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THE KINETICS OF THE ACID CATALYSED HYDROLYSIS OF SOME ISOPROPYLIDENE FURANOSES

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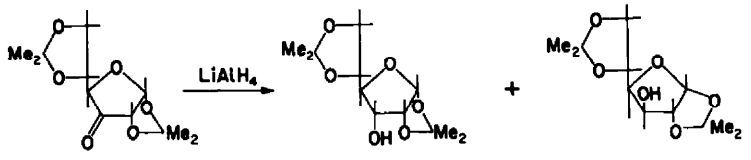
Abstract—The synthesis of 1,2:5,6-diisopropylidene and 1,2-monoisopropylideneallofuranose are reported.

The rates of hydrolysis of the 1,2-isopropylidene residues in 1,2-monoisopropylidenefuranoses and the 5,6-isopropylidene residues in 1,2:5,6-diisopropylidenefuranoses have been measured, mostly at two or more temperatures; the activation parameters have been calculated. The 1,2:5,6-diisopropylidenefuranoses investigated have the *gluco*- and *allo*-configuration and the 1,2-monoisopropylidenefuranoses have the *gluco*-, *allo*- and 3-*deoxy-allo*-configuration. The small differences in hydrolysis rates have been discussed in terms of the steric and electronic effects, produced by changes in the sugar configurations at *C*(3).

LITHIUM aluminum hydride reduction of the recently synthesized 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuran-3-ulose[1] (I) affords a mixture of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (diisopropylideneallose) II and its *gluco*-isomer (diisopropylideneglucose) III in a ratio of 7:3; shown by analysing the crude reaction product polarimetrically and NMR spectrometrically.

The $[\alpha]_D$ in chloroform for the crude reduction product, pure diisopropylideneallose, and pure diisopropylideneglucose were +22°, +38°, and −12·7° respectively. The crude reduction product also showed two doublets in the anomeric proton region τ 4·19, J 4 c/s equivalent to 0·3 protons and τ 4·29, J 4 c/s equivalent to 0·7 protons. The former was shown to be the *gluco*-isomer and the latter the *allo*-isomer. Chromatographically, pure, crystalline diisopropylideneallose was isolated from the mixture, after column chromatography on silica gel. This was characterized as its brosylate.



I II (70%) III (30%)

Although it is known that the 5,6-isopropylidene residue can be hydrolysed preferentially from diisopropylideneglucose III[2] and 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-*ribo*hexose (diisopropylidene-3-deoxyglucose),[3] there has been no general kinetic

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[1] P. J. Beynon, P. M. Collins and W. G. Overend, *Proc. Chem. Soc.* 342 (1964).
[2] E. Fischer and C. Rund, *Ber. Dtsch. Chem. Ges.* **49**, 88 (1916).
[3] E. J. Hedgley, W. G. Overend and R. A. C. Rennie, *J. Chem. Soc.* 4701 (1963).

study of the hydrolysis of isopropylidene sugar derivatives. It therefore seemed opportune now that diisopropylideneallose (II) and 1,2-O-isopropylidene-α-D-allofuranose (monoisopropylidene allose) IV are available for the first time,[4]† to undertake the investigation.

The hydrolysis of the compounds listed in Table 1 were followed spectrophotometrically at 270 mμ, usually at two temperatures. The hydrolyses of the 5,6-isopropylidene residue from diisopropylidenefuranoses were carried out in 0·03 M aqueous

TABLE 1. RATE COEFFICIENTS AND KINETIC PARAMETERS OF KETAL HYDROLYSIS

(a) 5,6-*Isopropylidene hydrolysis in* 0·03 M *hydrochloric acid*

1,2:5,6-Diisopropylidene derivative	Temp	$10^5 k_1$ sec^{-1}	E kcals. $mole^{-1}$	ΔS^* at 52° cals deg^{-1} $mole^{-1}$
Glucofuranose III	32·45	63·7	20·4	−1·5
	52·20	512		
Allofuranose II	25·10	31·3		
	32·47	71·0	20·4	−1·3
	52·20	55·5		

(b) 1,2-*Isopropylidene hydrolysis in* 0·1 M *hydrochloric acid.*

1,2-Monoisopropylidene derivative				
Glucofuranose V	52·30	22·5	23·3	−1·4
	62·85	69·8		
Allofuranose IV	63·00	228		
3-Deoxy-glucofuranose VI	52·30	145	22·4	−0·6
	63·00	436		

