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Acid Catalyzed Dehydration of Alditols. Part I. D-Glucitol and D-Mannitol

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The acid catalyzed dehydration of D-glucitol and D-mannitol has been studied using ^{13}C NMR spectroscopy to monitor the reactions. The products formed were identified and rate constants were measured. Dehydration of (1*S*)-1-^{2}H-D-mannitol with 3 M sulfuric acid was shown to yield (1R)-1-^{2}H-1,4:3,6-dianhydro-D-mannitol, showing that dehydration of D-mannitol to 1,4-anhydro-D-mannitol and, subsequently, to the 1,4:3,6-dianhydride takes place with inversion at the primary carbon atom.

The acid catalyzed dehydration of pentitols and hexitols yields anhydro- and dianhydro-alditols.[1,2] The dehydrations often lead to complex mixtures of products which have in many cases not been completely analyzed. Barker *et al.* carried out the most extensive investigation of the dehydration of pentitols and hexitols, using gas chromatographic analysis,[3,4] but concentrating primarily on the initial stages of the reactions whereas complete information as to the composition in the final stages was not provided. We have studied the dehydration of a series of alditols and deoxyalditols in 3 M sulfuric acid using ^{13}C NMR spectroscopy to monitor the reactions. In some cases dehydration with an acidic ion exchange resin was used for preparative purposes. In the present paper the dehydration of D-glucitol and D-mannitol is described.

Alditols and their anhydrides have simple ^{13}C NMR spectra, most of which have been described[5–9] (Table 1), and the composition of mixtures containing several of these compounds can be assessed from ^{13}C NMR spectra measured directly on the reaction mixtures. Although integrals or peak heights from ^{13}C NMR spectra may be

Table 1. ^{13}C NMR chemical shifts of alditols and anhydroalditols. All values were measured at 22.63 MHz in D_2O solution using internal dioxane (67.4 ppm) as reference.

Compound	Chemical shift/ppm					
	C-1	C-2	C-3	C-4	C-5	C-6
D-Glucitol (*1*)[5,8,9]	63.8	74.3	71.0	72.6	72.5	64.2
D-Mannitol (*7*)[5,9]	64.6	72.2	70.7	70.7	72.2	64.6
1,4-Anhydro-D-glucitol (*2*)[6,a]	74.3	77.3	76.8	80.8	70.3	64.5
3,6-Anhydro-D-glucitol (*3*)	63.8	71.6	81.3	71.3	72.3	72.2
1,4-Anhydro-D-mannitol (*8*)[6]	71.9	72.3	71.2	81.1	70.3	64.0
1,5-Anhydro-D-mannitol (*10*)[6]	70.8	70.0	74.5	68.2	81.5	62.1
2,5-Anhydro-D-glucitol (*9*)[6]	61.1	81.9	77.9	79.0	85.7	62.4
2,5-Anhydro-L-iditol (*4*)[6]	61.0	81.3	77.6	77.6	81.3	61.0
2,5-Anhydro-D-mannitol (*5*)[6]	61.9	83.2	77.3	77.3	83.2	61.9
1,4:3,6-Dianhydro-D-glucitol (*6*)[7]	76.2	76.6	88.5	82.5	72.9	72.2
1,4:3,6-Dianhydro-D-mannitol (*11*)[7]	73.0	73.0	82.7	82.7	73.0	73.0

[a] Some assignments reversed relative to original data.

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Table 2. Products resulting from boiling D-glucitol (2.9 g) in 3 M sulfuric acid (6.6 ml) at 104 °C.

Time h	Products/%					
	1	*2*	*3*	*4*	*5*	*6*
0	100	0	0	0	0	0
6	53.4	38.9	2.6	2.9	0.8	1.5
8	41.9	49.0	2.4	3.7	1.0	2.1
28	4	74	0	6	1	15
52	0	66	0	6	2	26
70	0	59	0	7	2	32
103	0	47	0	7	2	44
172	0	27	0	7	2	64
∞ [a]	0	0	0	6	2	92

[a] Calculated value. Calculated rate constants (h^{-1})

k_0	$k_{1,2}$	$k_{1,3}$	$k_{1,4}$	$k_{1,5}$	$k_{2,6}$	$k_{3,6}$
0.109	0.092	0.008	0.007	0.002	0.0059	0.136

misleading due to difference in relaxation rates it is possible to obtain rather accurate (*i.e.* ±2.5 %) quantitative data from carbon spectra (see Experimental).

