73. *Mechanisms of Reactions in the Sugar Series. Part III.* The Acid-catalysed Hydrolysis of t-Butyl β-D-Glucopyranoside and Other Glycosides.*

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The acid-catalysed hydrolyses of *o*-hydroxymethylphenyl β-D-glucopyranoside, lactose, maltose, and methyl 2-deoxy-α- and -β-D-glucopyranoside have been investigated. In the cases studied, bond fission occurs between the pyranosyl carbon and the glycosidic oxygen atom. The dependence of rate on acidity and the variation of rate with structure are best interpreted in terms of a mechanism involving pyranosyl carbonium ions. In contrast, the acid-catalysed hydrolysis of t-butyl β-D-glucopyranoside involves bond fission between the t-butyl group and the glycosidic oxygen atom, and this reaction is considered to proceed by the formation of an alkyl carbonium ion.

In Part I [1] the acid-catalysed hydrolysis of some simple glucosides was investigated. It was shown that the reactions proceed with hexose–oxygen bond fission and involve pyranosyl carbonium ions as intermediates. The present work, in which a more extensive series of glycosides has been studied, was undertaken with two primary objectives: (*a*) to investigate the anomalously fast hydrolysis of glycosides derived from 2-deoxy-D-glucose and of t-butyl β-D-glucopyranoside, and (*b*) to find an example of glycoside hydrolysis proceeding by the alternative position of bond fission.

Experimental

Materials.—Commercial samples of lactose and maltose had, respectively, $[\alpha]_D^{25}$ +137°, +54° (*c ca.* 2, in H_2O). A commercial sample of *o*-hydroxymethylphenyl β-D-glucopyranoside (salicin) was recrystallised from ethanol, then having $[\alpha]_D^{25}$ −63·5° (*c ca.* 3, in H_2O).

Dry t-butyl alcohol (150 g.), acetobromoglucose (50 g.), silver oxide (50 g.), and ether (400 c.c.) were refluxed together for 45 min. The ether was then removed and the crystals which separated were recrystallised from isopropyl ether. t-Butyl tetra-*O*-acetyl-β-D-glucopyranoside (19 g.) was obtained, with m. p. 143—144°, $[\alpha]_D^{25}$ −12·7° (*c ca.* 1·0, in $CHCl_3$) (Found: C, 53·4; H, 7·0. Calc. for $C_{18}H_{28}O_{10}$: C, 53·5; H, 7·0%). The tetra-acetate was catalytically deacetylated with sodium in anhydrous methanol. After recrystallisation from ethyl acetate, t-butyl β-D-glucopyranoside (6 g.) was obtained with m. p. 163—164°, $[\alpha]_D^{25}$ −19·3° (*c ca.* 1·0, in H_2O) (Found: C, 50·6; H, 8·5. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5%). The compound did not reduce Fehling's solution and gave D-glucose on acid-hydrolysis. The infrared spectrum was very similar to that of methyl β-D-glucopyranoside and showed a strong peak at 890 $cm.^{-1}$ characteristic of the β-D-glucose configuration.[2]

Methyl α-2-deoxy-D-glucopyranoside was prepared as described by Stacey and his co-workers.[3,4] It had m. p. 90°, $[\alpha]_D^{22}$ +132° (*c* 1·0, in H_2O) {lit.,[3,4] m. p. 90—92°, $[\alpha]_D^{22}$ +135° (in H_2O)}. Methyl β-2-deoxy-D-glucopyranoside, prepared by the method of Fischer, Bergmann, and Schotte,[5] had m. p. 122°, $[\alpha]_D^{20}$ −45° (*c* 1·0, in H_2O) (lit.,[5] m. p. 122—123°, $[\alpha]_D^{17}$ −48° in H_2O).

Kinetic Methods.—Runs at 25° were followed by determining, at appropriate time intervals, the optical rotatory power of solutions (usually containing *ca.* 2% of the substrate), contained in a jacketed polarimeter tube. The procedure described in Part I [1] was used for runs at higher temperatures.

Isotope Methods.—The positions of bond fission were determined by carrying out the reactions in water enriched in ^{18}O. The detailed procedures for isolating the appropriate

* Part II, *J.*, 1960, 4637.

[1] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[2] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[3] Overend, Stacey, and Stanek, *J.*, 1949, 2841.
[4] Hughes, Overend, and Stacey, *J.*, 1949, 2846.
[5] Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509.

products were: (*a*) Methyl α-2-deoxy-D-glucopyranoside. As previously described [1] for methyl α-D-glucopyranoside. (*b*) Maltose. A solution (50 c.c.) containing substrate (2·5 g.) in M-perchloric acid was heated at 73° until reaction was complete and then neutralised. Glucosazone, m. p. 201°, was prepared from the products. (*c*) t-Butyl β-D-glucopyranoside. A solution (200 c.c.) containing substrate (25 g.) in 0·92M-perchloric acid was kept at 25° for 47 hr. and then neutralised. The solution was fractionated and the leading fraction collected. Saturation with ammonium sulphate salted out t-butyl alcohol which was dried (Na_2SO_4) and distilled three times from sodium.