$\Delta S^* = (E - RT - 2{\cdot}303\ RT \log kT/h + 2{\cdot}303\ RT \log k_2)/T$ where $k_2 = k_1/h_0$[11].

acid ($\mu = 0{\cdot}05$), whereas the hydrolyses of the 1,2-isopropylidene residue from the monoisopropylidene derivatives were studied in 0·1 M aqueous acid. Good first-order rate coefficients were obtained for the hydrolysis of the monoisopropylidene derivatives to the free sugars using the normal first-order rate law. For the hydrolysis of diisopropylidene derivatives to the monoisopropylidene derivatives the calculation was made using the Guggenheim method. This was necessary, because of the slow but significant hydrolysis of the 1,2-isopropylidene residue. In Table 1 are collected the integrated first-order rate constants, activation energies and entropies of activation for all compounds investigated.

The hydrolysis of these isopropylidene derivatives will probably proceed by an A-1 mechanism as is the case for most simple acylic ketals.[5] The magnitude of ΔS^* is often

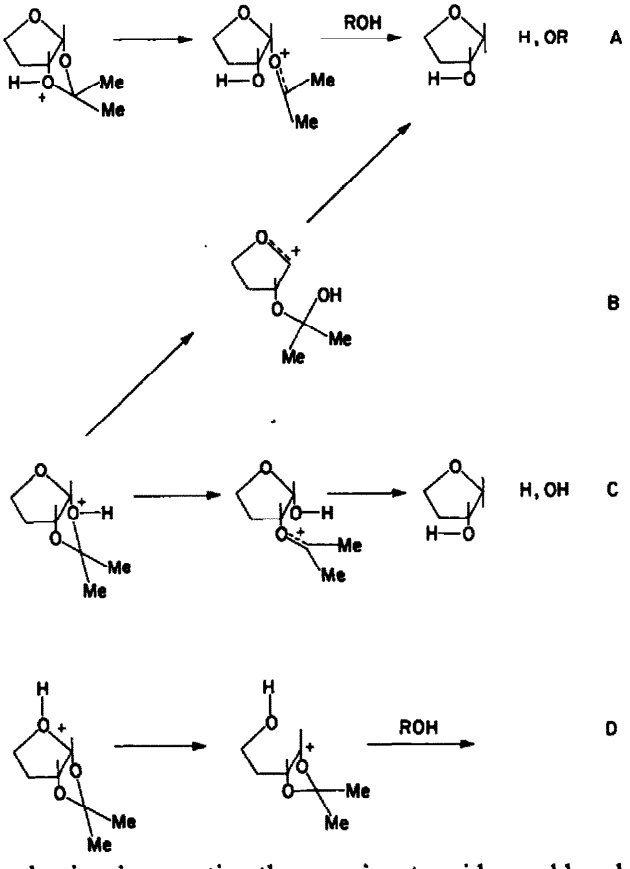
† Note added in proof: These compounds have now been reported. O. THEANDER, *Acta Chem. Scand.* **18**, 2209 (1964).

[4] J. Staněk, M. Černý, J. Kocourek and J. Pacák, *The Monosacharides* p. 336. Academic Press (1963).

[5] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 334. Cornell University Press, (1953).

used to distinguish between an A-1 or A-2 mechanism. The A-1 mechanism usually yields a more positive ΔS^* than an A-2 mechanism. However, for the hydrolysis reported here the ΔS^* values found are negative and small. Similar results to these have been found for aliphatic cyclic ketals[6] and interpreted as indicating an A-1 mechanism.[6,7] The results recorded in Table 1 will be discussed in terms of this mechanism.

The hydrolysis of the monoisopropylidenefuranoses. There are three oxygens in the ketals formed at the 1,2-position of the furanoses at which protonation can occur, see scheme.



If an A-1 mechanism is operating these conjugate acids would undergo slow rate-determining heterolysis to leave a carbonium ion, which will be solvolysed to give products. These are depicted in the scheme. An attempt was made to distinguish between these pathways by running the experiment in anhydrous acidified methanol instead of water. Protonation at the *C*(2) oxygen would give a conjugate acid, which could break down and then be attacked by methanol to give glycofuranosides as depicted in mechanism A. Heterolysis of the *C*(2) oxygen bond of the conjugate acid to form a carbonium ion at *C*(2) can be ruled out, since no epimers are found in the products. The conjugate acid, that would be formed by protonation of the ring oxygen, would break down to give a carbonium ion at *C*(1). This is depicted in mechanism

[6] P. Salomaa and A. Kankaanpera, *Acta Chem. Scand.* **15**, 871 (1961).
[7] L. L. Schaleger and F. A. Long, *Advances in Physical Organic Chemistry*. **1**, 27 (1961).