Solutions of D-glucitol (*1*) in 3 M sulfuric acid were heated under reflux (at 104 °C) and ^{13}C NMR spectra were measured at intervals. The results of one such experiment are presented in Table 2 and a typical ^{13}C NMR spectrum is shown in Fig. 2. From these data the rate constants (Table 2) were estimated using the following equations:

$$C_1 = C_0 \exp(-k_0 t)$$

$$C_2 = k_{1,2} C_0 (k_{2,6} - k_0)^{-1} [\exp(-k_0 t) - \exp(-k_{2,6} t)]; \quad (k_{2,6} \neq k_0)$$

$$C_3 = k_{1,3} C_0 (k_{3,6} - k_0)^{-1} [\exp(-k_0 t) - \exp(-k_{3,6} t)]; \quad (k_{3,6} \neq k_0)$$

$$C_4 = k_{1,4} C_0 k_0^{-1} [1 - \exp(-k_0 t)]$$

$$C_5 = k_{1,5} C_0 k_0^{-1} [1 - \exp(-k_0 t)]$$

$$C_6 = C_0 - C_1 - C_2 - C_3 - C_4 - C_5$$

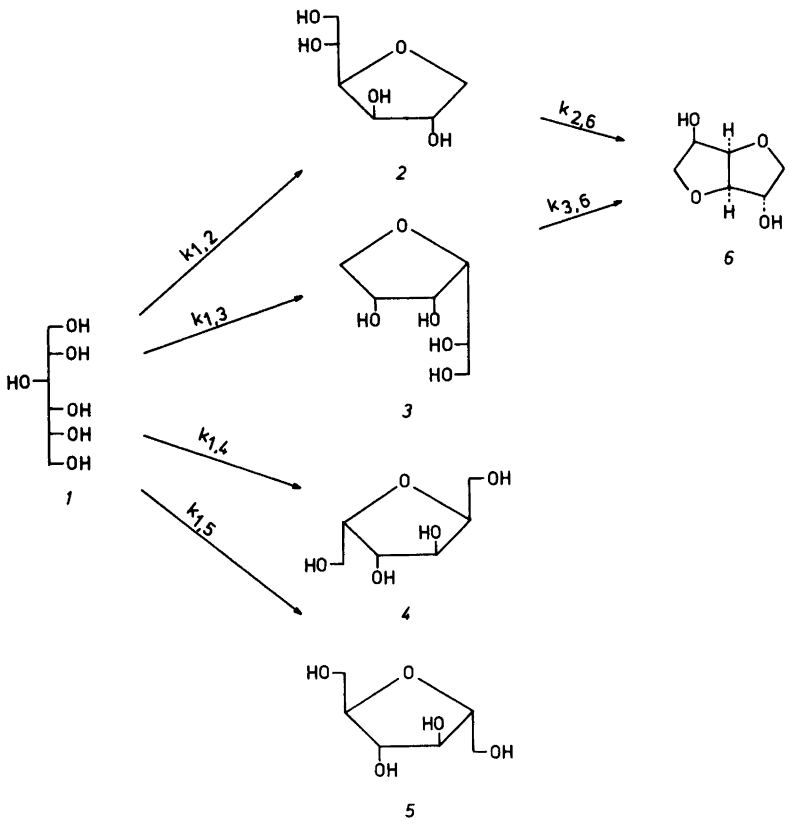

Fig. 1. Formation of *2*–*6* from D-glucitol (*1*).

(C are concentrations of compounds *1* to *6*, C_0 being the initial conc. of D-glucitol; $k_{1,2}$ *etc.* are the rate constants shown in Fig. 1; $k_0 = k_{1,2} + k_{1,3} + k_{1,4} + k_{1,5}$ is the rate constant for the disappearance of D-glucitol). For the calculations it was assumed that the reactions shown in Fig. 1 are irreversible.

