disecondary acetoxonium ion (X in Tables III and IV) was present in small amounts which was probably the 3,4-acetoxonium ion, since a 4,5-acyloxonium ion with a *cis*-substituted five-membered ring would be less stable. When 2 equiv. of acetic acid were used, only small amounts of **27** were formed and the main products observed initially were a mixture of two diacetoxonium ions, assumed to be the 1,2:5,6-diacyloxonium di-ion **33** and the 2,3:5,6-diacyloxonium di-ion **31** (Table IV and Fig. 1). Since they were present in nearly equal amounts, their ^{13}C-n.m.r. signals could not be assigned completely. However, of the twelve signals, five found at 89.2–92.9 p.p.m. (Table III) indicated secondary carbon atoms in acetoxonium ions (*cf.* the

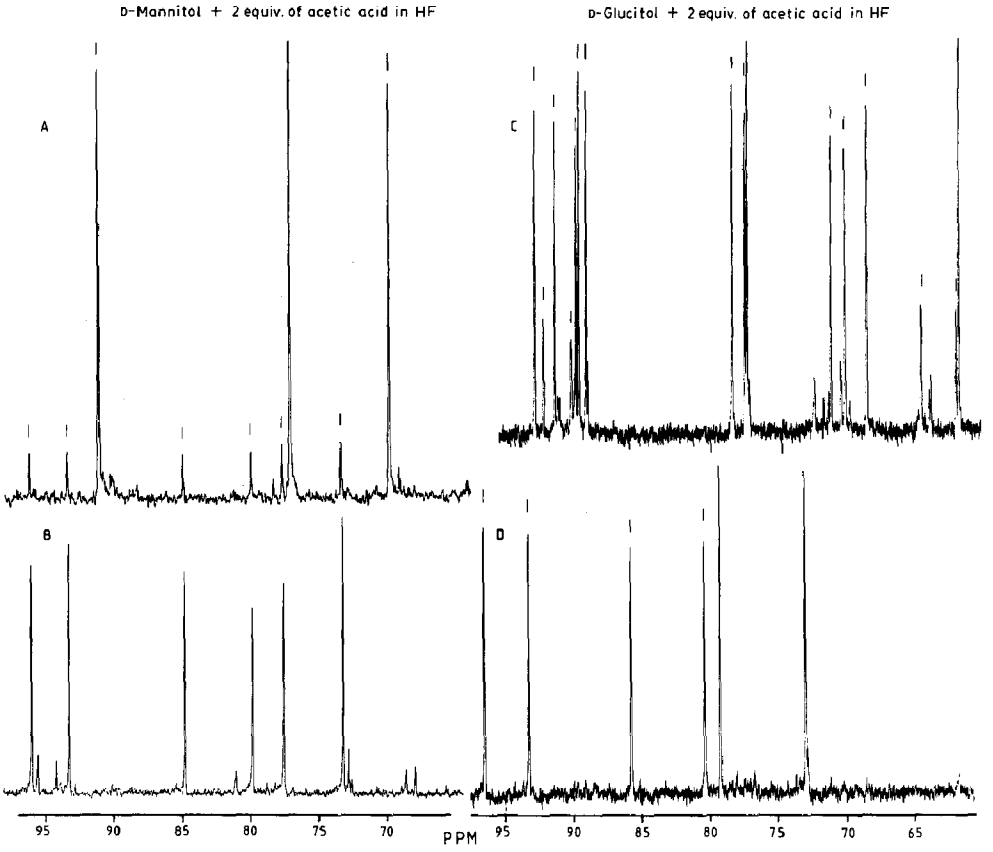


Fig. 1. ^{13}C-N.m.r. spectra for solutions in anhydrous hydrogen fluoride: *A*, after 2 h at 0°, the main product was **16**; *B*, after 27 h at 20°, the main product was **21**; *C*, after 5 h at 20°, the mixture contained mainly **31** and **33**; *D*, after 48 h at 20°, the only product was **34**.

spectra of **7**, **14**, and **16** in Table III). Three signals at 77.2–78.4 p.p.m. were probably primary carbon atoms in acetoxonium ions, and a signal at 61.9 clearly showed that an unreacted primary hydroxy group, probably HO-1 of **31**, was present. With 3 equiv. of acetic acid, **31** and **33** were also the preponderant species together with a third diacetoxonium ion which may be **32**, the 1-acetate of **31** (Tables III and IV). Since **32** was only present when 3 equiv. of acetic acid were used, its ^{13}C-n.m.r. signals could be obtained by comparison with the spectra obtained using 2 equiv. of acetic acid. From the shifts of **32**, those of **31** could be assigned tentatively through acylation shifts[8].