Methanol and t-butyl alcohol were pyrolysed to carbon monoxide [1] which was analysed mass spectrometrically. Glucosazone was decomposed by heating it with mercuric chloride, as described by Rittenberg and Ponticorvo,[6] and the carbon dioxide so obtained was analysed mass-spectrometrically.

Results

Kinetic Results.—Good first-order rate coefficients were obtained in all cases and, for each compound, the calculated and observed infinity values agreed within experimental error. The collected first-order rate coefficients (k_1, min.$^{-1}$) are given in Table 1. For each compound, a plot of the logarithm of the first-order rate coefficient against Hammett's acidity function,* H_0, gave a good straight line.

With the two glycosides derived from 2-deoxy-D-glucose, data obtained from experiments in which large concentrations of sodium perchlorate were present and from experiments in which acids other than perchloric acid were used, fitted the Hammett plots quite closely. The values of the slopes (S') of the Hammett plots are given in Table 2. Data for Part I,[1] recalculated

TABLE 1. *First-order rate coefficients for the hydrolysis of some glycopyranosides.*

o-Hydroxymethylphenyl β-D-glucopyranoside at 72·6°.								
$HClO_4$ (M)	0·90	1·50	2·00	2·50	3·00			
10^2k_1 (min.$^{-1}$)	0·362	0·88	1·48	2·45	3·73			
Lactose at 72·6°.								
$HClO_4$ (M)	0·90	1·50	2·00	2·50	3·00			
10^2k_1 (min.$^{-1}$)	0·33	0·775	1·31	1·82	2·65			
Maltose at 72·6°.								
$HClO_4$ (M)	1·50	2·00	2·50	3·00				
10^2k_1 (min.$^{-1}$)	0·66	1·16	1·72	2·34				
t-Butyl β-D-glucopyranoside at 24·7°.								
$HClO_4$ (M)	0·51	1·06	1·44	1·665	2·16	2·70	2·94	3·284
10^2k_1 (min.$^{-1}$)	0·0175	0·0598	0·121	0·187	0·398	0·83	1·21	1·83
Methyl α-2-deoxy-D-glucopyranoside.								
Temp.	25·0°	25·0°	25·0°	25·0°	35·0°	44·5°	44·5°	
$HClO_4$ (M)	1·04	1·95	0·98 [a]	0·495 [d]	1·98	0·503	1·01	
10^2k_1 (min.$^{-1}$)	0·157	0·599	0·139	0·639	2·89	1·19	3·49	
Temp.	44·5°	44·5°	44·5°	44·5°	44·5°	44·5°	44·5°	
$HClO_4$ (M)	1·52	2·03	2·11	1·01 [b]	2·02 [b]	1·03 [a]	1·213	
10^2k_1 (min.$^{-1}$)	7·41	13·2	16·1	2·87	9·34	3·48	10·80	
Methyl β-2-deoxy-D-glucopyranoside.								
Temp.	25·0°	25·0°	25·0°	25·0°	25·0°	44·6°	44·6°	44·6°
$HClO_4$ (M)	1·026	1·54	1·98	0·98 [a]	0·491 [d]	0·532	1·10	1·58
10^2k_1 (min.$^{-1}$)	0·471	1·04	1·75	0·465	1·59	3·46	8·96	18·7
Methyl α-D-glucopyranoside at 44·6°.								
$HClO_4$ (M)	4·03							
10^2k_1 (min.$^{-1}$)	0·0169							

[a] HBr. [b] HCl. [c] D_2O. [d] With 3·5M-$NaClO_4$.

* Values of H_0 as given by Paul and Long.[7]

[6] Rittenberg and Ponticorvo, *Internat. J. Appl. Rad. Isot.*, 1956, **1**, 208.

TABLE 2. *Kinetic parameters for the hydrolysis of glycosides.*

Compound ...	Maltose [a]	Lactose [a]	Salicin [a]	Ph β-G [b]	Me β-G	Bu^t β-G
S'	−0·89	−0·90	−0·95	−0·94	−0·93	−1·30

Compound ...	Me α-G [b]	Ph α-G [c]	Me α-2-deoxy-G [d]	Me β-2-deoxy-G [d]
S'	−0·95	−0·92	−1·04	−0·96
E	33·7	30·8	29·3	27·7
ΔS	+13·8	+13·2	+16·7	+13·7

G = D-Glucopyranoside.
[a] 72·6°. [b] 72·9°. [c] 57·4°. [d] 44·6°. [e] 24·7°.

with the values of H_0 given by Paul and Long,[7] are included. Values of the activation energy E, in kcal. mole^{-1}) and the entropy of activation (ΔS, in cal. mole^{-1} deg.$^{-1}$) have been calculated where the data are sufficient and are also given in Table 2.