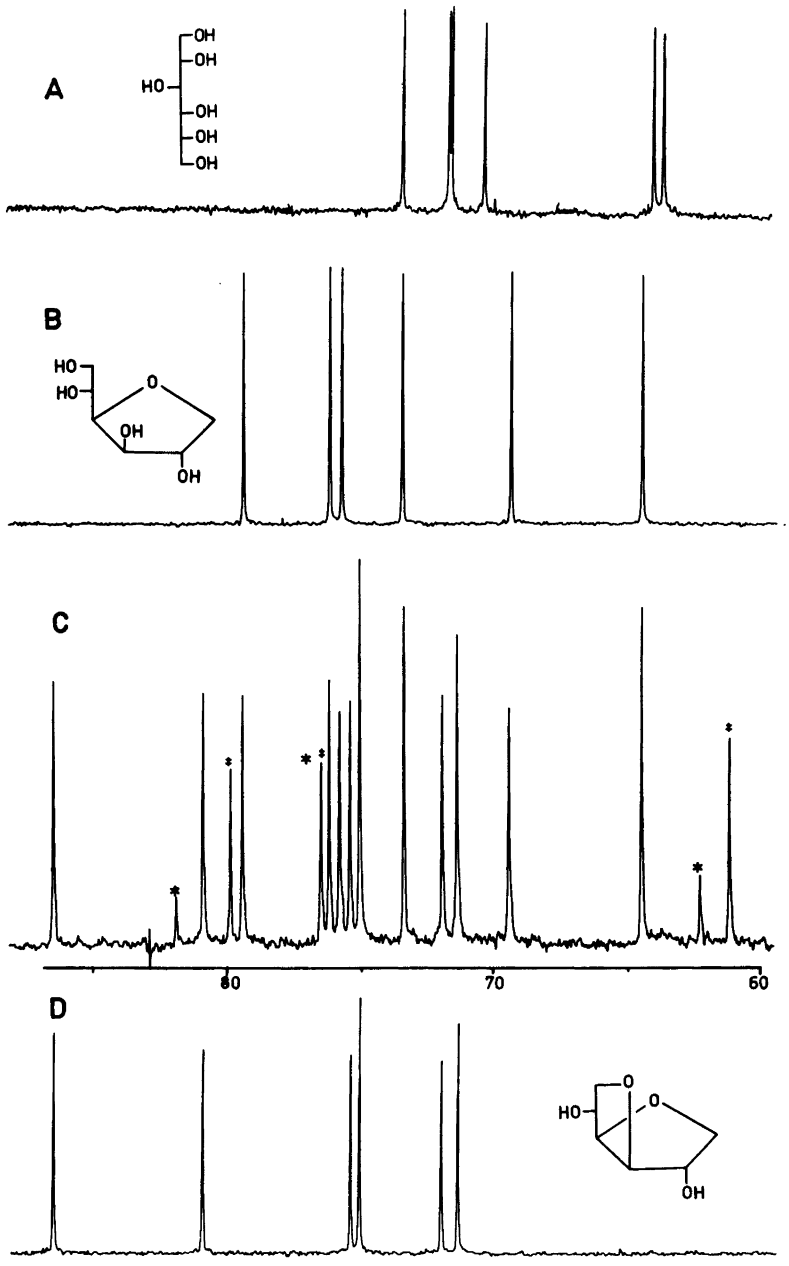

Fig. 2. ^{13}C NMR spectra in D_2O at 67.89 MHz. A. D-Glucitol. B. 1,4-Anhydro-D-glucitol. C. D-Glucitol boiled in 3 M H_2SO_4 for *ca.* 40 h. D. 1,4-3,6-Dianhydro-D-glucitol. *, 2,5-Anhydro-D-mannitol (*5*); ≠, 2,5-anhydro-L-iditol (*4*).

