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KINETICS OF BASE-CATALYZED DEGRADATION OF PHENYL D-GLUCOPYRANOSIDES

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ABSTRACT

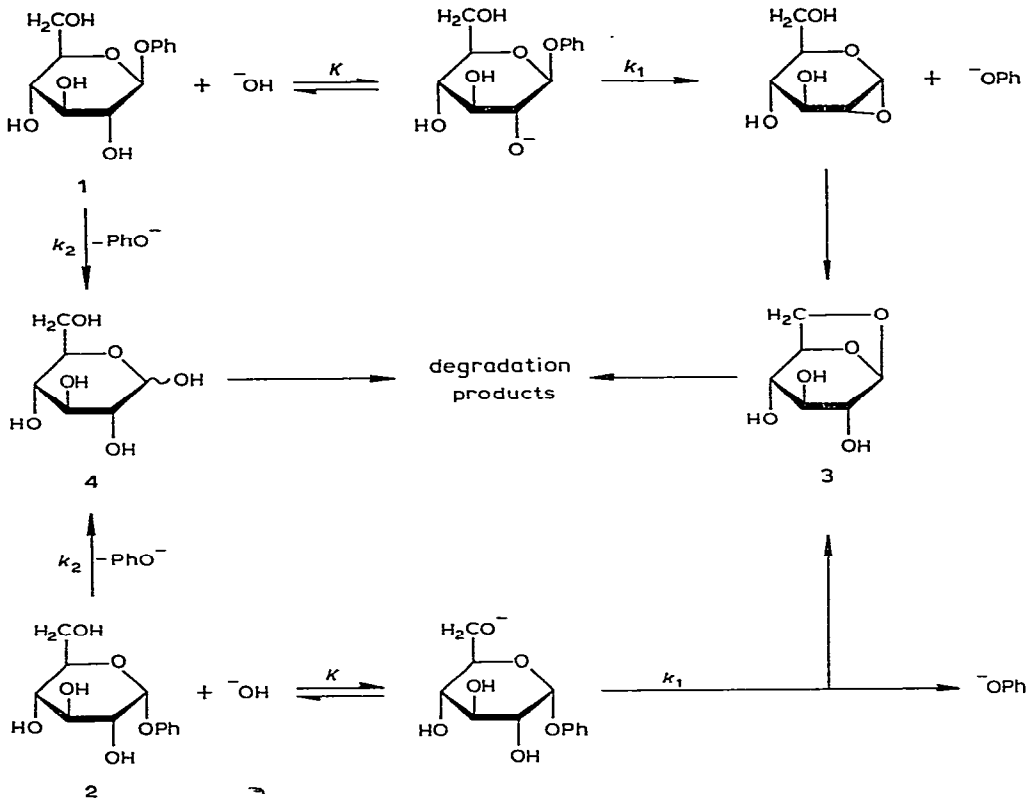
The kinetics of base-catalyzed cleavage of the glycosidic linkage in phenyl α- and β-D-glucopyranoside have been studied at various concentrations of base, and are interpreted in terms of formation of anionic species as reactive intermediates, accompanied by a minor mechanism of bimolecular, nucleophilic substitution.

The data indicate that, in <M sodium hydroxide solution, more than 80% of the cleavage reaction proceeds through an intramolecular-displacement process facilitated by the anchimeric assistance of the hydroxyl group at C-6, and C-2, for the α- and β-D-glycoside, respectively. However, the bimolecular substitution reaction becomes increasingly apparent as the alkalinity is raised above 1.5M concentration of base.

INTRODUCTION

The effects of hydroxyl-ion concentration on the kinetics of base-catalyzed cleavage of glycosidic linkages of simple glycosides have been reported by several investigators[1–7], and may be divided into two types. The first is consistent with the formation of anionic intermediates, as observed for methyl α- and β-D-glucopyranoside[4] and *p*-nitrophenyl α-D-glucopyranoside[5]. For these glycosides, the rate of reaction increases initially with the concentration of hydroxyl ion, but levels off to a constant value at ~1.5M concentration of the base. The second type was found with substituted phenyl glycosides[5], including *p*-chlorophenyl α- and β-D-glucopyranoside, and *p*-nitrophenyl β-D-glucopyranoside, for which the reaction rate is proportional to the concentration of the base, indicating the direct participation of hydroxyl ion.

