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Alkaline Cleavage of β-D-Xylofuranosides

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The rate constants for the hydrolysis of a few 3- and 4-substituted phenyl β-D-xylofuranosides have been measured in aqueous sodium hydroxide solutions of various concentrations. The formal kinetics followed are interpreted to suggest that the alkaline cleavage of these compounds proceeds by a pre-equilibrium formation of an anionic intermediate which undergoes a unimolecular rate-limiting decomposition. The equilibrium constants for the initial ionization and the first-order rate constants for the subsequent heterolysis have been calculated. The effects of the polar properties of the aglycon group on the values of these quantities suggest that the reactive species is the 2-oxyanion of the substrate. The possibility that the rate-limiting step would involve a spontaneous heterolysis of the 2-oxyanion to form a phenoxide and a cyclic oxocarbenium ion is discussed.

Although acetals are normally stable in aqueous base solutions, certain hemicyclic acetals exhibit a marked lability towards alkali. Especially some glycosides are cleaved quite readily under alkaline conditions.[1] The mechanisms for these reactions have been the subject of considerable interest, mainly because simple glycosides are excellent model compounds for the study of the degradation of polysaccharides. For the alkaline hydrolysis of glycopyranosides several tentative mechanisms have been proposed. Compounds with a hydroxyl group at C-2 *trans* to the aglycon group have been repeatedly suggested to react by neighboring group participation of the ionized C-2 hydroxyl function to yield a 1,2-epoxide intermediate, all subsequent reactions being fast.[1–4] In contrast, the mechanism for the hydrolysis of the corresponding *cis*-1,2-glycosides is more obscure. According to the suggestions made, either C-4 or C-6 oxyanion can act as an intramolecular catalyst,[1,3] or a nucleophilic substitution by hydroxide ion may take place at the anomeric or aromatic carbon.[1,5] For the cleavage of 4-nitrophenyl α-D-glucopyranoside a novel mechanism has been presented, which involves an intramolecular attack by the C-2 oxyanion on C-1 of the phenoxy group.[6,7]

Glycofuranosides are cleaved by alkali even more rapidly than glycopyranosides, but the experimental data concerning the mechanisms for these reactions are quite limited. Janson and Lindberg [8] reported the rate constants for the hydrolysis of several methyl aldofuranosides in aqueous 10 % sodium hydroxide solution at 443 K, and suggested that the somewhat higher reactivities of *trans*-1,2-glycosides compared to their *cis*-isomers would be the result of neighboring group participation as in the hydrolysis of glycopyranosides. To elucidate the mechanisms for the alkaline cleavage of aryl aldofuranosides, the hydrolysis of some 3- and 4-substituted phenyl β-D-xylofuranosides has been investigated in this work.

RESULTS AND DISCUSSION

The first-order rate constants for the hydrolysis of the substituted phenyl β-D-xylofuranosides in aqueous sodium hydroxide solutions of various concentrations are collected in Table 1. For all compounds studied the value of the reaction order with respect to base concentration deviates appreciably from unity. For example, in the case of the 4-cyanophenyl derivative the apparent second-order rate constant, $k(\mathrm{obs})/[OH^-]$, at a hydroxide ion concentration of 0.10 mol dm^{-3} is only half the value obtained in a 0.01 mol dm^{-3} solution, the ionic

Table 1. First-order rate constants ($k/10^{-4}$ s^{-1}) for the hydrolysis of substituted phenyl β-D-xylofuranosides in aqueous sodium hydroxide solutions of different concentrations [a] at 343.15 K.

OH^- / mol dm^{-3}	Substituent in the phenyl group None	4-Chloro	3-Chloro	4-Acetyl	4-Cyano
0.01	0.1379(19)	0.606(4)	1.359(21)	9.95(9)	18.84(19)
0.02	0.278(3)	1.090(18)	2.62(2)	19.96(27)	35.3(3)
0.03	0.397(4)	1.578(15)	3.87(4)	27.9(2)	48.1(6)
0.04	0.530(9)	2.05(3)	5.18(9)	36.1(2)	61.7(8)
0.05	0.639(7)	2.42(3)	5.98(9)	39.4(5)	70.6(10)
0.06	0.739(9)	2.83(2)	6.91(8)	48.4(2)	76.4(8)
0.07	0.862(10)	3.26(3)	7.78(7)	50.4(8)	88.1(10)
0.08	0.953(10)	3.73(3)	8.55(12)	54.1(4)	97.6(8)
0.09	1.030(11)	3.93(5)	8.84(11)	65.4(7)	103.5(14)
0.10	1.140(14)	4.27(5)	9.94(7)	65.6(5)	107.4(12)