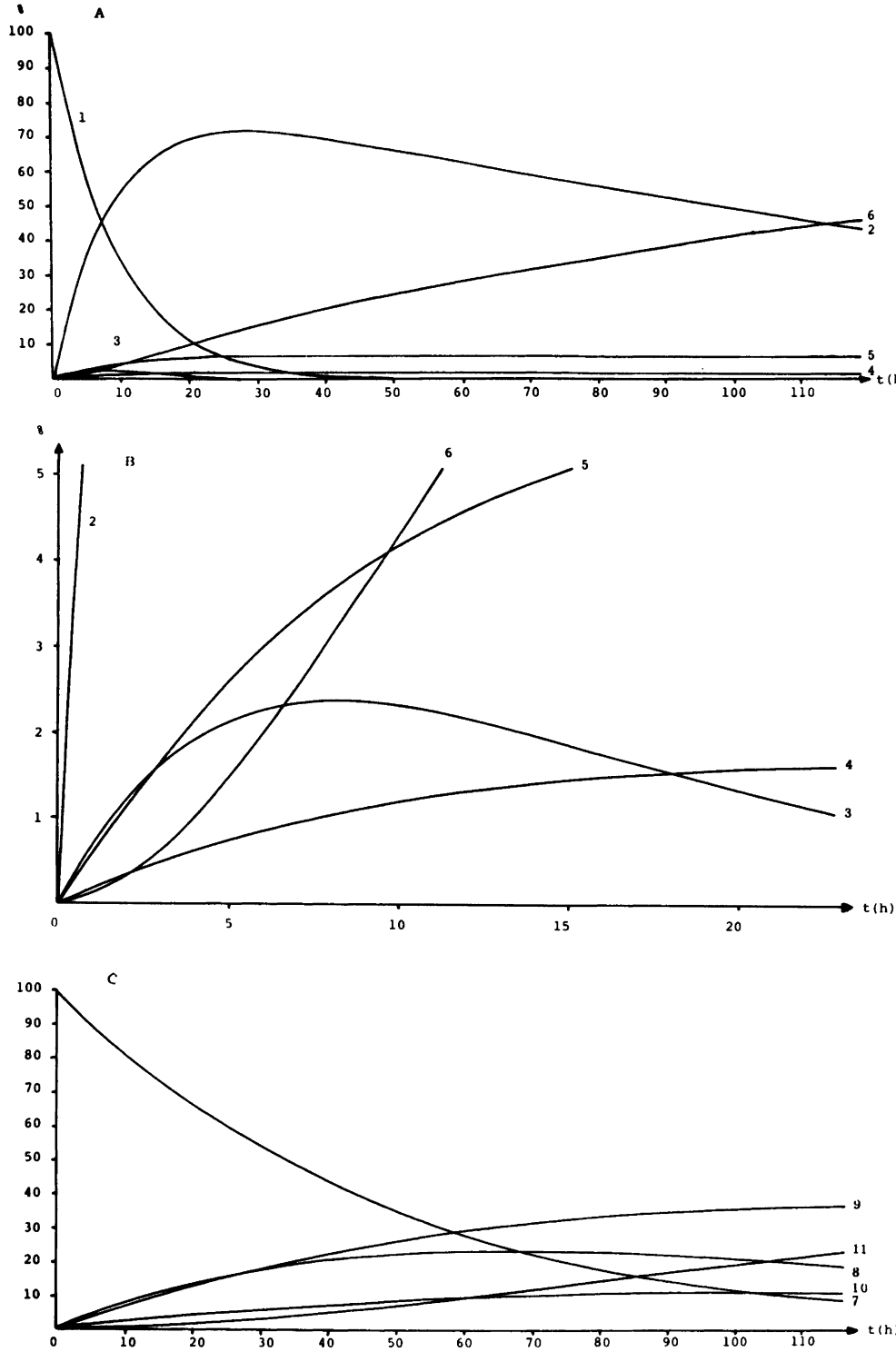

Fig. 3. Reaction curves calculated from the rate constant shown in Tables 2 and 3. A. Reaction of D-glucitol with 3 M H_2SO_4 at 104 °C. B. Enlarged part of A. C. Reaction of D-mannitol with 3 M H_2SO_4 at 104 °C. Numbering of the curves corresponds to the numbers in Figs. 1 and 4.

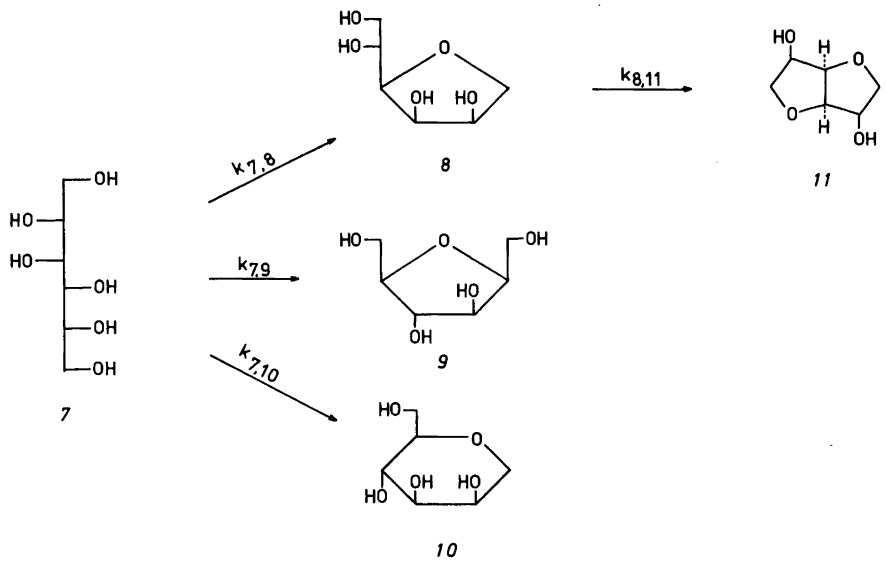

Fig. 4. Formation of *8-11* from D-mannitol (*7*).

