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Abstract

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Study of the Kinetics of Alkaline Hydrolysis of Some Phenyl- and Chlorophenylglycosides

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As is known, resistance to alkalis is one of the characteristic properties of most O-glycosides. At present, however, a number of alkali-labile glycosides are also known, such as glycosides of phenols, enols, and glycosides that have electronegative substituents in the β-position of the aglycone alcohol ([1]). Among these compounds, phenylglycosides have been most extensively studied with respect to hydrolysis. Thus, the literature contains data on the effect on the rate of hydrolysis of phenylglycosides of the configuration of the carbon atom at the glycosidic bond ([1]), and of the influence of certain substituents in the aglycone ([3,4]). Schemes have been proposed for alkaline hydrolysis, which apparently may proceed, depending on the nature of the glycoside, by three different mechanisms: 1) with double inversion (via a 1,2-anhydrosugar); 2) with one inversion; 3) by ionic dissociation ([1]). Despite the availability of the cited information, the degree of study of alkaline hydrolysis of glycosides is incomparable with that of acid hydrolysis, for which, however, two possible hydrolysis schemes are still being discussed ([5]).

In the present work we studied the kinetics of hydrolysis of phenyl- and *p*-chlorophenylglycosides of glucose, galactose, and xylose. The choice of these compounds was dictated by the following considerations:

1) there is no information in the literature on the alkaline hydrolysis of halogen-substituted phenylglycosides; 2) we had recently studied the acid hydrolysis of the named glycosides ([6]), and it seemed of interest to compare it with alkaline hydrolysis.

Alkaline hydrolysis of phenyl-β-*D*-glucoside, phenyl-β-*D*-galactoside, phenyl-β-*D*-xyloside, *p*-chlorophenyl-β-*D*-glucoside, *p*-chlorophenyl-β-*D*-galactoside, and *p*-chlorophenyl-β-*D*-xyloside was carried out in $4N$ NaOH, at $80 \pm 0.1^\circ$.

Carrying out the hydrolysis at several different temperatures (which would have made it possible to calculate the activation energy) unfortunately proved impossible, since even at 70° the hydrolysis of phenylglucoside proceeded extremely slowly, while at 90° the liberated sugars rapidly underwent secondary reactions and the solutions quickly darkened. We followed the course of hydrolysis polarimetrically; in addition, in the case of hydrolysis of *p*-chlorophenylglucoside,

galactoside, and xyloside, we used a colorimetric method, the applicability of which in the study of glycoside hydrolysis had recently been demonstrated by one of us together with V. A. Ignatyuk-Maistrenko and M. G. Chentsova ([7]) on the example of some phenyl-*N*-glycosides.

The essence of this method consists in coupling the phenol liberated during hydrolysis of the phenylglycoside with *p*-nitrophenyldiazonium chloride and colorimetrically measuring the azo dye formed.

The application to the same objects of two methods—polarimetric and colorimetric—was of considerable interest, since it made possible a check, especially desirable in view of the inevitable changes in sugars under the influence of alkalis. When applying the polarimetric method in calculations carried out according to the Arrhenius equation for first-order reactions in the hydrolysis of glucosides and galactosides, we considered 1,6-anhydrohexoses to be the final product ([1,8]); in the hydrolysis of xylosides, for the initial periods of hydrolysis, xylose.

Table 1

Study of the kinetics of hydrolysis of phenyl-β-*D*-glucoside at 80° by the polarimetric method

	0 min.	60 min.	120 min.	180 min.	240 min.	360 min.	480 min.	720 min.	∞
α	−1.77*	−1.70°	−1.64	−1.57	−1.52	−1.43	−1.36	−1.26	−1.05*
$K \cdot 10^3$ min^{-1}	–	1.70	1.80	1.81	1.79	1.78	1.76	1.71	–

$$K_{\text{av}} = (1.79 \pm 0.011) \cdot 10^{-3}$$

* Calculated.

The results of experiments on the study of the kinetics of hydrolysis of phenyl-β-*D*-glucoside by the polarimetric method are presented in Table 1. To save space, the data on the study of the kinetics of hydrolysis of other glucosides by the polarimetric method are given in abbreviated form in summary Table 2.

Table 2

Hydrolysis constants and half-lives of phenyl- and chlorophenyl glucosides at 80°, determined by the polarimetric method

Glycoside	K	t_h
Phenyl-β-*D*-glucoside	$(1.79 \pm 0.011) \cdot 10^{-3}$	6 h 45 min.

Glycoside	K	t_h
Phenyl-β-*D*-galactoside	$(3.19 \pm 0.014) \cdot 10^{-3}$	3 h 52 min.
Phenyl-β-*D*-xyloside	$(4.67 \pm 0.01) \cdot 10^{-3}$	2 h 46 min.
n-Chlorophenyl-β-*D*-glucoside	$(3.97 \pm 0.01) \cdot 10^{-3}$	2 h 55 min.
n-Chlorophenyl-β-*D*-galactoside	$(0.95 \pm 0.03) \cdot 10^{-2}$	1 h 13 min.
n-Chlorophenyl-β-*D*-xyloside	$(1.24 \pm 0.014) \cdot 10^{-2}$	55 min.

The results of experiments on the study of the kinetics of hydrolysis of *n*-chlorophenyl glucosides by the colorimetric method are presented in Table 3.

