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Abstract

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STUDY OF THE KINETICS OF ACID HYDROLYSIS OF CERTAIN PHENYL- AND CHLOROPHENYL GLYCOSIDES

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The study of the kinetics of hydrolysis of glycosides is of considerable interest. In particular, clarification of the question of which structural features of the sugar and aglycone stabilize or, conversely, labilize glycosidic bonds may serve as orienting material in developing routes for the directed synthesis of glycosides with the required degree of strength of the glycosidic bond, for example in the glycosidation of medicinal substances.

Many investigators have studied the acid-catalyzed hydrolysis of glycosides, and at present data have been obtained concerning the influence of the character of the ring [1,2], the configuration of the glycosidic carbon atom [3,4], and the configuration of the asymmetric carbon atoms in the sugar residue [5]; there are also data on the influence of the character of the aglycone and of various substituents in it [6–8]. However, comparatively little is known about the hydrolysis of substituted phenyl glycosides, and data on the hydrolysis of halogen-substituted phenyl glycosides with various sugar components are entirely absent.

In this connection, we set ourselves the aim of studying the hydrolysis of phenyl- and halogen-substituted phenyl glycosides of glucose, galactose, and xylose.

For this purpose glycosides were obtained with different sugar components and with chlorine as substituent, introduced into the para position of the benzene ring.

The basis of the method for the synthesis of phenyl- and halogen-substituted phenyl glycosides was the Helferich method [9], consisting of three stages: 1) acetylation of the monosaccharide with formation of the acetyl derivative; 2) condensation of the acetate with phenol—formation of the glycoside acetate; 3) saponification of the acetyl groups with formation of the free glycoside.

The second stage of the reaction is of greatest importance, since the first and third stages usually proceed with satisfactory yields. By varying the second stage of the reaction, we obtained different acetylated phenyl glycosides by convenient routes (see Table 1).

Table 1

	Melting point, °C	$[\alpha]_D$ in water	Method of preparation
Phenyl-β-*D*-glucoside	174–175	−72.9	(11,12)
Phenyl-β-*D*-galactoside	155–156	−42.3	(13)
Phenyl-β-*D*-xyloside	179–180	−50.8	(14)
p-Chlorophenyl-β-*D*-glucoside	173–174	−71.6	(14)
p-Chlorophenyl-β-*D*-galactoside	167–168	−47	(14)
p-Chlorophenyl-β-*D*-xyloside	153–154	−41	(15)

Saponification of the acetyl groups in the case of phenyl glycosides was carried out by the Paks method [10].

The physical constants of the glycosides obtained by us are given in Table 1.

In view of the laboriousness of glycoside syntheses, we used a semimicropolarimetric method to study the kinetics of hydrolysis, which made it possible to expend only 0.21-0.25 g of substance per experiment with 6-8 determinations of the constants.

Hydrolysis was carried out by us in 1 N HCl at two temperatures: 60 and 80°. The temperature was maintained with fluctuations of $±$0.05°.

The glycoside concentrations were from 2 to 3%. Samples in the amount of 0.5 ml were taken at various times and neutralized with an equal volume of NaOH solution, the concentration of which only very slightly exceeded normal. Neutralization stopped the hydrolysis, and the slight excess of alkali eliminated errors that could arise as a result of mutarotation. After neutralization the hydrolysate was transferred into a semimicropolarimetric tube 1 dm long and of 0.8 ml capacity.

Table 2

	0 min.	360 min.	540 min.	720 min.	840 min.	960 min.	1177 min.	∞
α	−1.77*	−0.54	−0.16	−0.09	+0.25	+0.40	+0.54	+0.91*

	0 min.	360 min.	540 min.	720 min.	840 min.	960 min.	1177 min.	∞
$K \cdot 10^3$, min.^{-1}	–	1.72	1.71	1.65	1.67	1.73	1.70	–

$$K_{\text{avg}} = (1.70 \pm 0.008) \cdot 10^{-3}$$

* Calculated.

The hydrolysis rate constants were calculated by the Arrhenius equation for a first-order reaction. The results of each experiment were subjected to statistical treatment: the mean probable error of the result was calculated. When the experiments were repeated, the calculated mean constants coincided. In Table 2, as an example, somewhat more detailed data are shown on the kinetics of hydrolysis of phenyl-β-*D*-glucoside at 60°.

Table 3

	Hydrolysis temp., °C	K	t_h	E, kcal/mole
Phenyl-β-*D*-glucoside	60	$(1.70 \pm 0.008) \cdot 10^{-3}$	6 h. 47 min.	29.86
Phenyl-β-*D*-glucoside	80	$(2.19 \pm 0.024) \cdot 10^{-2}$	52 min.	29.86
Phenyl-β-*D*-galactoside	60	$(6.01 \pm 0.039) \cdot 10^{-3}$	1 h. 55 min.	27.81
Phenyl-β-*D*-galactoside	80	$(6.51 \pm 0.133) \cdot 10^{-2}$	19 min.	27.81
Phenyl-β-*D*-xyloside	60	$(1.99 \pm 0.048) \cdot 10^{-2}$	58 min.	27.24
Phenyl-β-*D*-xyloside	80	$(2.05 \pm 0.006) \cdot 10^{-1}$	6 min.	27.24
p-Chlorophenyl-β-*D*-glucoside	60	$(1.29 \pm 0.016) \cdot 10^{-3}$	8 h. 53 min.	28.73

