989. *Reactions at Position* 1 *of Carbohydrates. Part IV.*[1] *The Kinetics and Mechanism of the Acid-catalysed Hydrolysis of Ethyl and Phenyl* 1-*Thio*-β-D-*glucopyranoside.*

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The hydrolyses in aqueous hydrochloric acid of ethyl and phenyl 1-thio-β-D-glucopyranoside have been studied, and Arrhenius parameters have been determined. If these thioglucosides and the corresponding *O*-glucosides undergo hydrolysis by the same mechanism then the results obtained are consistent only with that (Scheme A) proceeding *via* a cyclic carbonium ion.

ALTHOUGH both Fischer and Delbrück [2] and Purves [3] have commented on the relative slowness of the acid-catalysed hydrolysis of phenyl 1-thio-β-D-glucopyranoside, no precise kinetic study of the hydrolysis of a thioglycoside has been reported. Such an investigation has now been carried out and the results obtained are summarised in Table 1. In Table 2 kinetic parameters are listed for the acid-catalysed hydrolysis of analogous *O*-[1] and *S*-glucosides.

The formation of thiophenol and ethanethiol from the phenyl and ethyl thioglucoside, respectively (see below), indicates that glucosyl–sulphur bond fission occurs in both hydrolyses. The high positive entropies of activation and the better correlation of the rates with h_0 than with C_{H^+} (see Table 3) suggest [4,5] an *A*-1 mechanism. Hence the behaviour of these thioglucosides resembles that of the analogous *O*-glucosides studied by Bunton *et al.*,[6] and two mechanisms (A) and (B) for the hydrolyses are possible. Both are consistent with the thioglucosides' being hydrolysed more slowly than their oxygen counterparts. In mechanism (A) the equilibrium step (I $\rightleftharpoons$ II) would be more favourable if oxygen were substituted for sulphur because of the greater basicity of oxygen,[7]

[1] Part III, Overend, Rees, and Sequeira, *J.*, 1962, 3429.
[2] Fischer and Delbrück, *Ber.*, 1909, **42**, 1476. [3] Purves, *J. Amer. Chem. Soc.*, 1929, **51**, 3627.
[4] Cf. Long, Pritchard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362; Whalley, *Trans. Faraday Soc.*, 1959, **55**, 798.
[5] Cf. Long and Paul, *Chem. Rev.*, 1957, **57**, 935; Long, *Proc. Chem. Soc.*, 1957, 220.
[6] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[7] Cf. Tarbell and Harnish, *Chem. Rev.*, 1951, **49**, 1.

TABLE 1.

Hydrolysis rates in aqueous hydrochloric acid.

	Et 1-thio-β-D-glucopyranoside				Ph 1-thio-β-D-glucopyranoside			
[HCl] (M)	2·01	2·01	2·01	4·07	3·93	3·93	3·93	2·01
Temp.	60·0°	69·9°	80·0°	69·9°	70·15°	80·1°	90·0°	80·1°
10^6k (sec.$^{-1}$) (±2%)	5·32	21·5	88·2	133	5·58	21·9	87·5	3·46

TABLE 2.

The rates of acid-catalysed hydrolyses (2M-HCl) of *O*- and *S*-glucopyranosides.