This was confirmed by the fact that the 1,4-anhydride (*2*) and the 3,6-anhydride (*3*) gave only the dianhydride (*6*) when boiled with 3 M sulfuric acid, as also found previously.[10] From the latter two experiments independent values of $k_{2,6}$ and $k_{3,6}$ were obtained. Prolonged heating of the dianhydride (*6*) with sulfuric acid led to slow decomposition; none of the other products shown in Fig. 1 were detected. From the rate constants the curves shown in Figs. 3A and 3B were calculated.

The 3,6-anhydride (*3*) is formed rather slowly and rapidly dehydrates to the dianhydride (*6*) as seen from $k_{1,3}$ and $k_{3,6}$. The maximum amount of *3* is seen from Fig. 3B to be 2.5 %, present after 8 h reaction. The 1,4-anhydride (*2*) is formed more rapidly and dehydrates slowly ($k_{1,2}$ and $k_{2,6}$). From Fig. 3A it appears that 71 % of *2* is present after 25 h reaction; when a reaction mixture was worked up at this stage 52 % of *2* could be isolated as compared to the 37 % previously reported.[11] In order to prepare the dianhydride (*6*) it was found most convenient to heat D-glucitol in vacuum with an acidic ion exchange resin.[7] Using this procedure *6* could be obtained in 57 % yield. From the same reaction mixture the 2,5-anhydrides, *4* and *5*, were also obtained and characterized as their tetraacetates after separation by treatment with acetone, which converts *4* into a diisopropylidene derivative whereas *5* does not react.

The reaction of D-mannitol (*7*) with sulfuric acid was also studied by ^{13}C NMR spectroscopy and rate constants (Table 3) were calculated analogously to those of D-glucitol. The reactions (Fig. 4) were found to be irreversible by treatment of *8* and *11* with sulfuric acid in separate experiments. The calculated reaction curves (Fig. 3C) show that the maximum amount of 1,4-anhydro-D-mannitol (*8*) is 23 %, present after *ca.* 70 h. In agreement herewith only low yields of *8* have been obtained when D-mannitol was dehydrated with acid.[12,13] D-Mannitol reacts about 5 times slower with acid than D-glucitol and in order to complete the dehydration it was found most convenient to heat it to 170 °C in the presence of an acidic ion exchange resin as described above. This produced a crude product which contained 55 % of 2,5-anhydro-D-glucitol (*9*), 38 % of 1,4:3,6-dianhydro-D-mannitol (*11*), and 7 % of 1,5-anhydro-D-mannitol (*10*). Work-up of this mixture gave results similar to those described previously.[13]

The acid catalyzed dehydration of alditols has been envisioned as taking place *via* an S_N2 substitution of a protonated hydroxy-group.[3,14] Inversion at a secondary carbon atom obviously takes place in the formation of the 2,5-anhydrides (*4*, *5* and *9*); analogously, an S_N2 reaction would lead to inversion at the primary carbon atoms when the 1,4-anhydrides (*2* and *8*) and the dianhydrides (*6* and *11*)

are formed. In order to demonstrate this inversion we have prepared (1*S*)-1-^{2}H-D-mannitol (*12*) and studied its reaction with acid. Treatment of 1-^{2}H-D-glucose with "glucose isomerase" produces a mixture of 1-^{2}H-D-glucose and (1*S*)-1-^{2}H-D-fructose.[15] Reduction of this mixture with sodium