[a] The ionic strength was adjusted to 0.10 mol dm^{-3} with sodium chloride.

strength of which has been adjusted to 0.10 mol dm^{-3} with sodium chloride (Fig. 1). A difference of this magnitude is far too large to be accounted for by specific salt effects. Addition of sodium chloride in the reaction mixture (0.5 mol dm^{-3}), for example, reduced the observed rate constant by less than 10 %. The observed deviation from a linear dependence of k(obs) on [OH^-] rather suggests that the alkaline cleavage of phenyl β-D-xylofuranosides proceeds *via* formation of a kinetically significant intermediate. For instance, a mechanism involving an initial rapid ionization of the substrate (eqn. 1) agrees with the kinetic data in Table 1. The rate-law for this reaction

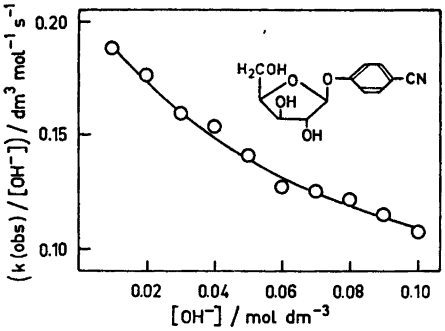


Fig. 1. The apparent second-order rate constants, k(obs)/[OH^-], at 343.15 K for the alkaline hydrolysis of 4-cyanophenyl β-D-xylofuranoside plotted against the hydroxide ion concentrations of the reaction solution.

$$SH + OH^- \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} S^- \longrightarrow P \qquad (1)$$

can be expressed by eqn. (2) where K denotes the equilibrium constant for the formation of

$$\frac{d[P]}{dt} = \frac{kK[OH^-][S]}{1+K[OH^-]} \qquad (2)$$

the anionic intermediate, S^-, and k stands for the first-order rate constant for the unimolecular decomposition of this species. [S] is the sum of [SH] and [S^-] at any given moment. When the initial substrate concentration is negligible compared to the hydroxide ion concentration, the reaction obeys first-order kinetics, and the observed rate constant, k(obs), is of the form (3). Accordingly, k(obs) is linearly

$$k(\text{obs}) \leqslant \frac{kK[OH^-]}{1+K[OH^-]} \qquad (3)$$

related to [OH^-] when the product K[OH^-] is much less than unity, and levels off to a constant value when K[OH^-] becomes greater than unity. Eqn. (3) can also be written in the form (4). In other words, a plot of [OH^-]/k(obs) *vs.* [OH^-] should yield a straight line if

$$\frac{[OH^-]}{k(\text{obs})} = \frac{1}{k}[OH^-] + \frac{1}{kK} \qquad (4)$$

the mechanism leading to eqn. (1) is followed. Fig. 2 clearly shows that this is the case in the hydrolysis of 4-cyanophenyl β-D-xylofurano-

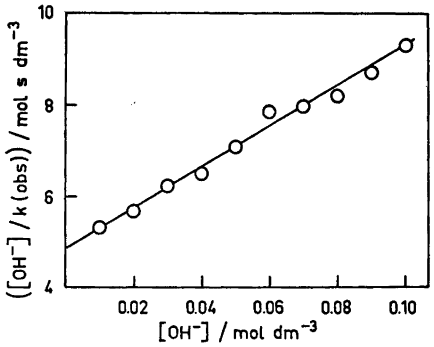


Fig. 2. Reciprocals of the apparent second-order rate constants, k(obs)/[OH^-], at 343.15 K for the alkaline hydrolysis of 4-cyanophenyl β-D-xylofuranoside plotted against the hydroxide ion concentration of the reaction solution.

side. The other xylosides investigated exhibit a similar kinetic behavior, but the ratio of the slope and intercept of eqn. (4) decreases systematically with the decreasing electronegativity of the aglycon group.

The fact that the formal kinetics of mechanism (1) is followed does not prove, however, that the anionic form of substrate would lie on the reaction pathway. Mechanisms involving a nucleophilic attack of hydroxide ion at the anomeric or aromatic carbon of the unionized substrate (eqn. 5) also lead to a linear relationship between [OH^-]/k(obs) and [OH^-] described by eqn. (6). Here K has the same meaning as in eqn. (2), but k denotes the second-order rate constant for the decomposition of SH. However, for the following reasons these

$$\begin{array}{l} SH + OH^- \longrightarrow P \\ \quad \rightleftarrows \\ S^- + H_2O \end{array} \qquad (5)$$

$$\frac{[OH^-]}{k(\text{obs})} = \frac{K}{k}[OH^-] + \frac{1}{k} \qquad (6)$$

routes seem less probable.