D. Solvation of this would give another ketal. This seems an unlikely route. Protonation of the oxygen at *C*(1) would give a conjugate acid, which could undergo heterolysis by route **B** or **C**. Mechanism **B** would yield glycosides, whereas mechanism **C** would give free sugar.

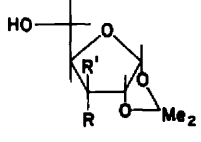
Chromatographic analysis of a solution of monoisopropylideneglucose (V) in anhydrous methanol (0·01 %) 0·1 M in methanesulphonic acid revealed that glucose was quickly formed, followed presently by methylglucofuranosides and then after a longer period methylglucopyranosides (i).

(i) Monoisopropylideneglucose → glucose → glucofuranosides → glucopyranosides.

This is supported by polarimetric analysis of the methanolysis at 32·2°. The optical rotation increased to a maximum during 2 hr ($k \simeq 4{\cdot}5 \times 10^{-4}$ sec^{-1}). This was owing to glucose formation. A slower ($k \simeq 1{\cdot}6 \times 10^{-4}$ sec^{-1}) decrease to a minimum then followed, owing to the formation of the α-β-furanosides.[8] The final ring expansion to pyranosides was indicated by the very slow increase in the optical rotation. In a separate experiment the optical rotation of an acidified methanol solution of glucose was shown to behave similarly to the glucose → furanoside → pyranoside section of the previous reaction. Thus the methanolysis of monoisopropylideneglucose would appear to occur *via* mechanism **C**, since it is only this one that yields free sugar.

The methanolysis of monoisopropylidene-3-deoxy-glucose (VI) was also shown, chromatographically, to go by the same mechanism and the rate differences found in this work for the stereoisomers will be discussed in terms of the hydrolysis occurring by mechanism **C**, where ROH is equivalent to H_2O. It must be noted, however, that a hydrolysis and methanolysis mechanism need not use the same reaction pathway,[9] but mechanism **C** does seem quite plausible for the hydrolysis.

Effects of structure on rates of hydrolysis. From the Table it can be seen that the effect of structure upon the rates of hydrolysis of the 1,2-isopropylidenefuranoses are small. The relative rates for compounds with the *gluco* (V) *allo* (IV) and 3-deoxy-gluco (VI) configuration being approximately 1:3:7. It has been pointed out[10,11] that sub-

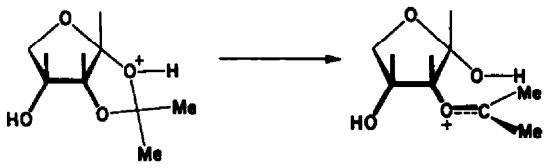


IV R' = H, R = OH
V R' = OH, R = H
VI R' = R = H

stituents can effect the rate of acetal hydrolysis in two ways. A substituent can alter the standing concentration of the conjugate acid and it can effect the ease of bond fission in the conjugate acid. In the present case (route **C**) the electronic properties of the substituent at *C*(3) will not greatly effect the electron density at the oxygen attached to *C*(1). Thus the conjugate acid concentration should be similar for compounds IV, V and VI. However, the carbonium ion formed by conjugate acid breakdown will be stabilized inductively by the two methyl groups and mesomerically by the oxygen attached to *C*(2) see Fig. 3. The magnitude of this latter effect should be

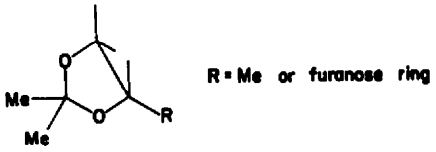
[8] B. Capon, G. W. Loveday and W. G. Overend, *Chem. & Ind.* 1537 (1962).
[9] B. Capon and W. G. Overend, *Advances in Carbohydrate Chemistry.* **15,** 11 (1960).
[10] B. Capon, W. G. Overend and M. Sobell, *Tetrahedron* **16,** 106 (1961).
[11] C. A. Bunton, T. A. Lewis, D. R. Llewellyn and C. A. Vernon, *J. Chem. Soc.* 4419 (1955).

influenced by the electronic properties of the substituent at *C*(3). Thus, substituting a hydroxyl group in place of one of the hydrogens at *C*(3) of compound VI to give either IV or V decreases the mesomeric assistance of the oxygen and thus reduces the rate of hydrolysis.