After 24-h reaction of D-glucitol with acetic acid in HF, the ions **27**, **31**, and **33** had almost disappeared and n.m.r. spectra showed that acetoxonium ions derived from 3,6-anhydro-D-glucitol were formed (Table IV). With 1 equiv. of acetic acid, the 4,5-acyloxonium ion **29** was the main product together with some 1,2:5,6-diacyloxonium ion **34**. Since neither **27** nor **31** could form **29** or **35**, they probably underwent hydrolysis and reacylation to give **28** (not observed) or **33** prior to ring closure. With 2

TABLE IV

Compounds observed[a] in solutions of D-glucitol (1 g) in HF + DF (1:1, 6 mL) containing 1–3 equiv. of acetic acid

Reaction time (h/temperature)	*Acetic acid (equiv.)*	*Compound (%)*									
		26	**27**	**31**	**33**	**X**	**34**	**29**	**36**[b]	**32**	**21**
0.5/0°	1	14	42	16	16	12					
5/0°	1	9	38	20	18	14					
2/20°	1	8	35	15	14	11	3	13			
20/20°	1		5				25	58	12		
48/20°	1						40	34	26		
0.5/0°	2	4	11	44	36	4					
5/0°	2		15	41	41	4					
2/20°	2			43	43		14				
20/20°	2			5	5		90				
48/20°	2						90				
1/20°	3		15	36	36	4				9	
2/20°	3			29	29		11			31	
24/20°	3			4	4		61			8	11
70/20°	3						73				27
145/20°	3						63		11		26

[a] The reactions were monitored through ^{13}C-n.m.r. spectroscopy (62.8 MHz) at −10°. Relative amounts (%) were calculated from the peaks of the secondary carbon atoms. [b] Partially acetylated.

equiv. of acetic acid, **34** was virtually the only product formed (Fig. 1), analogous to the result obtained with D-mannitol (see above), and this ion remained the main product for 1–2 weeks. Hydrolysis at this stage gave a good yield of 3,6-anhydro-D-glucitol (**30**) (Table II). With 3 equiv. of acetic acid, **34** was also the main product formed on prolonged reaction but was accompanied by the ion **21** (27% after 70 h; Table IV). The latter ion may have been formed from **32**, which could undergo rearrangement to give the 3-acetate of **16**. Subsequent loss of the acetyl group and ring closure would then give **21**. Its formation was confirmed by the isolation of 1,4-anhydro-D-mannitol after hydrolysis.

Thus, the reaction of D-glucitol is rather complex and, although most of the intermediates have been assigned tentatively, no explanation has been found for the exclusive formation of the 3,6-anhydride **30** in the presence of formic or acetic acid.

EXPERIMENTAL

General methods. — ^{13}C-N.m.r. spectra (internal 1,4-dioxane, 67.40 p.p.m.) were recorded on a Bruker WH-90 or AM-250 instrument. The spectra for solutions in HF were obtained in Teflon or polyethylene tubes each of which fitted tightly inside a 5-mm glass tube. Acetone-d_6 or DF was used for the lock. Melting points are uncorrected. All

reactions in anhydrous hydrogen fluoride (HF) were carried out in polyethylene bottles.

*3,6-Anhydro-*D*-glucono-1,4-lactone* (**2**). — A mixture of D-glucono-1,5-lactone (**1**, 10.0 g) and formic acid (2.1 mL, 1 equiv.) was dissolved in HF (40 mL) with ice-cooling. The solution was kept for 8 h at 20°, most of the HF was then evaporated in a stream of air, and water was evaporated three times from the residue, a solution of which in water was filtered through carbon and concentrated. Crystallisation from ethyl acetate then gave **2** (7.9 g, 87%), m.p. 111–114°. Recrystallisation gave a product with m.p. 114–116°, $[\alpha]_D^{20}$ +82° (*c* 6.4, water); lit.[18] m.p. 115°, $[\alpha]_D$ +82.3°. ^{13}C-N.m.r. data (D_2O): 178.8 (C-1), 83.5, 81.9 (C-3,4), 73.8, 73.6 (C-2,5), and 69.9 p.p.m. (C-6).