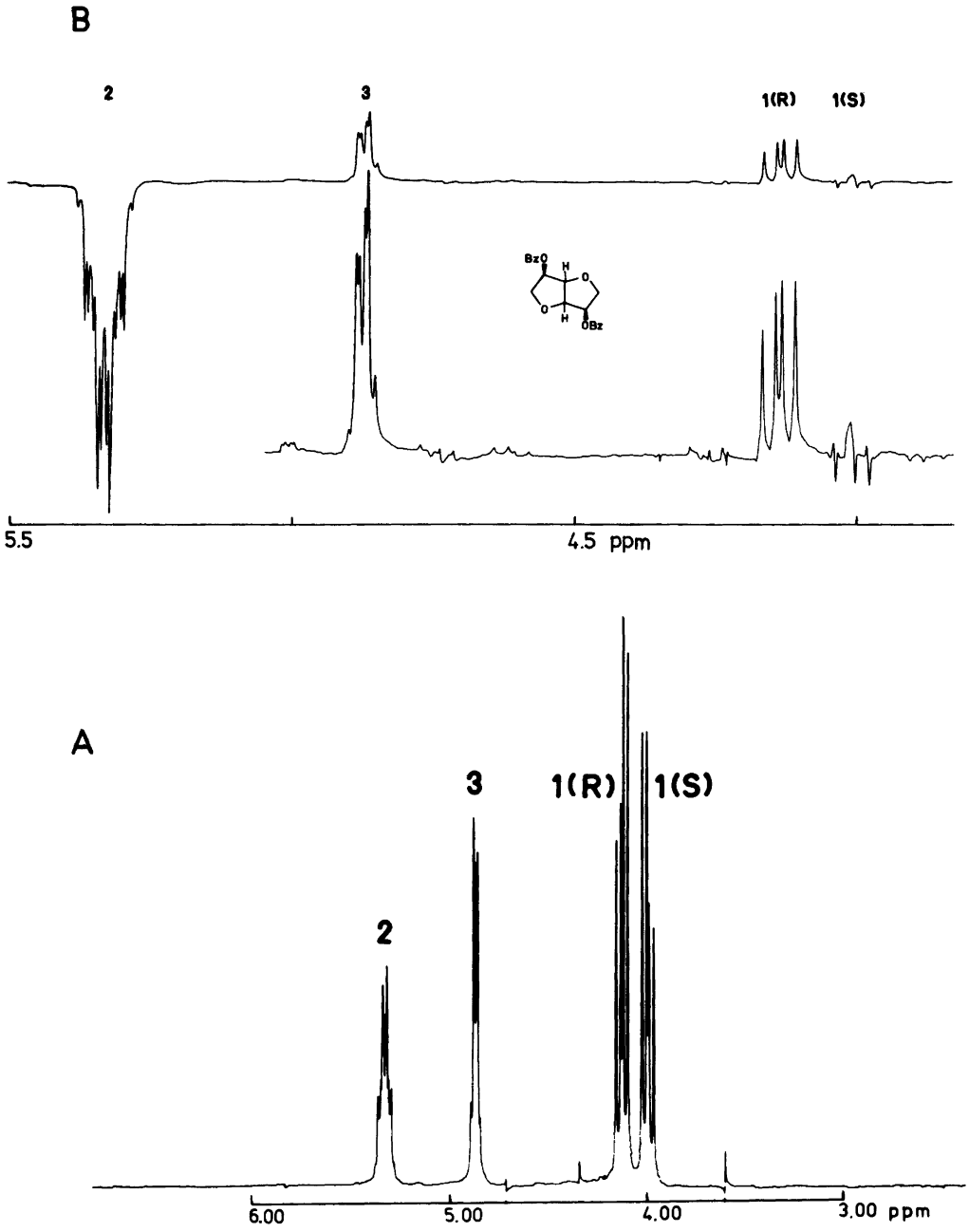

Fig. 5. A. 270 MHz ^{1}H NMR spectrum in $CDCl_3$ of 2,5-di-*O*-benzoyl-1,4-3,6-dianhydro-D-mannitol. B. Difference N.O.E. experiment with saturation of H-2.

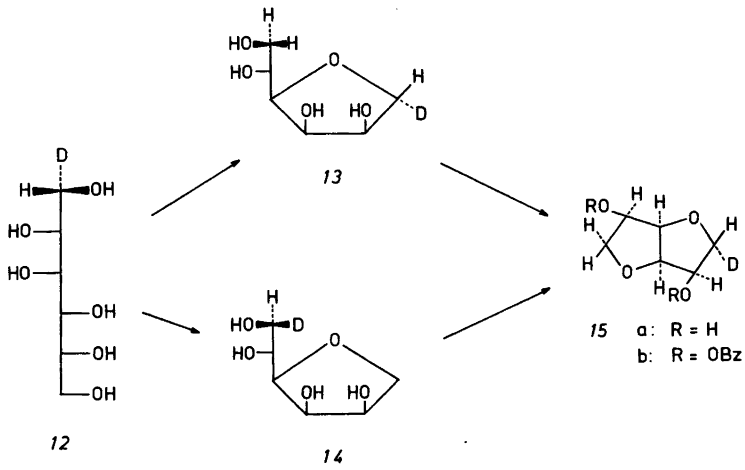

Fig. 6. Formation of *13*–*15* from (1*S*)-1-^{2}H-D-mannitol (*12*).

borohydride gave 1-^{2}H-D-glucitol and (1*S*)-1-^{2}H-D-mannitol (*12*). Subsequent treatment of this mixture with sulfuric acid as described above gave a complex mixture of anhydrides from which deuterated 2,5-di-*O*-benzoyl-1,4:3,6-dianhydro-D-mannitol (*15b*) could be isolated after benzoylation.