If eqn. (5) were the correct description for the alkaline cleavage of aryl β-D-xylofuranosides, the reciprocal intercepts of plots (6) would give the partial rate constants k. By applying this method to the kinetic data concerning the hydrolysis of the 4-cyanophenyl derivative a value of 0.2 dm^3 mol^{-1} s^{-1} is obtained for k at 343.15 K. Obviously a value of this magnitude is far too large to be consistent with an aromatic nucleophilic substitution. For comparison, the second-order rate constants for the hydrolyses of 4-nitrophenyl 2-*O*-methyl-β-D-galacto- and 2-*O*-methyl-α-D-mannopyranosides proceeding by this pathway can be estimated to be of the order 10^{-5} dm^3 mol^{-1} s^{-1} at this temperature.[2e] Accordingly, replacement of the leaving 2-*O*-methyl-glycopyranosyloxy anion by glycofuranosyloxy anion should accelerate the reaction by a factor of 10^4. This seems highly improbable, since the polar characters and steric requirements of both anions are quite similar. In fact, the rate-enhancing effect should be even greater, because a 4-nitro substituent facilitates nucleophilic attack on C-1 more than a 4-cyano group does. Similar arguments can be presented against the mechanism involving a direct displacement of the substituted phenoxy group by hydroxide ion. Of the glycosides studied, phenyl α-D-glucopyranosides with electropositive or weakly electronegative substituents in the aglycon group have been suggested to react by this mechanism.[1] Their reactivity is, however, low compared to the corresponding β-D-xylofuranosides. For example, the hydrolysis of the unsubstituted derivative exhibits the second-order rate constant of 3×10^{-6} dm^3 mol^{-1} s^{-1} at 343.15 K.[5] For the alkaline cleavage of more reactive *trans*-1,2-glycosides other mechanisms have been proposed. Because it is known that nucleophilic attack on five-membered rings occurs usually about a hundred times faster than on six-membered rings with equal electronic properties and steric hindrances,[9] a value of $10^{-6} - 10^{-5}$ dm^3 mol^{-1} s^{-1} would be expected at this temperature for the partial rate constant k (eqn. 6) of the hydrolysis of phenyl β-D-xylofuranoside. However, the data in Table 1 give a value of 1.4×10^{-3} mol^{-1} s^{-1}. The most obvious explanation for this discrepancy is that the pathway involving nucleophilic attack by hydroxide ion at the anomeric carbon is not the major one in the hydrolysis of aryl β-D-xylofuranosides. Some support for this claim comes from the finding that iodide ion (0.5 mol dm^{-3}) did not exert any rate-enhancing effect on the cleavage of the 4-cyanophenyl derivative, though it sometimes is a more powerful nucleophile than hydroxide ion.[10]

On the basis of the preceding discussion it seems probable that the alkaline cleavage of

Table 2. Ionization constants (see eqn. 7) for 3- and 4-substituted phenyl β-D-xylofuranosides in water at 343.15 K and the first-order rate constants for the decomposition of the corresponding 2-oxyanions at the same temperature.

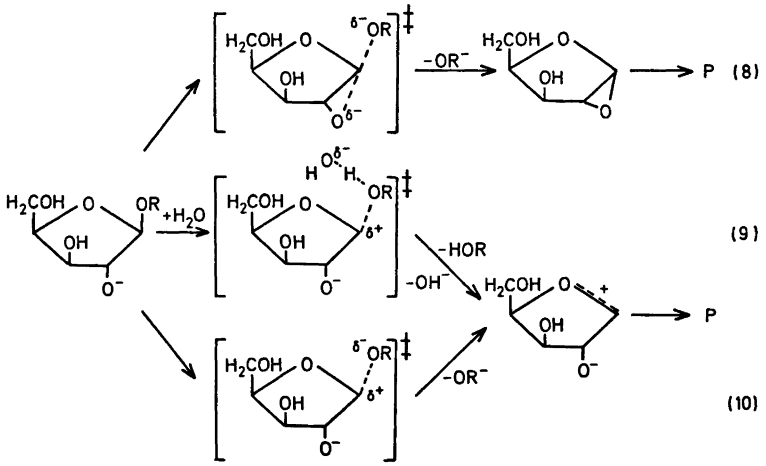
Substituent in the phenyl group	K^a / $dm^3\ mol^{-1}$	k^a / $10^{-3}\ s^{-1}$
None	2.7(2)	0.54(3)
4-Chloro	4.1(4)	1.46(12)
3-Chloro	4.8(5)	3.0(2)
4-Acetyl	6.7(9)	16.3(16)
4-Cyano	9.0(6)	23(1)