Isotope Results.—Table 3 gives the results obtained: N_S and N_M refer to the excess abundance (atom %) of ^{18}O in the solvent and isolated product, respectively; R is the proportion of total reaction at the time of isolation of the product; and Q is the proportion of the reaction apparently proceeding by hexose–oxygen bond fission.

TABLE 3. *Isotope results.*

Compound *	Conditions	R	N_S	N_M	Q
Maltose	2·4M-$HClO_4$, 73°	1·00	1·80	0·05	0·78
Me α-2-deoxy-G	2M-$HClO_4$, 45°	1·00	1·00	0·01	0·99
Bu^t β-G	0·92M-$HClO_4$, 25°	0·734	0·44	0·44	0·00

* G = D-Glucopyranoside.

With maltose, Q is given by $(1 - 8N_M/N_S)$. This arises because N_M refers to the isotopic composition of a product derivative (glucosazone) containing four oxygen atoms, all of which would be isotopically normal if the hydrolysis proceeded by hexose–oxygen bond fission and one of which would be isotopically half enriched if the alternative mode of bond fission occurred. The procedure is not sensitive and the difference between the observed value of Q and unity is probably experimental error, but it may also reflect small amounts of adventitious exchange involving the hydroxyl groups of the substrate or product.

With t-butyl β-D-glucopyranoside a complication arises because the product, t-butyl alcohol, undergoes oxygen exchange at a rate which is of the same order of magnitude as that of the hydrolysis. From Dostrovsky and Klein's data [8] we calculate that the first-order rate coefficient, k_E, for the oxygen exchange of t-butyl alcohol under our conditions (0·92M-$HClO_4$, 25°) is $0·82 \times 10^{-4}$ min.$^{-1}$. The isotopic enrichment in the product (N_M/N_S) arising from this exchange alone (*i.e.*, if $Q = 1·00$) is then given by the equation: [9]

$$(N_M/N_S)R = 1 - \{[k_1 \exp(-k_E t) - k_E \exp(-k_1 t)]/(k_1 - k_E)\}$$

where k_1 is the first-order rate coefficient for the hydrolysis and the other symobls are defined above. For our conditions ($k_1 = 4·7 \times 10^{-4}$ min.,$^{-1}$ $R = 0·734$, $t = 2820$ min.), this gives $N_M/N_S = 0·13$. Hence, the oxygen exchange of t-butyl alcohol does not account for the observed results and it must be concluded that the hydrolysis of t-butyl β-D-glucopyranoside proceeds with predominant alkyl–oxygen bond fission.

DISCUSSION

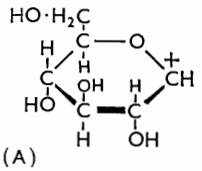
Except for t-butyl β-D-glucopyranoside, the Hammett slopes obtained with the compounds listed in Table 2 are all approximately −1·0.* A more complete kinetic study of the two deoxyglucosides has also shown that the dependence of rate on acidity function is not disturbed by the addition of sodium perchlorate, or by the use of acids other than

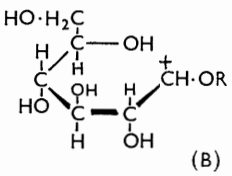
* Some of the observed deviation may arise because the rate data and the H_0 values refer, for the most part, to different temperatures.

[7] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[8] Dostrovsky and Klein, *J.*, 1955, 791.
[9] Bunton, Llewellyn, Oldham, and Vernon, *J.*, 1958, 3574.

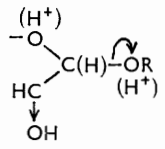
perchloric. The hydrolyses of these two compounds and of the methyl D-glucopyranosides have been found to involve large, positive entropies of activation, characteristic of acid-catalysed reactions proceeding by the $A1$ mechanism.[10] The large deuterium isotope effect (k_{D_2O}/k_{H_2O} = 2·5, 1·2M-$HClO_4$, 44·6°) observed with methyl α-2-deoxy-D-glucopyranoside, similar in magnitude to those reported for the acid-catalysed hydrolysis of sucrose and of acetals,[11] is also consistent with the $A1$ mechanism. The evidence suggests, therefore, that there is a common mechanism of hydrolysis of all the glycosides (except, for the moment, t-butyl β-D-glucopyranoside) and that this involves the rate-determining formation of carbonium ions. In Part I, it was shown that hydrolysis of phenyl and methyl D-glucopyranosides proceeds with hexose–oxygen bond fission: in the present work, the same result has been obtained with maltose and with methyl α-2-deoxy-D-glucopyranoside. By reasonable inference, the hydrolysis of lactose, salicin, and methyl β-2-deoxy-D-glucopyranoside may be assumed to follow the same course.

