

The Alkaline Hydrolysis of Phenyl β -Glucosides

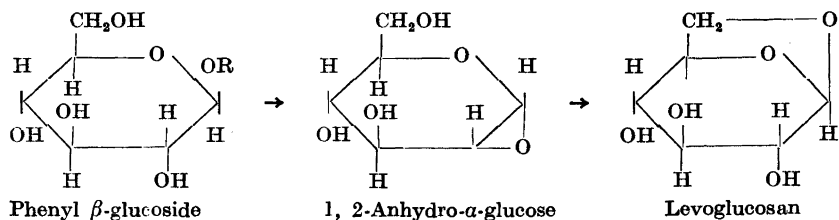
A Kinetic Investigation

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Glycosides generally are stable toward alkali, but several exceptions are known. The best known type of alkali-labile glycosides is phenyl β -glucosides. In 1894¹ Tanret proved that picein and some other glucosides yielded 1,6-anhydro- β -glucopyranose or levoglucosan, by the action of alkali. Montgomery, Richtmeyer and Hudson² have proved that this is a general reaction for phenyl β -glucosides, and have used the reaction for the preparation of levoglucosan and similar 1,6-anhydrides in excellent yields³.

The mechanism of this reaction has been studied by McCloskey and Coleman⁴. The starting material as well as the final product have β -configurations, so one must assume that the reaction involves an even number of Walden inversions. The direct formation of levoglucosan without any inversion is improbable, so the most simple assumption is that the reaction proceeds over an intermediate and involves two inversions. This intermediate, according to McCloskey and Coleman, is probably 1,2-anhydro- α -glucopyranose, because the reaction is blocked by the presence of a methoxyl group at carbon 2. Another consequence of this theory is that the phenoxyl group must be in *trans* position to the hydroxyl group at carbon 2 and in *cis* position to the terminal CH_2OH group if a phenyl glycoside is to be sensitive to alkali and yield a 1,6-anhydride. These restrictions are in excellent agreement with the experimental results.



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Fisher, Hawkins and Hibbert⁵ have studied the kinetics of the alkaline hydrolysis of some phenyl glucosides. All aglucones in their investigation, except phenol itself, contained methoxyl groups in *ortho* position to the hydroxyl groups and therefore, on account of steric effects, their material is not suitable for a quantitative treatment. From their experiments, however, as well as from the semiquantitative measurements of Montgomery, Richtmeyer and Hudson², it is clear that the velocity of the reaction increases with increasing acidity of the aglucone.

In the present investigation, the alkaline hydrolysis of a number of phenyl β -glucosides, substituted in *meta* or *para* position, has been studied kinetically. The reaction was found to be of second order, depending upon the concentrations of the hydroxyl ion and of the glucoside.

$$v = k [\text{OH}^-] [\text{phenyl } \beta\text{-glucoside}]$$

It was convenient to work with a large excess of alkali, so that the kinetics could be calculated as a first order reaction. The effect of the alkali concentration was therefore determined in a separate series of runs (Table 1). The excess of alkali was about 10-fold.

Table 1. Hydrolysis of *p*-chlorophenyl β -glucoside at 100° C.

c_{OH^-}	$k \cdot 10^3$
1.87	3.73
0.93	3.43
0.465	3.51

The glucosides of seven different phenols were investigated. All the runs were made at 100° C. The reactions were studied polarimetrically, except for *p*-nitrophenyl β -glucoside. This glucoside was so sensitive to alkali that very dilute solutions had to be used and the rotations of the solutions were consequently very small. In this case the concentration of nitrophenoxyl ion, formed by the hydrolysis, was determined photoelectrically. The results are summarized in Table 2.

For reactions which occur in the side chain of *meta* or *para* substituted benzene derivatives, Hammett's equation⁶ should be valid.

$$\log k - \log k_0 = \rho \cdot \sigma$$

Table 2. Velocity constants for the hydrolysis of some substituted phenyl β -glucosides at 100° C.

