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# A RE-INVESTIGATION OF THE KINETICS OF ALKALINE DEGRADATION OF PHENYL β-D-GLUCOPYRANOSIDE AND SOME OTHER GLYCOSIDES

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ABSTRACT

Previous investigators of mechanisms of alkaline degradation of glycosides in which the 2-hydroxyl group is *trans* to the aglycon concluded that the major reaction-pathway occurs *via* an SNicB substitution by the C-2 oxyanion at C-1. Recent reports also suggested that, for the phenyl D-glucopyranosides, direct SN2 substitution by hydroxyl ion at C-1 competes significantly with the SNicB pathway. We now conclude that the latter hypothesis was in error, because of failure to allow for variation in activity values for hydroxyl ion and water. For the nitrophenyl glycosides, however, we confirm that SN2AR reactions compete with the SNicB pathway.

## INTRODUCTION

The alkaline degradation of glycosides has been examined by several groups of workers[1–4], and several reaction pathways have been postulated. Comparison of the different reports is often difficult, because of the variety of degradation conditions employed, but one feature is clear, namely, that a *trans* relationship between the 2-hydroxyl group of the glycoside and the aglycon leads to a much more facile alkaline degradation than is the case for the *cis* analog. Thus, for example, β-D-glycopyranosides are degraded faster than α-D-glucopyranosides. This behavior has led to the postulation of an SNicB(2) mechanism[5] as a major pathway of degradation in glycosides having the required, *trans* arrangement. This mechanism involves an internal, conjugate-base attack at the anomeric carbon atom by the ionized hydroxyl group on C-2. Other competing mechanisms, including an SN2 attack by free base, have also been proposed[3,6,7].

As the degradations are often performed at high concentrations of base, the kinetics are further complicated by activity changes in the reaction medium, and we now consider that failure to take these into account has led to erroneous conclusions[6]. Previous workers have tried to overcome this problem either by performing the degradations at constant ionic strength[8,9] or by relating $[OH^-]$ to a function of the acidity constant[6,10] ($H_-$). In the first approach, a very high, constant, ionic strength is needed, and this is often experimentally difficult if high concentrations

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of base are to be used; in any event, the actual activities are still not known, and, hence, the absolute rate-constants cannot be calculated. The second approach is also inadequate, as errors must arise from the fact that the acidity-constant function[11] is based on data obtained[12] at 25°, whereas the alkaline degradations are typically conducted at 100°, or higher. Furthermore, this method makes no allowance for change in activity of the solvent.

## RESULTS AND DISCUSSION

It has been presumed that, in alkali, phenyl β-D-glucopyranoside (**1**) is degraded as shown in Scheme 1, mainly *via* an SNicB(2) pathway[3,5,6]. The *pseudo*-first-order rate-constant observed ($k_{obs}$) with an excess of base for such a system is given by equation *1*.

$$k_{obs} = kK[OH^-]/(1 + K[OH^-]) \qquad (1)$$

This rate equation predicts that, as the concentration of the base increases, $k_{obs}$ will increase, but at a decreasing rate, until it ultimately achieves a constant value equal to $k$. Experimentally, a plot of $k_{obs}$ *versus* the sodium hydroxide molarity does not show this behavior (see Fig. 1), but, rather, the opposite, with $k_{obs}$ increasing sharply with increase in the concentration of alkali. When the experiment is repeated with an added excess of sodium iodide as an inert electrolyte, such that the total, ionic strength of the reaction solutions is constant at 10M over the range of base concentrations used, $k_{obs}$ becomes a linear function of the concentration of sodium hydroxide, at least in the region of low concentration of base (see Fig. 1). This suggests that the curvature displayed in Fig. 1 is probably due to changes in the activity of the hydroxide ion, and, possibly, also to changes in activity of the solvent, as water is involved in the initial equilibrium (see Scheme 1).