The stereochemistry of the hydroxy group at *C*(3) has a small effect upon the rate (IV is hydrolysed faster than V). This could be explained by the higher ground state energy of the *allo*-isomer IV compared with the *gluco*-isomer V. This is owing to the interaction between the hydroxyl at *C*(3) and the methyl group of the isopropylidene residue in compound IV. This unfavourable interaction is lost on passing to the transition, as shown in Fig. 3.

The hydrolysis of the diisopropylidene furanoses. As might be expected the stereochemistry of the sugar ring has an insignificant effect upon the rate of hydrolysis of the 5,6-isopropylidene residue. The rates of hydrolysis for diisopropylideneglucose (III) and diisopropylideneallose (II) are in the ratio 1:1·1. Salomaa *et al.*[6] have measured



the hydrolysis rates for 1,3-dioxalones (Fig. 4 R = Me) and these were about ten times faster than the rates found in this work (Fig. 4 R = furanose ring). Explanation of this rate-difference is difficult, because the oxygen protonated in each case is not known.

EXPERIMENTAL

Optical rotations refer to water unless stated otherwise. NMR spectra were measured in CCl_4 using T.M.S. as reference.

1,2:5,6-*Di*-O-*isopropylidene*-α-D-*glucofuranose* (III). This was obtained from L. Lights Ltd. and used after two recrystallizations m.p. 110°, $[\alpha]_D^{31}$ −12·7° ($CHCl_3$). The anomeric proton appeared as a doublet τ 4·19 J 4 c/s. Reported[2] m.p. 110–111° $[\alpha]_D$ −18·5°.

1,2-O-*Isopropylidene*-α-D-*glucofuranose* (V). Diisopropylideneglucose 15·5 g was dissolved in EtOH (50 ml) containing 1 M HCl (5 ml). After 20 min at 22° crystallization occurred. The crystals were filtered after a further 10 min and recrystallized from EtOH–light petroleum (b.p. 60°–80°) to give 10·2 g fine needles m.p. 158–159°, $[\alpha]_D$ −12°. This material was shown to contain less than 1% glucose, by chromatographic analysis on thin layers of silica gel. Reported[10] m.p. 161–162°, $[\alpha]_D$ −11·8°.

1,2:5,6-*Di*-O-*isopropylidene*-α-D-*allofuranose* (II). 1,2:5,6-Di-O-isopropylidene-α-D-*ribo*-hexofuran-3-ulose 14·8 g, prepared by ruthenium tetroxide oxidation[1] of diisopropylideneglucofuranose, was reduced by heating under reflux with LAH in diethyl ether during 3·5 hr. The excess hydride was destroyed with water. Evaporation of the ether solution afforded crystals 11·8 g 79% $[\alpha]_D$ +22° ($CHCl_3$). In the anomeric proton region of the NMR spectrum there appeared two doublets τ 4·19 J 4 c/s equivalent to 0·3 protons and τ 4·29 J 4 c/s equivalent to 0·7 protons. The crystals (6·0 g) were chromatographed on silica gel (800 g) in a column 5 × 55 cms. This was developed and eluted with

ethyl acetate. The eluant was monitored by T.L.C. and this showed that all the *gluco*-isomer had been removed in the first 500 ml and that the following 700 ml eluant contained the pure *allo*-isomer. Evaporation of the latter afforded a solid, which upon recrystallization from light petroleum (b.p. 60–80°), gave *diisopropylideneallofuranose* m.p. 75–76° $[\alpha]_D^{22}$ +38° ($CHCl_3$). (Found: C, 55·28; H, 7·62: $C_{12}H_{20}O_6$ requires: C, 55·36; H, 7·75%.) The anomeric proton appeared as a doublet τ 4·29 J 4 c/s.

1,2:5,6-*Di*-O-*isopropylidene*-α-D-*allofuranose*-3-p-*bromobenzenesulphonate*. Diisopropylideneallose (1·4 g) was treated with brosyl chloride (1·5 g) in pyridine for 2 hr at 70°. After work up and recrystallization from EtOH–light petroleum (b.p. 60°–80°) (1:9), needles were obtained (1·4 g) m.p. 121–122°, $[\alpha]_D^{21}$ +69° (EtOH). (Found: C, 45·05; H, 4·75; Br, 17·1. $C_{18}H_{25}BrO_8S$ requires: C, 45·10; H, 4·84; Br 16·7%.)