Substituent in the phenyl group	c_{OH^-}	σ^*	k
<i>p</i> -OCH ₃	1.87	- 0.268	3.6 · 10 ⁻⁴
<i>p</i> -CH ₃	1.87	- 0.170	3.0 · 10 ⁻⁴
<i>m</i> -CH ₃	1.87	- 0.069	6.6 · 10 ⁻⁴
None	1.87	0.000	9.7 · 10 ⁻⁴
<i>p</i> -Cl	1.87	+ 0.227	3.7 · 10 ⁻³
<i>p</i> -CH ₃ CO	0.208	+ 0.874	7.5 · 10 ⁻²
<i>p</i> -NO ₂	0.0185	+ 1.27	2.0

* The values of σ are taken from Hammett⁶.

Here k and k_0 are velocity (or equilibrium) constants for the substituted and unsubstituted benzene derivatives. ρ is the reaction constant and σ is the substituent constant. This linear relationship was found to be valid for the alkaline hydrolysis of phenyl β -glucosides. In Fig. 1 the values of $\log k$ are plotted against the corresponding values of σ . The ρ value was + 2.5.

When the values of $\log k$ are plotted against the pK_s values for the phenols (48.9 % ethanol, $t = 20^\circ\text{C}$), determined by Schwarzenbach and Rudin⁷, a still better agreement is obtained (Fig. 2). This is quite natural since the systematic errors are smaller the more related the compared substances are. It is evident that the σ -value for *p*-OCH₃ (-0.268) is too low in this case. Both the pK_s of the phenol and the $\log k$ for the glucoside indicate a higher value (about - 0.13). These irregularities are clearly shown if one compares the *p*-OCH₃ derivatives with the corresponding *p*-CH₃ derivatives. Of the acids, the *p*-CH₃ is the stronger, but if one compares the phenols, the *p*-OCH₃ is somewhat more acidic.

In none of the reactions studied was the final rotation in agreement with the assumption that all the phenyl β -glucoside had been converted to levoglucosan. If one assumes that the byproduct is glucose, which under these conditions is transformed into substances without any optical rotation, the yield of levoglucosan can be calculated to 80—90 % in good agreement with the values found by Montgomery, Richtmeyer and Hudson². This side reaction does not seem to influence the kinetics of the reaction appreciably.

If, according to McCloskey and Coleman, 1,2-anhydro- α -glucose is an intermediate in this reaction, the formation of this substance must be the slow, rate determining step of the reaction, and its transformation into levo-

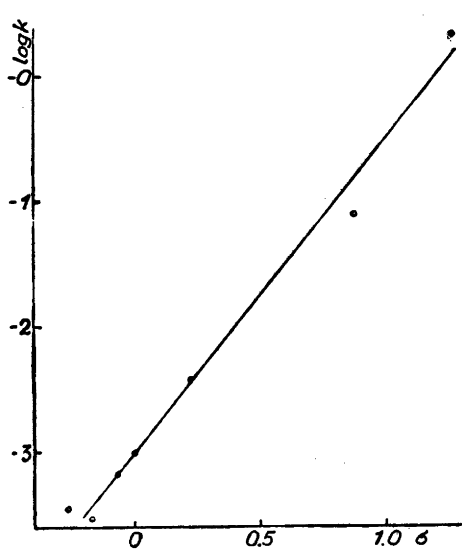


Fig. 1. Linear relationship between $\log k$ and Hammett's σ -values.