On the other hand, the kinetics of base-catalyzed cleavage of unsubstituted phenyl glycosides has not been systematically studied, although their reaction mechanisms are now reasonably well understood. The reaction of phenyl β-D-glucopyranoside (**1**) is well established[8–10] as proceeding through the intermediate formation of a 1,2-anhydride, providing a facile method[11] for the preparation of 1,6-anhydro-β-D-glucopyranose (levoglucosan, **3**), whereas the α-D anomer (**2**) has recently been shown[12] to react primarily through a direct-displacement mechanism involving the



Scheme 1. Possible mechanisms for the alkaline cleavage of phenyl β- and α-D-glucopyranoside.

ionized hydroxyl group on C-6 (see Scheme 1). The latter reaction also gives levoglucosan, but it takes place at a rather high temperature. However, a bimolecular substitution-reaction has often been suggested as being involved in the cleavage of aryl α-D-glucopyranosides.

The purpose of this work was to determine the extent to which the effects of the hydroxyl-ion concentration on the base-catalyzed cleavage-reaction of phenyl α- and β-D-glucopyranoside can be described in terms of the formation of the anionic intermediates shown in Scheme 1.

RESULTS AND DISCUSSION

Phenyl β-D-glucopyranoside. — The effect of the concentration of the base on the cleavage of this glycoside was studied in sodium hydroxide solution of concentration ranging from 0.5 to 8.1M, at 100°. The reaction, monitored by colorimetric determination of the phenol liberated, was found to fit the pseudo-first-order rate-equation *1*.

$$\ln (1/c) = k_{obs}.t, \qquad (1)$$

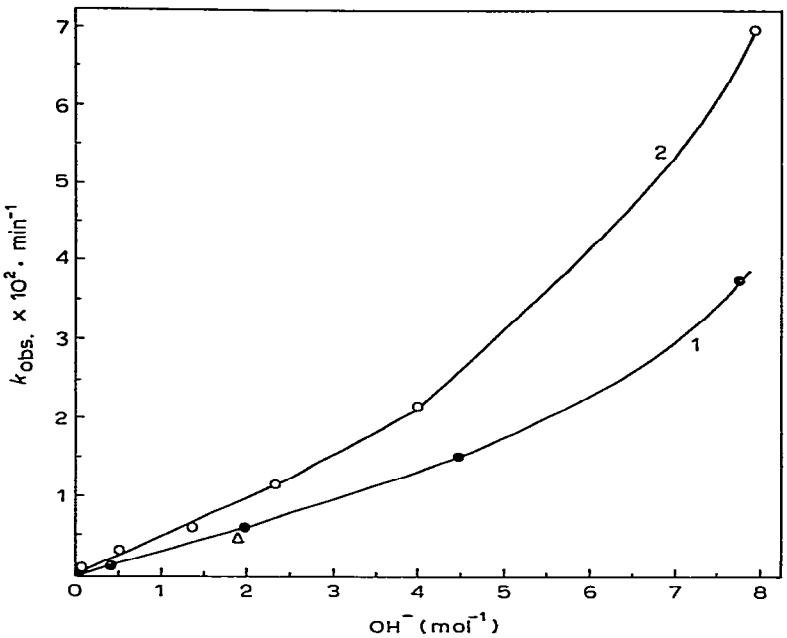


Fig. 1. Dependence of observed rate-constant ($k_{obs.}$) on the hydroxyl-ion concentration. [1, phenyl β-D-glucopyranoside at 100°: ● current data, and △, datum reported in ref. 7; and 2, phenyl α-D-glucopyranoside at 170°.]

where c is the mole fraction of unreacted glycoside after reaction time t, and $k_{obs.}$ is the pseudo-first-order rate-constant. The resulting data, summarized in Fig. 1, show that the reaction rate is directly proportional to the concentration of hydroxyl ion up to 2M, and that it increases sharply thereafter. This observation is, apparently, inconsistent with the mechanism generally accepted to account for the high yield of levoglucosan (88%) formed under mild conditions. According to this mechanism[4], the rate will increase with increase in the concentration of hydroxyl ion, and level off to a constant value at ~1.5M concentration of base. Thus, the foregoing data indicate the involvement of a second pathway, namely, a bimolecular, nucleophilic (SN2) substitution-reaction that becomes increasingly important at higher concentrations of alkali.