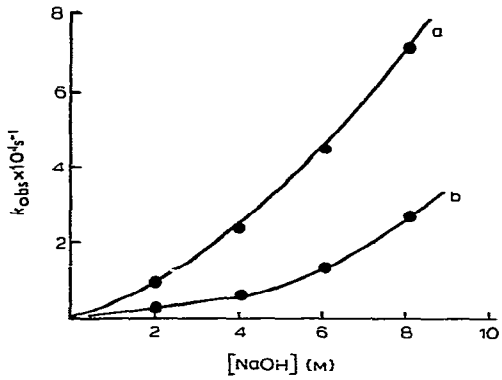
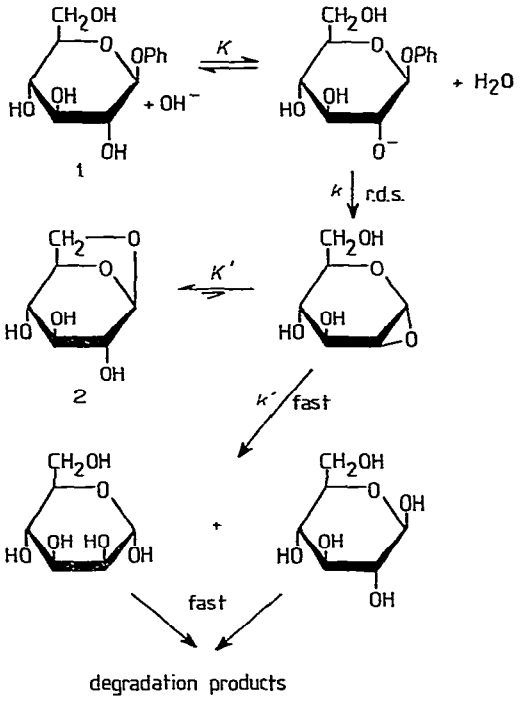



Fig. 1. Phenyl β-D-glucopyranoside at 100°, (a) in sodium hydroxide solution, and (b) in sodium hydroxide plus sodium iodide solution at constant ionic strength, 10 M.




Scheme 1

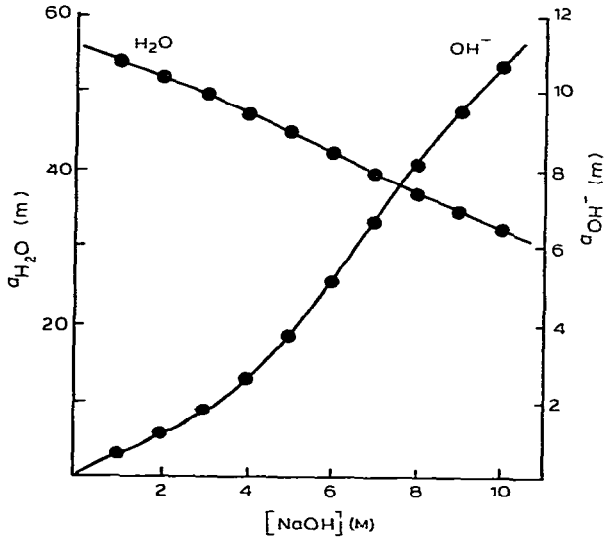



Fig. 2. Variation of $a_{H_2O}$ and $a_{OH^-}$ values with changing concentration of aqueous sodium hydroxide solutions at 100°.

A better formulation of the rate equation is given by Eq. *2*.

$$k_{obs} = kKA/(1 + kA), \tag{2}$$

where

$$A = a_{OH^-}/a_{H_2O} \quad \text{and} \quad K = [G^-]a_{H_2O}/[G]a_{OH^-}. \tag{3}$$

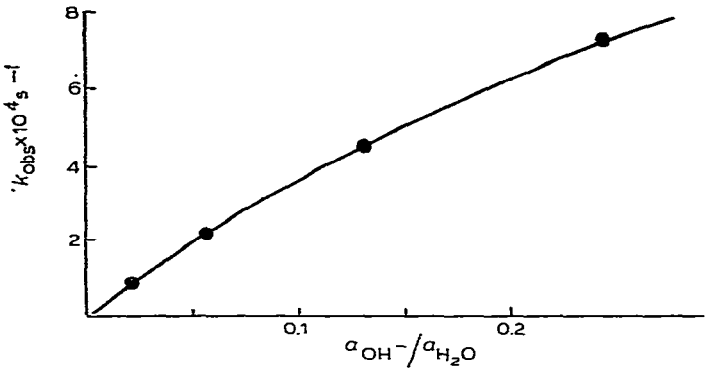



Fig. 3. Phenyl β-D-glucopyranoside in sodium hydroxide solution at 100°.