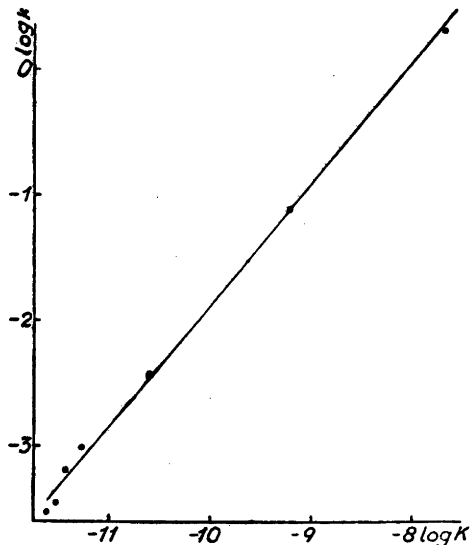


Fig. 2. Linear relationship between $\log k$ and $\log K$ for the corresponding phenols.

glucosan must be rapid. Only in this case could one expect the kinetics actually found. This hypothetical intermediate is not known* but its triacetate has been prepared by Brigl⁶. When this substance is treated with water, the ethylene oxide ring is split up and α -glucose triacetate is formed. If the substance were treated with strong alkali, however, one might expect that the ester groups (or at least a great deal of them) would be hydrolyzed before the ethylene oxide ring reacted. Then the solution would contain 1,2-anhydro- α -glucose, which, if the above theory were correct, would yield levoglucosan. When the 1,2-anhydride triacetate was dissolved in 1.25 N KOH in water-dioxane (2 : 1) at room temperature, the rotation of the solution decreased rapidly to negative values, indicating the formation of levoglucosan. This substance also was isolated from the reaction mixture. The theory of McCloskey and Coleman has thus been strongly supported.**

* Pictet and Castan claim to have synthesized this substance (*Helv. Chim. Acta* **3** (1920) 645). Their results, however, are disputed by Brigl (*Ber.* **62** (1929) 1716). It seems rather certain that their substance, which could not be obtained in a crystalline state by other investigators, can not be 1,2-anhydro- α -glucose. The present investigation also supports Brigl's opinion.

** (Added in proof)

In the 25 May issue of *Chemical Abstracts*, **44** (1950) 4425, a paper by Bardolph and Coleman [*J. Org. Chem.* **15** (1950) 169] is abstracted. They have, previous to us, demonstrated that levoglucosan is formed by the action of alkali on triacetyl-1,2-anhydro- α -glucose.

EXPERIMENTAL

The glucosides used in this investigation are, with one exception, described in the literature. They were synthesized as tetraacetates by conventional methods and deacetylated catalytically with potassium ethoxide in ethanol⁹. For *m*-cresyl β -glucoside and its tetraacetate, we were not able to obtain the melting points recorded by Helferich and Philipp¹⁰. Our highest values for the glucoside and its acetate were 174–175° and 109–111° while Helferich and Philipp report 183–184° and 137–139°, respectively. Our values for the optical rotation, however, were in excellent agreement with those of H. and P.

p-Chlorophenyl β -glucoside tetraacetate

p-Chlorophenyl β -glucoside tetraacetate was prepared from β -glucose pentaacetate and *p*-chlorophenol, with *p*-toluenesulfonic acid as catalyst, using the fusion procedure of Helferich and Schmitz-Hillebrecht¹¹. The substance was recrystallized from ethanol

$[\alpha]_D^{20} = -20.0^\circ$ (Chloroform $c = 2$). Yield 65%. M. p. 123–124°, (Uncorr).

$C_{20}H_{23}O_{10}Cl$ (458.8)	Calc.	Acetyl CH_3CO	37.5
	Found	»	»
			37.3

p-Chlorophenyl β -glucoside

p-Chlorophenyl β -glucoside tetraacetate was deacetylated catalytically with potassium ethoxide in ethanol according to Bonner and Koehler⁹. The yield of deacetylated product was almost quantitative. After two recrystallizations from ethanol, the substance melted at 173–174° and further recrystallizations did not change this value.

$[\alpha]_D^{20} = -69.5^\circ$ (Water, $c = 1$).

$C_{12}H_{15}O_6Cl$ (290.7)	Calc.	Cl	12.2
	Found	»	12.1

Procedure for the kinetic determination

The alkaline hydrolysis of six phenyl β -glucosides were studied polarimetrically. The results are summarized in Table 2. Here only a typical series of runs is described.