Therefore, the total reaction of this glycoside should be discussed in terms of these two pathways, which are represented by the following scheme:

$$\begin{array}{lcl} & \overset{K}{} \quad \overset{k_1}{} & \\ \mathrm{GlcOR} + \mathrm{OH^-} \rightleftarrows \mathrm{H_2O} + \mathrm{GlcOR^-} & \rightleftarrows & \text{levoglucosan} \qquad (2) \\ \downarrow \qquad\qquad \downarrow & & \downarrow \\ \qquad\qquad \downarrow + \mathrm{OH^-}_{k_2} & & \text{degradation} \qquad (3) \\ \qquad\qquad \longrightarrow & & \text{products} \end{array}$$

where GlcOR is the original glycoside, $GlcOR^-$ is the anionic intermediate, K is the equilibrium constant between the neutral and ionized species, k_1 is the specific rate-

constant in the conversion of anionic intermediates into levoglucosan, and k_2 is the rate-constant for the SN2 reaction.

As shown before[4,6], the observed reaction-rate ($k_{obs.}$) for such a mixed mechanism may be represented by equation *4*.

$$k_{obs.} = k_2[OH^-] + k_1 K [OH^-]/(1 + K [OH^-]) \quad (4)$$

It is assumed that, for the SN2 reaction, both un-ionized and ionized glycosides are reactive species.

It has been reported[6] that, because the activity coefficient of the hydroxyl ion changes with its concentration, the rate of alkaline cleavage of some glycosides is better correlated with the function K_w/h_- [where K_w is the dissociation constant of water, and h_- is related to the acidity function ($H_- = -\log h_-$)] than with the stoichiometric concentration of the base. Consequently, the $[OH^-]$ in eq. *4* is replaced by K_w/h_-, which is a measure of the proton-abstracting ability of the solution, or of the activity of the hydroxyl ion, to give equation *5*.

$$k_{obs.} = k_2[K_w/h_-] + k_1K[K_w/h_-]/(1 + K[K_w/h_-]) \quad (5)$$

However, it should be noted that the K_w/h_- values calculated by using $K_w = 10^{-14}$ and the H_- (25°) of Yagil[13] for aqueous sodium hydroxide are practically the same as the molar concentration of base, up to 1.5M.