*3,6-Anhydro-*D*-mannono-1,4-lactone* (**9**). — Treatment of D-mannono-1,4-lactone (**6**, 2.5 g) with HF–formic acid, as described above, and crystallisation of the product from ethanol–ethyl acetate gave **9** (1.35 g, 60%), m.p. 108–110°, $[\alpha]_D^{20}$ +125° (final) (*c* 2.8, water): lit.[19] m.p. 113°, $[\alpha]_D$ +115.3°. ^{13}C-N.m.r. data: 178.4 (C-1), 81.8 (C-4), 78.4 (C-3), 72.0, 70.9, and 70.1 p.p.m. (C-2,5,6).

*1,4:3,6-Dianhydro-*D*-mannitol* (**24**). — A mixture of D-mannitol (**12**, 10 g) and formic acid (2.1 mL, 1 equiv.) in HF (40 mL) was kept for 10 h at 20°, then concentrated in a stream of air, and water was evaporated 3 times from the residue (8.9 g), which was distilled in vacuum to give **24** (5.4 g, 67%), b.p. 100–102° (133 Pa). Crystallisation from ethyl acetate–pentane gave material (4.2 g) having m.p. 87–88.5°, $[\alpha]_D^{20}$ +91° (*c* 3.1, water); lit.[20] m.p. 86.0–86.5°, $[\alpha]_D$ +90.9°.

*1,4:3,6-Dianhydro-*D*-glucitol* (**36**). — A mixture of D-glucitol (5 g) and formic acid (1.0 mL) in HF (20 mL) was kept for 20 h at 20° and then worked-up as described above, to give **3b** (2.8 g, 70%), b.p. 125° (133 Pa), which crystallised on cooling. Recrystallisation from ethyl acetate–ether gave a product with m.p. 61–63°, $[\alpha]_D^{20}$ +45.5° (*c* 1.7, water); lit.[13] m.p. 62–64°, $[\alpha]_D$ +44.8°.

*1,4-Anhydro-*D*-mannitol* (**22**). — A mixture of D-mannitol (5 g) and acetic acid (3.1 mL, 2 equiv.) in HF (30 mL) was kept for 45 h at 20°, then worked-up as described above. The product was deacetylated conventionally with methanolic sodium methoxide to give a product (4.5 g) that contained 93% of **22** (^{13}C-n.m.r. spectrum; Table I). Crystallisation from ethanol–ethyl acetate gave **22** (3.1 g, 69%), m.p. 134–137°. An additional recrystallisation yielded a product with m.p. 143–145°, $[\alpha]_D^{20}$ −24° (*c* 2.5, water): lit.[20] m.p. 145–148°, $[\alpha]_D$ −23.7°.

Alternatively, a mixture of D-mannitol (2.0 g) and formic acid (0.42 mL, 1 equiv.) in HF (5 mL) was kept for 8 min. Water (1 mL) was then added, and the solution was concentrated in a stream of air at 60°. Water was evaporated from the residue, which was crystallised from ethanol–ethyl acetate to give **22** (1.12 g, 62%), m.p. 139–141°.

*3,6-Anhydro-*D*-glucitol* (**30**). — Treatment of D-glucitol (5.0 g) with acetic acid (3.1 mL) and HF (30 mL) for 45 h, as described above, gave a product (4.2 g) that contained 82% of **30** (^{13}C-n.m.r. spectrum; Table II). Crystallisation from ethanol–ethyl acetate gave **30** (2.5 g, 56%), m.p. 105°. Recrystallisation gave a product with m.p. 110–112°, $[\alpha]_D^{20}$ −7.3° (*c* 1.7, water); lit.[18] m.p. 113°, $[\alpha]_D$ −7.5°.

*1,4-Anhydro-*D*-mannitol* (**22**) *from* D*-glucitol.* — A mixture of D-glucitol (5 g) and acetic acid (4.75 mL, 3 equiv.) in HF (30 mL) was kept for 96 h at 20°, then concentrated

to 10 mL in a stream of air. Water (5 mL) was added and the solution was concentrated in a stream of air at 60°. Water (3 × 20 mL) was evaporated from the residue under vacuum at 60°. Crystallisation from ethanol gave a product (800 mg) that was a 1:1 mixture of **22** and 3,6-anhydro-D-glucitol (**30**). Three recrystallisations from ethanol gave **22** (150 mg), m.p. 141–143°, $[\alpha]_D^{20}$ −24° (*c* 1.2, water). A ^{13}C-n.m.r. spectrum confirmed the structure and purity of the product.