If the dehydration proceeds *via* protonation of the primary hydroxy-groups followed by ring closure with inversion, *12* will initially form the (1*R*)-1-^{2}H-1,4-anhydride (*13*) and the (1*S*)-1-^{2}H-3,6-anhydride (*14*). On further reaction both *13* and *14* will yield (1*R*)-1-^{2}H-1,4:3,6-dianhydro-D-mannitol (*15a*).

The proton NMR spectrum of nondeuterated di-*O*-benzoyl-1,4:3,6-dianhydro-D-mannitol is well resolved (Fig. 5A) and shows the four H-1 and H-6 protons as two groups of signals at 4.01 and 4.14 ppm, respectively. A nuclear Overhauser experiment [16] in which H-2 and H-5, at 5.34 ppm, were irradiated showed a much stronger enhancement of the signal at 4.14 than of that at 4.01 (Fig. 5B). This suggests that the protons resonating at 4.14 ppm are situated closer to H-2 (H-5) than those giving the signal at 4.01 and therefore they must be the two pro-(*R*)-protons. In the ^{1}H NMR spectrum of the deuterated benzoate (*15b*) the signal at 4.14 ppm integrated for only one proton, showing that one of the two pro-(*R*)-protons has been replaced by deuterium. The high field signal of *15b*, integrating for two protons, showed a doublet at 3.99 ppm corresponding to (*S*)-H-1 of *15b*, shifted 0.02 ppm upfield because of the deuterium in the (*R*)-position. From these spectra it is concluded that *15b* has the (*R*)-configuration at C-1 and, hence, that acid-catalyzed ring closure of D-mannitol and most likely of other alditols, takes place with inversion at the primary carbon atom.

EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography (TLC) was performed on silica gel (Merck PF_{254}), preparative TLC on 1 mm layers of silica gel. Optical rotations were measured on a Perkin Elmer 141 polarimeter. ^{1}H and ^{13}C NMR spectra were obtained on Bruker HX-90, WH-90, and HX-270 instruments.

3,6-Anhydro-D-glucitol (3) was prepared by reduction of 3,6-anhydro-D-glucose,[17] and characterized through its ^{13}C NMR spectrum; (Table 1).

The Reaction of Polyols with Sulfuric Acid

The reactions were carried out in boiling 3 M sulfuric acid at 104 °C (Tables 2 and 3). Samples were removed at intervals and ^{13}C NMR spectra measured in 10 mm sample tubes using a capillary with D_2O for lock; dioxane was used as external reference. The spectra were measured on a Bruker WH-90 instrument using 8K of computer memory for the FID and a sweep with of 3000 Hz, corresponding to an acquisition time of 1.36 s. An exponential line broadening of 1 Hz was used. The amounts of components present in the reaction

Table 3. Products resulting from boiling a solution of 4.3 g of D-mannitol in 10 ml of 3 M H_2SO_4 at 104 °C.

Time h	Product/%				
	7	*8*	*9*	*10*	*11*
0	100	0	0	0	0
7.75	87	7	6	0	0
27	57	18	17	5	3
31	52	20	20	5	3
54	32	23	28	8	9
78	19	23	34	10	14
175	2	10	40	13	35
∞ [a]	0	0	47	12	41

[a] Calculated value. Rate constants (h^{-1})

k_0	$k_{7,8}$	$k_{7,9}$	$k_{7,10}$	$k_{8,11}$
0.0209	0.0097	0.0086	0.0025	0.0104

mixtures were calculated in percent from the computer compiled peak height of the secondary carbon atoms. Spectra measured on standard mixtures of D-glucitol, 1,4-anhydro-D-glucitol, and dianhydro-D-glucitol showed that the maximum deviation under these conditions was 2.5 %.

1,4-Anhydro-D-glucitol (2). A solution of D-glucitol (50 g) in 3 M sulfuric acid (25 ml) was heated under reflux for 18 h. It was then passed through a column of ion exchange resin Amberlite IR 4B (OH^-) and the column was washed with water. The eluent was filtered through activated carbon and evaporated. The residue was dissolved in ethanol which was evaporated and the syrup thus obtained (44.5 g) was crystallized from ethanol yielding 23.5 g (52 %) of *2*, m.p. 108–111 °C, $[\alpha]_D^{19}$ −21.3°. After three additional recrystallizations the product melted at 112–112.5 °C, $[\alpha]_D^{20}$ −22.4° (c. 5.4, H_2O); (reported[11] m.p. 115–116 °C, $[\alpha]_D^{27}$ −21.9°).