At low concentrations of sodium hydroxide, the actual participation of an

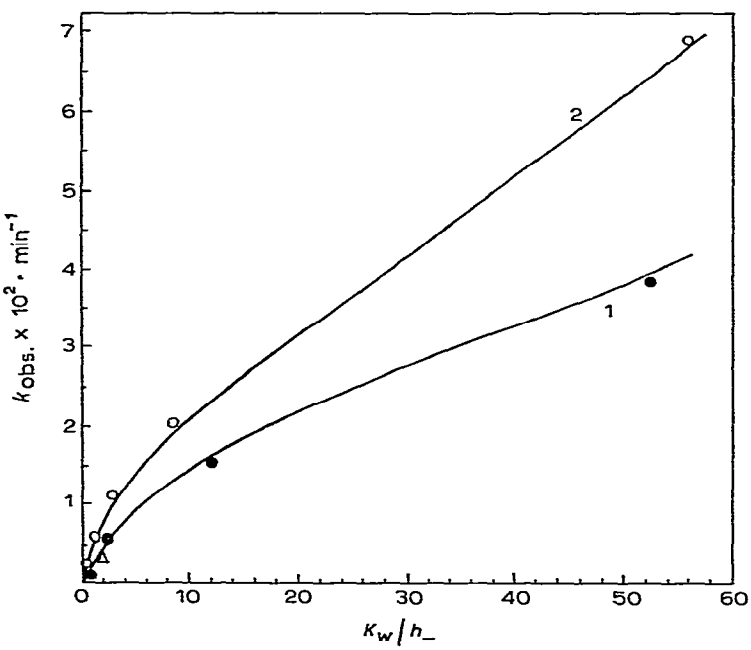


Fig. 2. Comparison of the experimental rate-data with theoretical curves derived from eq. *5* by use of the values of K, k_1, and k_2 shown in Table I. [1, phenyl β-D-glucopyranoside at 100°: ●, current data, and △, datum reported in ref. 7; and 2, phenyl α-D-glucopyranoside at 170°.]

SN2 mechanism in the cleavage of this glycoside must be relatively small, because levoglucosan may be isolated in 88% yield under mild conditions (1.3M KOH at 100°). Thus, eq. *5* may be simplified to

$$k_{obs.} = k_1K[k_w/h_-]/(1 + K[k_w/h_-]). \quad (6)$$

As shown previously[4], the magnitudes of k_1 and K may be obtained by plotting $1/k_{obs.}$ against h_-/K_w according to the inverse form of eq. *6*, shown in eq. *7*.

$$1/k_{obs.} = 1/k_1 + 1/k_1K[k_w/h_-] \quad (7)$$

From such a plot, k_1 and K were estimated to be 1.4×10^{-2} min^{-1} and $0.20M^{-1}$, respectively. The values of k_1 and K were then used to compute, using eq. *5*, the most probable value of k_2, which was found to be 5.1×10^{-4} $mol^{-1}.min^{-1}$.

These rate constants were then used to generate, with eq. *5*, a theoretical curve

TABLE I

OBSERVED EQUILIBRIUM CONSTANTS (K) AND SPECIFIC RATE-CONSTANTS OF INTRAMOLECULAR DISPLACEMENT (k_1) AND SN2 (k_2) REACTIONS OF PHENYL AND METHYL[a] D-GLUCOPYRANOSIDES

Glucoside	*Temp. (degrees)*	*K*	$k_1 \times 10^3$ *(min^{-1})*	$k_2 \times 10^3$ *(mol^{-1}.min^{-1})*
β-D-Glucopyranoside				
Phenyl (1)	100	0.20	14.30	0.51
Methyl	170	1.50	0.13	
α-D-Glucopyranoside				
Phenyl (2)	170	0.55	12.50	1.00
Methyl	170	0.60	0.08	

[a]Reported in ref. 4.

TABLE II

PSEUDO-FIRST-ORDER RATE-CONSTANTS FOR THE ALKALINE CLEAVAGE OF PHENYL D-GLUCOPYRANOSIDES

Phenyl D-glucoside	*Temp. (degrees)*	*NaOH* (M)	$k_{obs.} \times 10^3$ *(min^{-1})*
β Anomer	80	2.0	0.82
	100	2.0	6.05
	110	2.0	19.00
	120	2.0	31.70
α Anomer	140	1.4	1.45
	150	1.4	2.35
	160	1.4	4.38
	170	1.4	6.00

TABLE III

THERMODYNAMIC ACTIVATION-FUNCTIONS FOR REACTIONS OF PHENYL AND METHYL[a] D-GLUCOPYRANOSIDES

Glucoside	*Temp.* *(degrees)*	*NaOH* (M)	*Function (kJ.mol^{-1})*			*ΔS* *(J.deg^{-1}.mol^{-1})*
			Ea	*ΔH*	*ΔF*	
β-D-Glucopyranoside						
Phenyl (1)	100	2.0	100.5	97.1	112.2	−31.4
Methyl	170	2.5	149.1	145.3	157.8	−28.5
α-D-Glucopyranoside						
Phenyl (2)	170	1.4	76.2	74.9	109.3	−77.9
Methyl	170	2.5	134.8	131.0	168.7	−85.4

[a]Reported in ref. 4.

(Fig. 2) showing the dependence of the pseudo-first-order rate-constant ($k_{obs.}$) on the function K_w/h_-. The excellent agreement between the experimental points and the theoretical curve confirms the validity of the kinetic expression derived.