In Eq. *3*, *G* and $G^-$ are, respectively, the D-glucoside and its (C-2) ionized form. Values for the activity of water at various concentrations of sodium hydroxide are available[13] from 0–70°. By plotting these values, and making the small extrapolation to 100°, an estimate was obtained for the activity of water at 100° in various concentrations of sodium hydroxide. Conversion from the mole-fraction scale to the molal scale[14] then gave $a_{H_2O}$ values suitable for use in Eq. *2*. These values are shown, plotted as a function of sodium hydroxide molality, in Fig. 2. By a similar procedure, $a_{\pm}^{NaOH}$ values, where $a_{\pm}$ represents a mean, ionic activity, were obtained[13]. Because values for $a_{OH^-}$ are not available, it was assumed that $a_{OH^-} = a_{\pm}^{NaOH}$, and this is probably a reasonable assumption[14–16]. Values of $a_{\pm}^{NaOH}$ (hereafter assumed to be equal to $a_{OH^-}$) are also shown in Fig. 2.

For the alkaline degradation of the D-glucoside **1**, $k_{obs}$ was now plotted against $a_{OH^-}/a_{H_2O}$ (see Fig. 3). The resultant curve corresponded to that predicted for a mechanism described by Eq. *2*, and is in marked contrast to that shown in Fig. 1. Re-arrangement of Eq. *2* leads to Eq. *4*,

$$1/k_{obs} = 1/kKA + 1/k \qquad (4)$$

and, by plotting $(k_{obs})^{-1}$ against $(a_{OH^-}/a_{H_2O})^{-1}$, it is possible to obtain values for $k$ and $K$. In this way, Fig. 4 yields values of $k = 2.1 \times 10^{-3} s^{-1}$ and $K = 2.2$. The linearity of the data in Fig. 4 supports the mechanism postulated in Scheme 1. The most likely alternative mechanism would involve competition from a bimolecular, nucleophilic attack by free base (either at the anomeric carbon atom or the aglycon). The complete rate-equation for such a mechanism is given by Eq. *5*.

$$k_{obs} = k_2 a_{OH^-} + kKA/(1 + KA), \qquad (5)$$

where $k_2$ is the average rate-constant for the SN2 components. Examination of this equation reveals that a plot of $(k_{obs})^{-1}$ *versus* $(a_{OH^-}/a_{H_2O})^{-1}$ would be non-linear, with the degree of curvature reflecting the relative importance of $k_2$ to $k$ (compare Fig. 5). The linearity of Fig. 4 is thus a good indication that, if the SN2 mechanism occurs, it is insignificant compared to the SNicB process (*i.e.*, $k_2 \ll k$).

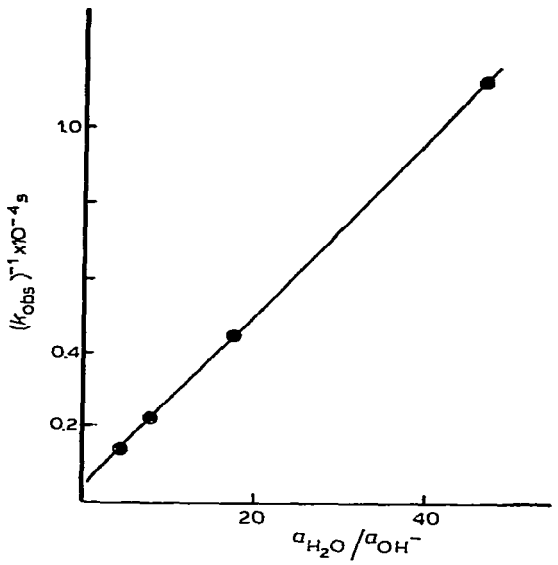



Fig. 4. Phenyl β-D-glucopyranoside in sodium hydroxide solution at 100°.