As previously pointed out,[1] some ambiguity exists about the structure of the carbonium ions formed from glycosides by hexose–oxygen bond fission. The ions may arise by direct cleavage of the hexose–oxygen bond or by ring opening, giving structures such as (A) and (B), respectively.* Irrespective of this, however, the carbonium-ion mechanism provides an immediate interpretation of the decrease in rate of hydrolysis in passing from the 2-deoxy-D-glucopyranosides to the parent compounds. The inductive effect of the 2-hydroxyl group impedes formation of either carbonium ion (A) or (B). Hydrolyses of


(A)


(B)

t-butyl chloride and 2-chloro-2-methylpropan-1-ol (C) provide appropriate structural comparisons since both these compounds [13,14] are known to react through carbonium ions. The relevant rate data are summarised in Table 4.



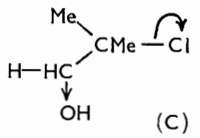

(C)

TABLE 4.

Compound	10^3k_1 (min.$^{-1}$)	Ratio (k_H/k_{OH})
Me α-2-deoxy-G [a]	150	2500
Me α-G [a]	0·06	
Bu^tCl [b]	104	103
2-Chloro-2-methylpropan-1-ol	1·01	

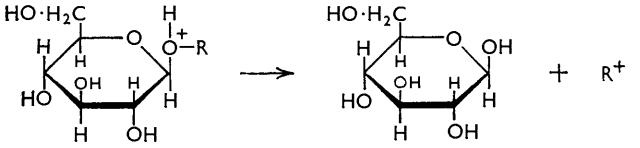
G = D-glucopyranoside. [a] M-$HClO_4$, 72·9°, value for the deoxy-compound by extrapolation from 44·6°. [b] In water, 25°, from data in refs. 14 and 15.

It can be seen that a large acceleration occurs in both systems by the removal of a hydroxyl group from a position one atom removed from the reaction centre. The effect

* Evidence derived from the stereochemical course of the reactions and from studies of the oxygen-isotope effect will be presented in a later paper in favour of the view that the reactions actually involve the cyclic ion (A).[12]

[10] Long, Pritchard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.
[11] Wiberg, *Chem. Rev.*, 1955, **55**, 713.
[12] Banks, Meinwald, Rhind-Tutt, and Sheft, unpublished experiments.
[13] Swain, Cardin, and Ketley, *J. Amer. Chem. Soc.*, 1955, **77**, 934.
[14] Ley and Vernon, *J.*, 1957, 3256.

is larger in the sugar compounds, perhaps because the inductive effect of the hydroxyl group impedes both the formation of the conjugate acid and its breakdown into the carbonium ion.*



The hydrolysis of t-butyl β-D-glucopyranoside is much faster than that of the corresponding methyl compound (*ca.* 1000 in M-$HClO_4$, 25°). This larger rate difference becomes intelligible, however, because of the discovery that the hydrolysis of the former compound involves alkyl–oxygen bond fission. This is the first known example of this type of reaction in the glycoside series. The mechanism must involve the production of the alkyl carbonium ion ($R^+ = Bu^{t+}$), and will presumably occur in any glycoside for which the stability of R^+ is greater than that of the glycopyranosyl carbonium ion. Consistently, the reaction rate is dependent on H_0. The Hammett slope, however, is greater than unity and significantly different from the values observed with the glycosides hydrolysing with hexose–oxygen bond fission. This difference in Hammett slope is difficult to interpret. However, stereochemical studies of nucleophilic substitution in tetra-*O*-methyl-D-glycopyranosyl chlorides (Part II) and of the methanolysis of glycosides [12] leads to the conclusion that, in the D-glucose series, carbonium-ion reactions involve transition states in which the nucleophile is well orientated and at no large distance from the reaction centre. For steric reasons, substitution at the t-butyl centre presumably involves a transition state in which the nucleophile is more remote.

Other reactions which are known to involve transition states with well orientated nucleophiles include the acid-catalysed opening of epoxides [15] and the acid-catalysed oxygen exchange of s-butyl alcohol.[16] For both reactions the values of the Hammett slopes are near to unity. It may be that this type of carbonium-ion reaction is a distinct class and is characterised by, among other things, a simple dependence of rate on h_0. In this connection, it would be interesting to have the appropriate data for the D-mannopyranosides since, for these compounds, the evidence suggests (Part II) that the nucleophile cannot approach closely to the reaction centre in the transition state.

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* Conformational effects may also be important with the pyranosides. However, the inductive effect of the hydroxyl group must produce an effect in the observed direction and, since no quantitative estimate can be given, the part played by conformational differences must remain uncertain.

[15] Pritchard and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 2667.
[16] Bunton and Llewellyn, *J.*, 1957, 3402.