Table 3

Study of the kinetics of hydrolysis of *n*-chlorophenyl-β-*D*-glycosides at 80° by the colorimetric method

n-Chlorophenyl-β-*D*-glucoside

	90	120	150	180	210	240
Duration, min.	90	120	150	180	210	240
Hydrolysis, %	29.4	37.3	42.4	48.97	55.03	60.2
$K \cdot 10^3$, min^{-1}	3.87	3.89	3.68	3.74	3.80	3.84

$$K_{\text{av}} = (3.80 \pm 0.02) \cdot 10^{-3}$$

n-Chlorophenyl-β-*D*-galactoside

	25	35	45	60	95	130
Duration, min.	25	35	45	60	95	130
Hydrolysis, %	22.4	28.9	35.9	45.2	63.4	65.8
$K \cdot 10^2$, min^{-1}	1.01	0.97	0.98	1.00	1.06	0.83

$$K_{av} = (0.98 \pm 0.02) \cdot 10^{-2}$$

n-Chlorophenyl-*β*-*D*-xyloside

	25	35	45	55	70	90
Duration, min.	25	35	45	55	70	90
Hydrolysis, %	28	37.3	44.3	51.3	60.16	68.1
$K \cdot 10^2$, min^{-1}	1.31	1.33	1.30	1.31	1.31	1.21

$$K_{av} = (1.31 \pm 0.001) \cdot 10^{-2}$$

The hydrolysis constants obtained by such different methods proved to be quite close. Thus, for *p*-chlorophenylglucoside and galactoside the hydrolysis constants differed by 4 and 3%, respectively; in the case of the xyloside, whose hydrolysis proceeded with yellowing of the solution (an obstacle to the use of both methods), the difference in the constants slightly exceeded 5%.

Thus, we have once again ([7]) demonstrated the applicability of the colorimetric method for determining the liberated aglycone to the study of the kinetics of glycoside hydrolysis. In some cases it can serve as an important checking method, and sometimes as the only method.

As is seen from the data in Table 2, both phenyl- and chlorophenylgalactosides are hydrolyzed faster than the corresponding glucosides (by a factor of 2–2.5), while xylosides are hydrolyzed faster than the corresponding galactosides (approximately 1.5-fold).

The same sequence was also observed in the alkaline hydrolysis of alkyl glycosides, which are hydrolyzed much more slowly, under more severe conditions ([2]).

Thus, the order of arrangement of glycosides according to the stability of their glycosidic bond in alkaline hydrolysis proves to be the same as in acid hydrolysis ([6]). If one takes into account that the conditions of alkaline hydrolysis were more severe (4*N* NaOH) than those of acid hydrolysis (1*N* HCl), whereas the hydrolysis constants obtained are higher in acid hydrolysis, it must be considered that the glycosidic bonds of phenylglucosides are much more labile toward acid hydrolysis than toward alkaline hydrolysis.

The influence of the halogen in the aglycone was manifested very clearly in alkaline hydrolysis: chlorine-substituted glycosides are hydrolyzed 2–3 times faster than those not containing halogen.

Experimental Part

Syntheses of glycosides were carried out as described in the preceding paper ([6]), which also gives the constants of these substances.

Experiments on the study of the kinetics of hydrolysis. Accurate weighed portions of glycosides (usually 0.21–0.25 g) in flasks with 5 ml were hydrolyzed with $4N$ NaOH in a thermostat at $80 \pm 0.1^{\circ}$. At various time intervals, 0.5-ml samples were taken from the reaction mixture; in each experiment the hydrolysis constant was determined 6–8 times. The course of hydrolysis was followed by two methods: a) the semimicropolarimetric method and b) the colorimetric method.

a) When using the **semimicropolarimetric method**, the samples were diluted with an equal amount of water and rapidly cooled to room temperature. Under these conditions hydrolysis practically ceased: specially performed experiments showed that solutions of glucosides in $2N$ NaOH do not change their rotation on prolonged standing (12 h).

The hydrolysate diluted with water was transferred into a semimicropolarimetric tube 1 dm long and of 0.8 ml capacity. The optical activity of the solution was determined with a Schmidt and Haensch polarimeter and a sodium spectral lamp. The constants were calculated from the Arrhenius equation for first-order reactions; the mean values of the constants and the mean probable errors of the result were calculated. The latter did not exceed 1–3%. Half-life periods were also calculated.

b) When using the **colorimetric method**—with respect to the liberated aglycone—we made use mainly of the method developed previously in the study of the kinetics of hydrolysis of *N*-glycosides ([7]). The difference was that in the present work we could avoid extracting the aglycone (phenol), since dilution with water and cooling of the reaction mixture stops the hydrolysis (see above). In addition, specially performed

The experiments showed that the unhydrolyzed glycoside does not give a dye under the conditions of the coupling reaction.

Samples of the hydrolysate, 0.5 ml each, were transferred into 50-ml volumetric flasks and diluted to the mark with water. From these, 10-ml samples of the diluted hydrolysate were transferred into 250-ml flasks (usually three parallel determinations were carried out). To the same flasks were added 2.5 ml of *p*-nitrophenyldiazonium chloride and 6 ml of 1% NaOH; under these conditions the pH of the solution becomes 7–7.5. The dye is thereby precipitated immediately. After standing in a refrigerator for 30 min, an additional 2.5 ml of 10% NaOH was added to the flasks (until the dye had dissolved completely); then, after another half-hour, the flasks were made up to the mark with water and their contents thoroughly mixed. Colorimetry was carried out with an FEK-M photocolorimeter using a green light filter (530 mμ). The content of the aglycones—phenol and *p*-chlorophenol—was determined from an empirical curve

obtained on the basis of measurements of the optical density of solutions of the corresponding dyes formed upon coupling of various amounts of phenols. These data were used to calculate the constants.

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