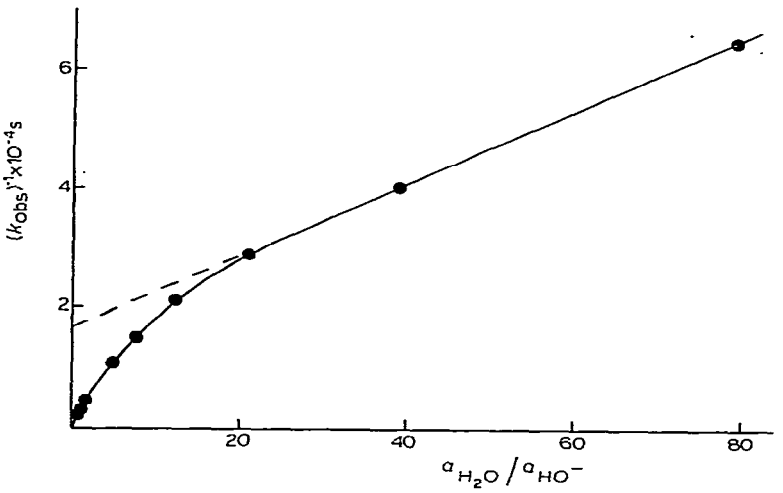



Fig. 5. *p*-Nitrophenyl β-D-glucopyranoside in sodium hydroxide solution at 22°.

The alkaline degradation of **1** would thus seem to be well-described by Scheme 1, and it does not involve any significant, competing reaction *via* an SN2 pathway. This conclusion is in direct contrast to that of a previous report[6], in which the authors correlated $k_{obs}$ with a function of the acidity constant ($H_-$), and deduced that almost 20% of the reaction occurred *via* the SN2 pathway. We now consider that the reported values of $k$ ($2.3 \times 10^{-4}$ s$^{-1}$) and $k_2$ ($8.5 \times 10^{-6}$ mol.$^{-1}$s$^{-1}$) are incorrect, because of errors arising from neglect of temperature effects on $H$ values and changes in

$a_{H_2O}$. An earlier report[17] that levoglucosan (**2**) accounted for only 88% of the products is difficult to interpret accurately, because of insufficient information on the degradation conditions employed. However, calculations based on our values for $k$ and $K$ indicate that, under the conditions probably used, only 90% of the starting material would have reacted.

In contrast to the foregoing, the alkaline degradation of *p*-nitrophenyl β-D-glycopyranosides is known, by product analysis, to involve some reaction *via* a completing SN2AR mechanism[7]. In this case, the strongly electron-withdrawing nature of the aglycon favors the SN2AR process, so that it accounts for a significant contribution to the overall rate. Treatment of the previously reported data[10] at 22° for *p*-nitrophenyl β-D-glucopyranoside in the manner just outlined yields a plot of $(k_{obs})^{-1}$ *versus* $(a_{OH^-}/a_{H_2O})^{-1}$ (see Fig. 5) that shows marked curvature at high concentrations of base. It is in this region that the SN2AR mechanism would predominate. Comparison of the results in Figs. 4 and 5 thus confirms the effective absence of any SN2 process in the degradation of phenyl β-D-glucopyranoside.

Assuming that the degradation of *p*-nitrophenyl β-D-glucopyranoside is described by Eq. *5*, it is possible, for high concentrations of base, to make the approximation that $Ka_{OH^-}/a_{H_2O} \gg 1$, and Eq. *5* becomes

$$k_{obs} = k_2 a_{OH^-} + k. \tag{6}$$

The plot of $k_{obs}$ against $a_{OH^-}$ (see Fig. 6) then yields values for $k_2$ ($1.0 \times 10^{-5}$ mol.$^{-1}$ s$^{-1}$) and $k$ ($1.1 \times 10^{-5}$ s$^{-1}$). In the region of low concentration of base, the reverse approximation holds (*i.e.*, $Ka_{OH^-}/a_{H_2O} \ll 1$) and Eq. *5* becomes