Samples of phenyl β -glucoside (0.6 g) were dissolved in 1.87 *N* potassium hydroxide (10 ml), preheated to 100° in a thermostatically controlled glycerol bath, and were kept in the bath. At regular intervals a sample was taken out of the thermostat and was rapidly chilled and neutralized with 3.5 *N* sulfuric acid. For the faster reactions, the reaction was interrupted by rapid neutralization with 3.5 *N* sulfuric acid. For the 8 hours and longer runs, the neutralization had to be omitted on account of the voluminous precipitate of silicic acid formed. It was found, however, that the rotation was independent of the pH of the solution. The solution was diluted to 25.0 ml and the optical

rotation of the solution (if necessary filtered) was determined in a 40 cm tube. The velocity constant $k \cdot c_{\text{OH}^-}$ was calculated for a first order reaction, time in minutes, and expressed in Brigg's logarithms. The different runs are summarized in Table 3.

Table 3. Alkaline hydrolysis of phenyl- β -glucoside.

Time in minutes	α	$k \cdot c_{\text{OH}^-} \cdot 10^3$
0	- 6.12°	—
60	- 5.43	1.83
120	- 4.90	1.82
240	- 4.13	1.86
480	- 3.48	1.72
840	- 3.15	(1.68)
1440	- 3.03	—

Mean value 1.81

If all the glucoside had been converted to levoglucosan, the final rotation would be -3.55° . If one assumes that optically inactive substances are formed as byproducts, the yield of levoglucosan can be calculated to be 85 %.

This method could not be used for the *p*-nitrophenyl glucoside. Instead a photo-electrical method was used. The instrument was a Spekker absorptiometer. (Filter, Ilford 601.) A calibration curve for *p*-nitrophenol in alkaline solution, in concentrations between 10 and 75 mg per liter was constructed. *p*-Nitrophenyl β -glucoside (30 mg) was then treated with 0.0185 *N* KOH (100 ml) at 100° , the reaction interrupted by neutralization and the free nitrophenol determined. The results are summarized in Table 4.

Table 4. Alkaline hydrolysis of *p*-nitrophenyl- β -glucoside.

Time in minutes	% <i>p</i> -nitrophenol	$k \cdot c_{\text{OH}^-}$
4	27.6	0.0353
6	39.8	0.0368
10	58.2	0.0379
20	84.5	0.0405

Mean value 0.038

Experiments with 1,2-anhydro- α -glucose triacetate

1,2-Anhydro- α -glucose triacetate (1.5 g) was dissolved in dioxane (12.5 ml) and 1.87 *N* potassium hydroxide (25 ml) was added. The initial positive rotation of the solution changed within a few minutes to a constant negative value. The solution was allowed to stand for half an hour and was then neutralized with 2 *N* sulfuric acid, concentrated to dryness under reduced pressure, and the residue acetylated with acetic anhydride (8 ml) and anhydrous sodium acetate (0.5 g) by heating on a steam bath for two hours. The mixture was poured into ice water and extracted with chloroform. The chloroform solution was washed with sodium bicarbonate solution and with water, dried over calcium chloride, filtered through aluminium oxide, which removed much of the dark brown color, and concentrated. The remaining sirup was dissolved in boiling water. After cooling, crystals separated, which after further recrystallizations melted at 107.5–108.5°, alone or in mixture with authentic levoglucosan triacetate. The yield was about 20 %.

SUMMARY

The alkaline hydrolysis of seven phenyl β -glucosides has been investigated kinetically. The reaction was found to be of the second order, depending on the concentrations of the glucoside and the hydroxyl ion. A linear relationship between the values of $\log k$ and Hammett's σ -values for the substituents has been demonstrated. The reaction constant, ρ , was 2.5.

1,2-Anhydro- α -glucose triacetate was found to yield levoglucosan by alkaline hydrolysis. This strongly supports the theory of McCloskey and Coleman that 1,2-anhydro- α -glucose is an intermediate in the alkaline hydrolysis of phenyl β -glucosides into levoglucosan.

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