According to eq. *4*, or *5*, the relative importance of the two different mechanisms participating in the cleavage of phenyl β-D-glucopyranoside will depend upon the concentration of hydroxyl ion. By use of the values of k_1 and K shown in Table I, it is estimated that, in 1.3M alkali solution, 82% of the reaction would proceed by participation of the ionized hydroxyl group on C-2. This value is in good agreement with the actual yield of levoglucosan (88%) reported[8] under similar conditions.

Similarly, the observed rate-constant ($k_{obs.}$) was determined at various temperatures in 2.0M sodium hydroxide solution. Although the reaction proceeds by at least two different mechanisms, these rate data (see Table II) fitted the Arrhenius equation well. The apparent, thermodynamic activation-functions for this reaction, calculated in the usual way, are summarized in Table III. Theoretically, this apparent activation-energy is a complex function of at least three energy differences, namely, the heat of activation for the proton-transfer reaction, and the activation energies of the intramolecular displacement (eq. *2*) and SN2 (eq. *3*) reaction.

However, the heat of activation for the proton-transfer reaction of D-glucosides is probably small, and close to that of D-glucose, which had previously been determined[14] to be 20.9 kJ.mol^{-1}. Also, under certain experimental conditions (2M sodium hydroxide), the intramolecular-displacement mechanism was estimated to account for ~80% of the total reaction. Thus, it is not unreasonable to assume that the thermodynamic activation-functions shown in Table III primarily reflect the nature of the reaction facilitated by the anchimeric assistance of the ionized hydroxyl group on C-2 (see Scheme 1 and eq. *2*). Interestingly, the value of the activation entropy for phenyl β-D-glucopyranoside is very close to that reported[4] for methyl β-D-glucopyranoside, indicating the involvement of a similar intermediate.

Phenyl α-D-glucopyranoside. — Similarly, the effect of base concentration on the

cleavage of this glycoside was studied, but at a temperature of 170°. The resulting data (see Fig. 1) showed a pattern similar to that of the β anomer, indicating the direct involvement of the hydroxyl ion. However, this glycoside had previously been shown to react primarily through an intramolecular-displacement mechanism. Thus, these data were also analyzed according to the rate eq. *5*, in terms of the two reaction-schemes depicted in eqs. *2* and *3*.

Table I summarizes the equilibrium constants (K), and rate constants for the intramolecular displacement (k_1) and SN2 reaction (k_2). It may be noted that the K value estimated for this α-D-glucoside is almost identical to that previously reported for methyl α-D-glucopyranoside[4] at 170°. However, the value of k_1 for this α-D-glucoside is ~150 times that for the corresponding methyl α-D-glucoside.

The dependence of this reaction, in 1.4M sodium hydroxide solution, on temperature is also listed in Table II. From the kinetic data shown in Table I, it is estimated that, at this concentration of base, ~90% of the total reaction proceeds by the intramolecular-displacement mechanism. Thus, as already discussed, the thermodynamic activation-functions calculated for this α-D-glucoside (see Table III) should reflect the nature of this displacement reaction. Again, it is noticeable that the value of the activation entropy for this glucoside is very close to that previously reported[4] for methyl α-D-glucopyranoside under similar reaction-conditions, indicating the formation of a similar intermediate.

CONCLUSION

The preceding data clearly indicate that, in dilute alkali, the kinetics of base-catalyzed degradation of both phenyl α- and β-D-glucopyranoside are consistent with the established mechanism shown in Scheme 1, involving the formation of anionic species as reactive intermediates. These intermediates then undergo intramolecular displacement of the aglycon, resulting in the formation of levoglucosan. However, a minor mechanism involving bimolecular, nucleophilic substitution also obtains, and becomes apparent in aqueous alkali of concentration > 1.5M.

This bimolecular reaction could involve nucleophilic attack of a hydroxyl ion at either C-1 of the glycosyl group or of the phenyl ring[1]. The product expected of such a direct-displacement reaction would be D-glucose (**4**), which would be degraded further, to products other than a 1,6-anhydride. Thus, the relative importance of these two mechanisms, and the theoretical yield of levoglucosan, would vary with the concentration of base used. The rate constants summarized in Table I provide such an estimate, at a given concentration of hydroxyl ion, by the use of eq. *5*.