$$k_{obs} = k_2 a_{OH^-} + kKa_{OH^-}/a_{H_2O}.$$

Because, in this region, $a_{H_2O}$ is almost constant (approaching 55.5 m), this can be further simplified to

$$k_{obs} = k_2 + kK/55.5a_{OH^-}. \tag{7}$$

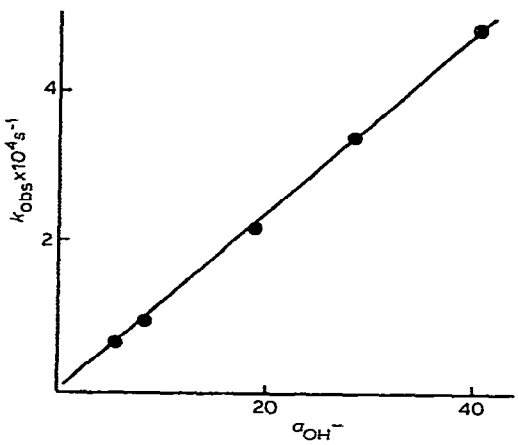



Fig. 6. *p*-Nitrophenyl β-D-glucopyranoside in concentrated sodium hydroxide solution at 22°.

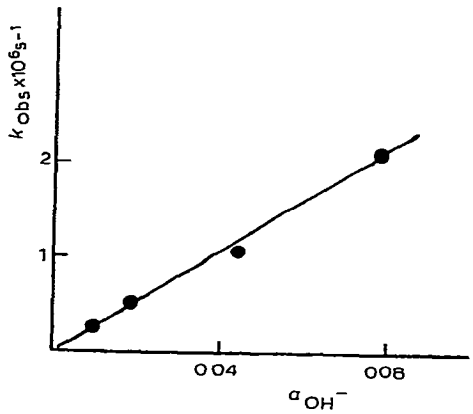



Fig. 7. *p*-Nitrophenyl β-D-glucopyranoside in dilute sodium hydroxide solution at 22°.

A plot of $k_{obs}$ against $a_{OH^-}$ in this region of concentration (see Fig. 7) thus yields a straight line, of slope $(k_2 + kK/55.5)$, passing through the origin. Use of the values of $k$ and $k_2$ obtained from Fig. 6 then gives the value $K = 91$. The zero intercept in Fig. 7 indicates the absence of any mechanisms that are independent of base, such as an "ionic" SN1 mechanism[3,5]. These values of $k$, $k_2$, and $K$ are in reasonable agreement with those, reported earlier[10], that were based on the acidity constant approach [*viz.*, $k = 2.7 \times 10^{-5}\ s^{-1}$, $k_2 = 0.34 \times 10^{-5}\ mol.^{-1}s^{-1}$, and $K = 0.82$ $(\times a_{H_2O}) = 44.5$]. This agreement is associated with the fact, that in this instance, the reactions were performed at a temperature very close to that at which the acidity-constant data had been obtained.

## EXPERIMENTAL

*Materials.* — Phenyl β-D-glucopyranoside (m.p. 176–177°) was obtained commercially, and used without further purification.

*Kinetic experiments.* — Samples of 1% solutions of the D-glucoside **1** in various concentrations of sodium hydroxide (0.9–8.39M) were placed in glass vials, sealed with Teflon septa, and heated in an oil bath at 100 ±0.1°. Where necessary, the required amount of sodium iodide was added, to give a total ionic strength of 10M. (Preliminary experiments, using stainless-steel reaction-vessels and exclusion of oxygen, showed that glass vessels and oxygen had no observable influence on $k_{obs}$.)

At intervals, a vial was removed, and rapidly cooled to room temperature. A 50 μL (weighed) sample was taken from each vial, and diluted to 5 mL with M NaOH, and the optical absorbance was measured[18,19] at 287 nm. From this measure of the concentration of phenolate anion, the amount of unreacted D-glucoside at various times was calculated. These data were then used to calculate a pseudo-first-order rate-constant ($k_{obs}$) by use of a linear, least-squares computing-method. All calculations were performed on solution concentrations expressed in molal units (m). Wherever molar solutions are mentioned they are designated by M.

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