1,2-O-*Isopropylidene*-α-D-*allofuranose* (IV). Diisopropylideneallose (2·7 g) in EtOH (200 ml) containing 50% HCl aq (2·0 ml) was maintained at 33°. The reaction was monitored by measuring the absorption of the acetone formed. After 20 min one mole-equivalent acetone had appeared. $NaHCO_3$ was added, and the neutralized solution, on evaporation, yielded a solid. Recrystallization gave plates (1·0 g), 44% which T.L.C. on silica gel showed to be homogeneous, m.p. 129–130° $[\alpha]_D$ +48° (H_2O). (Found: C, 49·2; H, 7·7. $C_9H_{16}O_6$ requires: C, 49·1; H, 7·67%.)

Kinetic procedure

(a) *For the monoisopropylidenefuranoses.* Into water (10 ml) a weighed amount of monoisopropylidenefuranose was added to give an approximately 0·4 M solution. This solution (1·80 ml) was placed in a stoppered 1 cm silica cell, which was situated in a thermostated compartment of a Unicam 3.P700 spectrophotometer. To this solution 1·0 M HCl aq (0·2 ml) was added. Both solutions had equilibriated to thermostat temp for at least ½ hr. The increase in optical density at

TABLE 2. HYDROLYSIS OF SOME MONOISOPROPYLIDENEFURANOSES

(a) 1,2-O-*Isopropylidene*-α-D-*glucofuranose* (62·85°)

Time (sec):	0	360	540	720	1080	1440	1980	∞
D_t:	0·110	0·257	0·318	0·370	0·463	0·535	0·605	0·77
10^5 k(sec^{-1}):		70·0	69·5	70·1	70·9	71·7	70·0	

Mean $k = 70·3 \pm 0·3 \times 10^{-5}$ sec^{-1}

(b) 1,2-O-*Isopropylidene*-α-D-*allofuranose* (63·00°)

Time (sec):	0	90	113	225	270	315	450	∞
D_t:	0·123	0·237	0·262	0·400	0·439	0·471	0·550	0·74
10^5 k(sec^{-1}):		227	226	227	231	230	229	

Mean $k = 228 \pm 0·5 \times 10^{-5}$ sec^{-1}

(c) 3-*Deoxy*-1,2-O-*isopropylidene*-α-D-*ribohexofuranose* (52·30°)

Time (sec):	0	120	240	360	420	600	720	∞
D_t:	0·135	0·203	0·264	0·312	0·333	0·391	0·420	0·570
10^5 k(sec^{-1}):		142	147	145	145	148	148	

Mean $k = 146 \pm 0·5 \times 10^{-5}$ sec^{-1}

Where D_t = absorbance at time t.

270 mμ was plotted against time for at least 65% reaction. After 10 half-lives the optical densities of all reactions were measured. Thin layer and paper chromatography showed that free sugars were the only products in the hydrolysates.

(b) *For the diisopropylidene derivatives.* The procedure was similar to (a) except 0·2 ml of 0·3 M HCl aq, which was 0·2 M in NaCl, was added to 1·8 ml of the sugar solution. The reaction was followed for about 3 to 5 half lives. The optical density at ten times the half life was always too large, because of the slow concomitant hydrolysis of the 1,2-isopropylidene residue. The rate constants were calculated by the Guggenheim[12] method, which gave reproducible rate constants. This should

[12] A. A. Frost and R. G. Pearson, *Kinetic and Mechanism* p. 48. J. Wiley (1953).

not introduce too large an inaccuracy, since the 1,2-isopropylidene residue would be hydrolysed 80 times slower under these conditions for the *gluco*-isomers and about 30 times slower for the *allo* isomer.

At least two studies were made on each hydrolysis and the difference in the mean values of the rate constants never differed by more than 3·5%. In Table 2 are listed detailed values for representative reactions.

Acknowledgements—The author is indebted to Dr. E. J. Hedgley for the gift of 3-deoxymonoisopropylideneglucofuranose and to Dr. D. Thacker for a sample of methylglucofuranoside and useful discussions. Prof. W. G. Overend is thanked for his encouragement.