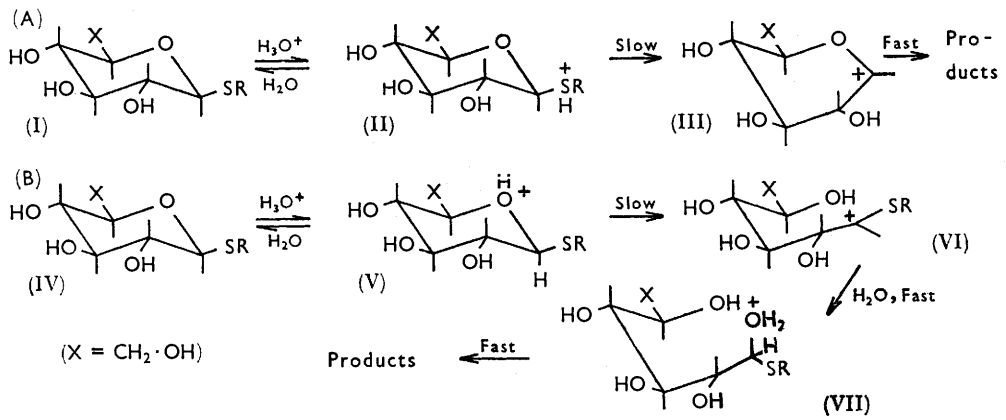
β-D-Glucopyranoside	10^5k (70°) (sec.$^{-1}$)	E (±0·6) (kcal. mole^{-1})	log A	$\Delta S^{\ddagger}$ (±1·7 e.u.)
Methyl	7·10	34·3	17·6	18·3
Ethyl	7·07	—	—	—
Ethyl 1-thio-	2·13	32·8	15·9	12·4
Phenyl	31·6	31·0	16·3	12·6
Phenyl 1-thio-	0·088	33·7	15·6	10·8

TABLE 3.

The dependence of hydrolysis rates on acidity.

C_{H^+}	h_0	10^6k (sec.$^{-1}$)	$10^6k/C_{H^+}$	$10^6k/h_0$	C_{H^+}	h_0	10^6k (sec.$^{-1}$)	$10^6k/C_{H^+}$	$10^6k/h_0$
Ethyl 1-thio-β-D-glucopyranoside at 69·9°.					*Phenyl 1-thio-β-D-glucopyranoside at* 80·1°.				
2·01	4·9	21·5	10·7	4·4	2·01	4·9	3·46	1·72	0·71
4·07	26	133	32·7	5·1	3·39	24	21·9	5·57	0·91

whereas in mechanism (B) the slow heterolysis (V ⟶ VI) would be more rapid if oxygen were substituted for sulphur owing to the greater tendency of oxygen to release electrons mesomerically.[8] Because of these considerations, a recent statement[9] that a mechanism analogous to (B) " fails to account for the relative inertness of *S*-phenyl 2,3,4,6-tetra-*O*-methyl-β-D-thioglucopyranoside to methanolysis," is incorrect in our view.



It is seen from Table 2 that the phenyl : ethyl rate ratio for the thioglucosides is 1 : 25, whereas for the oxygen glucosides it is 4 : 1. This reversal of reactivity when oxygen is substituted for sulphur is a reflexion of a 350-fold difference in rate between the phenyl thioglucoside and phenyl glucoside, but only a 3-fold difference between the corresponding

[8] Cf. Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, New York, 1953, p. 77.
[9] Banks, Meinwald, Rhind-Tutt, Sheft, and Vernon, *J.*, 1961, 3240.

ethyl compounds. If it is assumed that all the glucosides are hydrolysed by the same mechanism, then these results must mean that (i) $Ph\overset{+}{O}H$ is a much better leaving group relative to $Ph\overset{+}{S}H$ than is $Et\overset{+}{O}H$ to $Et\overset{+}{S}H$, and/or (ii) Gl–SPh is a much weaker base relative to Gl–OPh than is Gl–SEt to Gl–OEt (Gl = glucosyl) (mechanism A), or (iii) the mesomeric electron release from $Ph–\overset{\curvearrowright}{O}—$ relative to $Ph–\overset{\curvearrowright}{S}—$ is much greater than that of $Et–\overset{\curvearrowright}{O}—$ relative to $Et–\overset{\curvearrowright}{S}—$, and/or (iv) the ring-oxygen of Gl–SPh is more weakly basic relative to Gl–OPh than is that of Gl–SEt to Gl–OEt (mechanism B). Of these possibilities only (i) is consistent with the greater mesomeric interaction of oxygen than sulphur [10] with a benzene ring. Hence these results suggest that the mechanism of hydrolysis of *O*-glucosides is analogous to scheme (A) and that the small value of the rate ratio k_{GlSPh}/k_{GlOPh} as compared with k_{GlSEt}/k_{GlOEt} arises from the relative weakness of protonated thiophenoxyl as a leaving group. These conclusions are consistent with those of Vernon and his co-workers [9] that methyl α-D-glucopyranoside is hydrolysed by a mechanism analogous to scheme (A).