	Hydrolysis temp., °C	K	t_h	E, kcal/mole
p-Chlorophenyl-*β*-*D*-glucoside	80	$(1.51 \pm 0.048) \cdot 10^{-2}$	77 min.	28.73
p-Chlorophenyl-*β*-*D*-galactoside	60	$(4.51 \pm 0.070) \cdot 10^{-3}$	2 h. 33 min.	27.30
p-Chlorophenyl-*β*-*D*-galactoside	80	$(4.87 \pm 0.087) \cdot 10^{-2}$	25 min.	27.30
p-Chlorophenyl-*β*-*D*-xyloside	60	$(1.84 \pm 0.035) \cdot 10^{-2}$	1 h. 1 min.	26.57
p-Chlorophenyl-*β*-*D*-xyloside	80	$(1.80 \pm 0.008) \cdot 10^{-1}$	6 min.	26.57

Not being able to present equally detailed experimental data for the hydrolysis of all the glycosides at different temperatures, we give the final results in the form of a summary table (Table 3), where the half-life periods (t_h) and activation energies E calculated by us are also given. The probable errors in calculating the constants were usually 1–2%.

A comparison of glycoside hydrolysis leads to the following conclusions. The rate of hydrolysis of phenyl-*β*-*D*-galactoside at two temperatures (60 and 80°) is on average 3–4 times greater than the rate of hydrolysis of phenyl-*β*-*D*-glucoside. Approximately the same ratios were also observed by other authors ([16]) when comparing the rates of hydrolysis of alkyl glycosides, although the latter

are hydrolyzed considerably more slowly than phenyl glycosides. Thus, the difference in configuration at the 4th carbon atom (glucose—galactose) has a noticeable effect on the stability of glycosides toward the action of acids.

The rate of hydrolysis of phenyl-*β*-*D*-xyloside under the same conditions is approximately 10–12 times greater than the rate of hydrolysis of phenyl-*β*-*D*-glucoside. The xylosides and glucosides studied in these experiments have the same configuration of the first four asymmetric atoms, but differ in the presence in glucose of the 6th carbon atom. Thus, this latter factor has a considerably greater effect on the rate of hydrolysis than does the configuration at the 4th carbon atom.

reaction scheme

Figure 1: reaction scheme

conformational scheme C1 to H1

Figure 2: conformational scheme C1 to H1

A much smaller effect on the rate of hydrolysis, both at 60° and at 80°, is exerted by a halogen introduced into the para position of the benzene ring, as is evident from comparison of the hydrolysis constants of three pairs of glycosides.

The activation energies of the glycosides are close values, 26–29 kcal/mole; for galactosides their values are somewhat lower than for glucosides, and for xylosides somewhat lower than for galactosides.

The data we have obtained on the dependence of hydrolysis on the sugar component are in good agreement with current ideas on the mechanism of acid hydrolysis and on the conformations of sugars (17) and, in turn, constitute new material confirming these ideas.

Of the two schemes of hydrolysis—Bunton' s (18) and Edward' s (19)—which have been discussed in the literature in recent years, apparently the greatest number of facts is explained by Edward' s scheme (see (20)), developed chiefly for alkyl glycosides:

The unstable oxonium ion exists in the half-chair conformation H1. The transition of the chair conformation C1, in which the majority of pyranosides exist, into the H1 conformation is accompanied by a slight rotation of the atomic groups of the molecule about bonds 2,3 and 4,5.

Since the rate of hydrolysis is determined by the rate of the slow phase—the rate of formation of the half-chair form H1—factors affecting the rotation of atomic groups about these bonds (2,3 and 4,5) are of great importance. In this connection, of course, it is necessary to take into account the general principles associated with transitions of conformational forms: bulky substituents tend to occupy equatorial positions.

From this point of view it is clear that bulky substituents located at C_5 must move into a position somewhat approaching axial, and such substituents will hinder rotation, i.e., the rate of hydrolysis. This, apparently, explains the lower rate of hydrolysis of glucosides (I) in comparison with xylosides (II) in our experiments.

Together with this, the hydroxyl at C4, which in galactosides (III) is in the axial position, with the indicated rotation—on transition to the H1 half-chair form—will approach an equatorial position, which accelerates the hydrolysis of galactosides in comparison with the corresponding glucosides.

It should also be noted that the data we have obtained do not contradict the

scheme of glycoside hydrolysis postulated by Bunton [18], according to which hydrolysis is preceded by opening of the ring of the sugar component. In this connection it should be mentioned that earlier, in studying the content of the open form of various sugars in solutions [21], we arranged the sugars in the following order according to decreasing content of the oxo form: glucose > galactose > xylose—that is, this series corresponds completely to the series of the corresponding glycosides.

With regard to the influence of the substituent in the aromatic aglycone on the rate of glycosides, the following should be noted. There are some data in the literature indicating that orienting groups of the first order, such as, for example, methyl, butyl, and propyl, increase the rate of hydrolysis [7]; in a previously published paper it was shown that the hydroxyl in arbutin doubles the rate of hydrolysis in comparison with that of phenylglucoside [22].

Halogens, as is known, behave in a distinctive way as orienting substituents: they are orienting groups of the first order, but at the same time they lower the electron density in the ring.

The somewhat slower hydrolysis of the three *n*-chlorophenyl-β-D-glycosides in comparison with the corresponding phenylglycosides, observed in our experiments, is evidently explained by the lowering of the electron density in the ring, which also hinders the addition of a proton to the oxygen of the glycosidic bond.

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Note: Figure translations are in progress. See original paper for figures.