Methyl 3,6-anhydro-α- and -β-D-glucofuranoside (**39**). — A mixture of D-glucose (10 g) and formic acid (2.1 mL, 1 equiv.) in HF (40 mL) was kept overnight at 20°. Methanol (40 mL) was then added with cooling and, after 2 h at 20°, the solution was concentrated in a stream of air at ~50°. Methanol was evaporated from the residue, a solution of which in methanol was neutralised ($CaCO_3$), filtered through activated carbon, and concentrated to give a syrup (8 g) that consisted mainly of **39** (ref. 21). Distillation gave a syrup (5.5 g), b.p. 120–130° (133 Pa), which was a mixture of α- and β-**39** in the ratio 4:6 (^{13}C-n.m.r. spectrum in D_2O): α-**39**: 106.0 (C-1), 87.8, 79.5 (C-3,4), 77.2, 76.7 (C-2,5), 70.8 (C-6), 56.2 p.p.m. (OMe); β-**39**: 111.5 (C-1), 87.0, 84.6 (C-3,4), 79.6, 71.6 (C-2,5), 70.9 (C-6), 56.3 p.p.m. (OMe).

2-Acetamido-3,6-anhydro-2-deoxy-D-glucose (**41**). — (*a*) *From 2-acetamido-2-deoxy-D-glucose.* To a mixture of 2-acetamido-2-deoxy-D-glucose (**40**, 5 g) and formic acid (0.5 mL) was added anhydrous hydrogen fluoride (20 mL), and the solution was kept at 20° for 6 h. The HF was then evaporated in a stream of air, and a solution of the residue in water was neutralised with calcium carbonate, filtered, and concentrated. The syrupy residue was crystallised from ethanol–ethyl acetate to give **41** (3.0 g, 67%), m.p. 136–137°, $[\alpha]_D^{25}$ +108° (*c* 1, water). ^{13}C-N.m.r. data: 103.2 (β C-1), 98.5 (C-1α), 86.6, 86.5 (C-4), 83.6 (C-3α), 79.7 (C-3β), 71.9, 71.1 (C-6), 62.7 (C-2α), 59.5 (C-2β), and 22.6 p.p.m. (H_3CC–O).

Anal. Calc. for $C_8H_{13}NO_5$: C, 47.29; H, 6.40; N, 6.89. Found: C, 47.32; H, 6.50; N, 6.23.

(*b*) *From chitin.* A mixture of chitin (5 g) and HF (20 mL) was stirred at 20° until a homogeneous solution was obtained (~10 min), then kept overnight[22]. Formic acid (0.5 mL) was added and, after 6 h at 20°, the mixture was processed as described in (*a*) to give, after three recrystallisations, **41** (2.1 g, 47%), m.p. 135–137°, $[\alpha]_D^{25}$ +105° (*c* 1, water).

Methyl 2-acetamido-3,6-anhydro-2-deoxy-β-D-glucofuranoside (**42**). — (*a*) *From 2-acetamido-2-deoxy-D-glucose.* A mixture of 2-acetamido-2-deoxy-D-glucose (5 g), formic acid (0.5 mL), and HF was kept for 6 h at 20°, then cooled, and methanol (10 mL) was added. The solvents were evaporated in a stream of air and subsequently in vacuum, and a solution of the residue in methanol was neutralised ($CaCO_3$), filtered, and concentrated to give **42** (2.6 g, 53%) as a hygroscopic powder. ^{13}C-N.m.r. data: 110.3 (C-1), 86.2 (C-4), 85.4 (C-3), 71.7 (C-5), 71.1 (C-6), 62.8 (C-2), 56.4 (OMe), 22.6 (H_3CCO), and 174.5 p.p.m. (C–O).

Anal. Calc. for $C_9H_{15}NO_5$: C, 49.77; H, 6.91; N, 6.45. Found: C, 49.90; H, 7.03; N, 6.35.

The product was contaminated with unreacted **40** (25%, ^{13}C-n.m.r. data), and $<5\%$ of the α-glycoside was found.

(*b*) *From chitin.* The same product as in (*a*) was obtained from chitin by depolymerisation with HF followed by treatment with formic acid and evaporation with methanol.

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