Experimental

Materials.—Ethyl 1-thio-β-D-glucopyranoside, prepared by Lemieux's method,[11] was recrystallised successively from ethyl methyl ketone and ethyl acetate and had m. p. 99·5—100·5°, $[\alpha]_D^{20}$ −58·2° (*c* 3·2 in H_2O). Phenyl 1-thio-β-D-glucopyranoside, prepared by Purves's method,[3] was recrystallised from ethyl acetate containing a little methanol and had m. p. 113°, $[\alpha]_D^{20}$ −72·1° (*c* 1·8 in H_2O).

Kinetic Procedure.—The reaction rates were measured by determining the D-glucose liberated after known intervals of time by a modification of Hagedorn and Jensen's method.[12] The glucose solution (10 ml.) and alkaline potassium ferricyanide solution (10 ml.) [1·65 g. of $K_3Fe(CN)_6$ + 10·6 g. of Na_2CO_3 per l.] were heated in a boiling-water bath for 20 min. The mixture was then cooled and 0·3—0·4 ml. of acid zinc sulphate (1 volume of 40% aqueous $ZnSO_4$ and 2 volumes of 45% H_2SO_4) added, followed by 1 ml. of starch–iodide indicator solution. The liberated iodine was titrated with 0·005N-sodium thiosulphate. Since the reaction of glucose with ferricyanide is non-stoicheiometric, a calibration curve was prepared with standard glucose solutions (0·0002M to 0·002M at 0·0002M-intervals). Since ethanethiol and thiophenol interfere with this determination they were removed and the kinetic runs were carried out as follows:

(*a*) *Hydrolyses of ethyl* 1-*thio*-β-D-*glucopyranoside.*—Portions (7 ml.) of a 0·002M-solution in hydrochloric acid were transferred by pipette into nitrogen-flushed "Pyrex" bulbs. These were sealed and placed simultaneously in a thermostat-bath and when they had reached thermostat temperature two were withdrawn and frozen in acetone–solid carbon dioxide. This time was taken as zero and bulbs were removed in duplicate after measured intervals, frozen, and opened, and a 5 ml. portion was withdrawn by pipette. The acid was neutralised by titration with potassium carbonate solution of approximately equal normality and the solution was boiled for 3 min to expel ethanethiol, then cooled and analysed for glucose as described. Both polarimetric and iodometric analysis of the thiol were unsatisfactory owing to the accumulation of insoluble thiol in the solution, and to the slow and incomplete reaction between the thiol and iodine.

(*b*) *Reactions of phenyl* 1-*thio*-β-D-*glucopyranoside.* Portions (~ 3 ml.) of a 0·025M-solution of the glycoside in hydrochloric acid were placed in a series of bulbs which were sealed and placed in a thermostat-bath. After various time intervals the bulbs were cooled and 2-ml. aliquot parts were withdrawn. These were neutralised, the thiophenol was extracted with benzene (10 ml.), and the aqueous solutions were diluted to 25 ml. with water. An aliquot part (10 ml.) of each solution was then analysed for glucose as described. Control experiments

[10] Cf. Tarbell and Harnish, *J. Amer. Chem. Soc.*, 1952, **74**, 1862; also ref. 8.
[11] Lemieux, *Canad. J. Chem.*, 1951, **29**, 1079.
[12] Hagedorn and Jensen, *Biochem. Z.*, 1923, **46**, 135.

showed that water saturated with benzene had no effect on the glucose analyses. The extraction was complete since the aqueous layer, when made alkaline, gave no absorption in the ultraviolet region characteristic of the thiophenoxide ion.