1,4:3,6-Dianhydro-D-glucitol (6). D-Glucitol (29 g) was dried by heating it to melting under water-pump vacuum. Amberlite IR-120 (H^+) (approx. 10 g) was then added and the mixture was heated to approx. 170 °C and stirred under vacuum for 2 h (the pressure should be down to 10 mmHg for at least 30 min). The mixture was then cooled, dissolved in water, filtered through activated carbon, and evaporated. The colorless syrup (18.1 g) contained 93 % of *6*, 4 % of *4*, and 3 % of *5* as seen from a ^{13}C NMR spectrum. Distillation in vacuum gave 13.2 g (57 %) of a fraction with b.p. 131–134 °C (0.8–0.9 mmHg). This fraction crystallized on seeding, m.p. 53–59 °C. Two recrystallizations from ethyl acetate gave *6* with m.p. 57–61 °C, $[\alpha]_D^{18}$ +43.8° (c. 3.9, H_2O); (reported[10] m.p. 62–64 °C, $[\alpha]_D$ +45.2°).

2,5-Anhydro-L-iditol (4) and 2,5-anhydro-D-mannitol (5). The high boiling residue from the above-mentioned distillation was acetylated with acetic anhydride in pyridine and the acetylated product (6.0 g) was again deacetylated with sodium methoxide in methanol. The syrupy product (3.0 g) thus obtained was stirred for 3 days in acetone (75 ml) containing 6 drops of sulfuric acid. The acetone solution was then decanted off and the insoluble, syrupy residue was washed twice with acetone. The combined acetone solution was neutralized with calcium hydroxide, filtered through carbon and evaporated. The residue was extracted twice with boiling hexane and the hexane was evaporated leaving 440 mg of crude 1,3:4,6-di-*O*-isopropylidene-2,5-anhydro-L-iditol. The isopropylidene groups were removed by boiling in 70 % aqueous acetic acid and the product was then acetylated to give 600 mg of a material which was purified by preparative TLC (ether–pentane, 3:1). This gave the syrupy tetra-*O*-acetyl-2,5-anhydro-L-iditol, $[\alpha]_D^{20}$ −16.8° (c. 3.5, $CHCl_3$); (reported[18] $[\alpha]_D$ −13.2°). ^1H NMR ($CDCl_3$): δ 5.33 (H-3 and H-4): 4.44 (H-2 and H-5); 4.18 (H-1 and H-6); 4.10 (H-1′ and H-6′); $J_{1,2}=J_{5,6}$ 6.5 Hz; $J_{1',2}=J_{5,6'}$ 5.0 Hz; $J_{2,3}=J_{4,5}$ 3.5 Hz.

The acetone insoluble material was acetylated with acetic anhydride in pyridine to give 50 mg of syrup. Purification by preparative TLC (ether–pentane, 3:1) gave tetra-*O*-acetyl-2,5-anhydro-D-mannitol, $[\alpha]_D^{20}$ +30.6° (c. 0.8, $CHCl_3$); (reported[19] $[\alpha]_D$ +27.5°). ^1H NMR ($CDCl_3$): δ 5.13 (H-3 and H-4); 4.22 (H-1, H-2, H-5 and H-6). $J_{2,3}=J_{4,5}$ 0 Hz.

(R)-1-^{2}H-2,5-Di-O-benzoyl-1,4:3,6-dianhydro-D-mannitol. A crude mixture containing approx. 60 % 1-^{2}H-D-glucose and 40 % (*S*)-1-^{2}H-D-fructose was prepared as described elsewhere.[15] This mixture (0.26 g) in water (10 ml) was cooled in ice and stirred for 30 min with sodium borohydride (0.1 g). The solution was then deionized (Amberlite IR-120 (H^+)), evaporated and evaporated with methanol leaving a syrup (0.25 g) which was a mixture of approx. 85 % 1-^{2}H-D-glucitol and 15 % (*S*)-1-^{2}H-D-mannitol.

This product was boiled for 26 h with 6 M sulfuric acid (4.0 ml). The solution was then passed through Amberlite IR-4B (OH^-) and evaporated. The resulting syrup (0.25 g) was benzoylated with benzoyl chloride in pyridine to give a syrup (0.46 g). Preparative TLC (ether–pentane, 3:1) gave 20 mg of syrupy *15b*, characterized through its ^1H and ^{13}C NMR data which were identical with those of an authentic specimen[20] except for the isotopic substitution in the 1(*R*)-position.

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