For example, it is estimated that the intramolecular-displacement reaction by ionized hydroxyl group at C-2 would account for 82% of the total reaction of phenyl β-D-glucopyranoside in a 1.3M alkali solution. This value is in a good agreement with the reported yield (88%) of levoglucosan at the same alkalinity.

In dilute alkali, the kinetic data obtained for these phenyl D-glucosides are essentially the same as those for the corresponding methyl D-glucosides. These

similarities are clearly reflected in the magnitude of the equilibrium constant K (see Table I) and the activation entropy (see Table III), indicating the formation of common intermediates. However, the phenyl D-glucosides have significantly lower activation enthalpies than the methyl D-glucosides.

A comparison of the values of k_1 for the phenyl and methyl D-glucopyranosides, shown in Table I, should indicate the effect of the leaving group. Such an estimate for the α anomer showed that the phenoxide ion is 150 times better than the methoxide ion as a leaving group. However, a factor of 7,000 was obtained for the β anomer by extrapolation of the k_1 value of phenyl β-D-glucopyranoside to 170°, which was estimated to be $\sim 1.0\ min^{-1}$. Such a profound, anomeric effect must be due to the relative stabilities of their $^1C_4$(D) conformers, needed for the intramolecular-displacement process.

The data in Table III also show that the α-D-glucoside has a significantly lower activation entropy than the β-D-glucoside. This seems to indicate that the loss of rotational and vibrational degrees of freedom in forming the 1,6-anhydride (from the α anomer) is greater than that in the formation of the 1,2-anhydride (from the β anomer). The difference in the magnitude of this entropy change and in the stability of their $^1C_4$(D) conformers probably account for the very low reactivity of phenyl α-D-glucopyranoside at 100°.

Finally, the foregoing data strongly support the contention[4] that alkaline degradation of methyl α- and β-D-glucopyranoside is facilitated by anchimeric assistance of the hydroxyl group at C-6 and C-2, respectively. It is known that, in contrast to the high yield of levoglucosan obtainable from the phenyl D-glucosides, only traces of this anhydride can be detected from the reactions of the methyl D-glucosides, which were usually conducted at 170°. However, this observation is not surprising, considering the fact that levoglucosan is degraded 100 times as fast as the original methyl D-glucoside under the experimental conditions[15].

EXPERIMENTAL

Samples. — Phenyl β-D-glucopyranoside (**1**), m.p. 176–177°, and phenyl α-D-glucopyranoside (**2**), m.p. 174–175°, were obtained commercially from Sigma Chemical Company, and used without purification. The purity of these samples after per(trimethylsilyl)ation was analyzed by gas–liquid chromatography (g.l.c.), which gave a single peak having a retention time identical with that of the corresponding authentic compound.

Analytical methods. — G.l.c. of the phenyl D-glucosides was performed in a Varian 2860 gas chromatograph having a stainless-steel column packed with 3% of SE-52 on Gas Chrom Q. Base-catalyzed, cleavage reactions of these D-glucosides were monitored by the amounts of phenol liberated, as determined colorimetrically, with a Varian 635 UV spectrophotometer[16], by the u.v. absorption maximum at 287 nm.

Kinetic experiments. — Samples of the D-glucoside **1** or **2** (4mM) in various

concentrations of sodium hydroxide solution (0.14–8.1M) were sealed in small autoclaves (10 mL) under a nitrogen atmosphere, and heated isothermally in an oil-bath for various periods of time in the temperature range of 100–170°. The mixture was then cooled, and a 1-mL aliquot of the solution was diluted with M sodium hydroxide (10 mL). The amounts of liberated phenol in the final solution, determined by the u.v. method mentioned, were used to calculate the mole fraction (c) of unreacted glycoside. The resulting data were then employed in calculating the pseudo-first-order rate-constants ($k_{obs.}$) according to equation *1*. Fig. 1 and Table II summarize the effects of base concentration and temperature on the rate of reaction.

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