Attempts to follow this hydrolysis by measuring the rate of thiophenol formation iodometrically and spectrophotometrically were unsatisfactory, as some thiophenol was always oxidised to diphenyl disulphide.

Demonstration that Thiophenol and Ethanethiol are Reaction Products.—Phenyl 1-thio-β-D-glucopyranoside (200 mg) was heated with 4N-hydrochloric acid for 60 hr. in an atmosphere of

TABLE 4.

Hydrolysis of ethyl 1-thio-β-D-glucopyranoside (0·00211M) in 2·01M-hydrochloric acid at 69·9°.

Time (min.)	60	120	240	400	636	842	1014
Hydrolysis (%)	7·6	14·7	26·1	60·3	56·9	65·9	72·5
10^5k (sec.$^{-1}$)	2·19	2·19	2·10	2·15	2·21	2·13	2·13

Mean $k = 2{\cdot}16\ (\pm 0{\cdot}03) \times 10^{-5}$ sec.$^{-1}$.

Hydrolysis of phenyl 1-thio-β-D-glucopyranoside (0·025M) in 3·93M-hydrochloric acid at 90·0°.

Time (min.)	20	45	67	95	124	194	261	353	∞
Hydrolysis (%)	9·74	20·7	28·3	38·0	46·3	62·0	79·5	91·0	112·0
10^5k (sec.$^{-1}$)	9·02	8·86	8·55	8·67	8·67	8·75	10·10 *	11·25 *	

Mean $k = 8{\cdot}75\ (\pm 0{\cdot}16) \times 10^{-5}$ sec.$^{-1}$.

* Value omitted from mean k.

nitrogen. The solution, which smelled strongly of thiophenol, was neutralised and an excess of an ethanolic solution of iodine was added. The precipitated diphenyl disulphide (52 mg., 65%) was filtered off, washed with water, and dried; it had m. p. 59—60°.

Ethyl 1-thio-β-D-glucopyranoside (200 mg.) was heated with 2N-hydrochloric acid for 8 hr. in an atmosphere of nitrogen. The solution, which smelled strongly of ethanethiol, was neutralised with deoxygenated sodium hydroxide solution and an ethanolic solution of mercuric cyanide was added. The solution was evaporated to one-quarter bulk and the precipitated mercury derivative (72 mg., 44%) of ethanethiol was filtered off, washed with water, and dried; it had m. p. 73—76°. (Although precautions were taken to prevent oxidation, it is suspected that the low yield is due in part to some oxidation of the ethanethiol.)

Results.—Detailed values for some of the reactions are given in Table 4. Ethyl 1-thio-β-D-glucopyranoside yielded steady first-order coefficients, but those for phenyl 1-thio-β-D-glucopyranoside rose after about 70% reaction and the values quoted in Table 2 are the means for the first 70% of the reaction. Duplicate kinetic runs were performed and the differences in the mean coefficients for each reaction were never greater than 2%. The t_∞ titration, performed after ten half-lives, for ethyl 1-thio-β-D-glucopyranoside corresponded to 99—100% hydrolysis, but that for phenyl 1-thio-β-D-glucopyranoside corresponded to 110% hydrolysis. This was probably owing to the formation of some more strongly reducing entity from glucose under the vigorous conditions needed to hydrolyse this glucoside. Paper chromatography (butanol–ethanol–water; 5 : 1 : 4) of the final run solutions showed spots with R_F 0·04 and 0·19 in addition to the spot for D-glucose, R_F 0·13. Similar spots were found on the chromatograms of the mixtures obtained by heating D-glucose with 4N-hydrochloric acid at 10°, 80°, and 90° for several hours. It is possible that the spot with R_F 0·04 was that of a disaccharide and that the spot with R_F 0·19 corresponded to a fragmentation product or a furan derivative.

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