[a] Calculated by eqn. (4) from the data in Table 1.

aryl β-D-xylofuranosides would proceed *via* pre-equilibrium formation of an anionic intermediate. One possible way to elucidate the structure of this species is to study the effects that polar substituents in the aglycon group exert on the initial ionization of the substrate. According to eqn. (4) the equilibrium constant, K, for this stage (eqn. 7) is equal to the ratio of the slope and intercept of the plot of $[OH^-]/k(\text{obs})$ *vs.* $[OH^-]$. Table 2 summarizes the results obtained by this method for the β-xylosides studied. They are of the order expected for the dissociation of a hydroxyl group in a carbohydrate molecule.[11] Although the experimental errors in the kinetically determined ionization constants are rather large, it is clearly seen that electron-attracting substituents in the phenoxy group facilitate the pre-equilibrium dissociation of phenyl β-D-xylofuranosides. The only ionizable group in these compounds, the acidity of which would be expected to depend markedly on the polar character of the aglycon group, is the hydroxyl group at C-2. Hence the 2-oxyanion of the substrate appears to be the reactive species. In consistence with this conclusion three kinetically indistinguishable mechanisms can be suggested for the alkaline cleavage of aryl β-D-xylofuranosides. First, neighboring group participation by the ionized hydroxyl group at C-2 may occur, analogous to the hydrolysis of aldopyranosides with a *trans*-1,2-configuration (eqn. 8). Second, water can act as a general acid donating a proton to the glycosidic oxygen atom concerted with carbon-oxygen bond rupture (eqn. 9). Third, the anionic form of substrate may decompose spontaneously to a phenoxide and a cyclic oxo-carbenium ion (eqn. 10).

$$K = [S^-]/[SH][OH^-] \qquad (7)$$

The first-order rate constants calculated by eqn. (4) for the rate-limiting decomposition of the 2-oxyanions of substituted phenyl β-D-xylofuranosides are collected in Table 2. It is clearly seen that the cleavage is greatly facilitated by electron-attracting substituents in the phenoxy group. Plotting the logarithms of the partial rate constants, k, against the polar substituent constants, σ^-, gives a fairly good linear correlation line with a slope of 1.8 ± 0.1 (Fig. 3). If σ values are used instead, the points



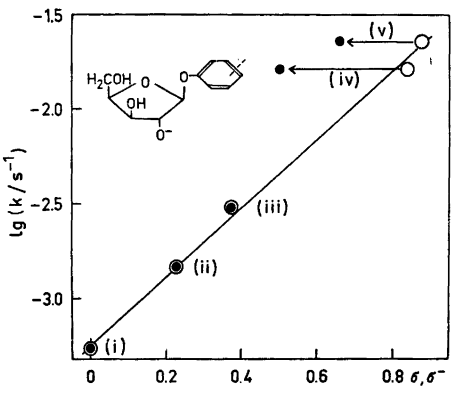


Fig. 3. Heterolysis of the 2-oxyanions of 3- and 4-substituted phenyl β-D-xylofuranosides in water at 343.15 K. Logarithms of the first-order rate constants plotted against the σ (filled circles) and σ^- (open circles) values of the substituents in the phenyl group. Notation: (i) phenyl, (ii) 4-chlorophenyl, (iii) 3-chlorophenyl, (iv) 4-acetylphenyl, and (v) 4-cyanophenyl derivative.

for 4-acetyl and 4-cyano groups fall far above the line the other substituents yield. The need for modified substituent constants, σ^-, to correlate the heterolysis rates, indicates that the reaction occurs with formation of an electron-rich center in direct conjugation with the benzene nucleus. This is what happens if mechanism (8) or (10) is followed. In contrast, no marked change in the resonance interactions between the glycosidic oxygen atom and the benzene ring will take place if the former is protonated by water concerted with the covalent bond fission. For example, the rates for the general acid-catalyzed hydrolysis of 2-(4-substituted phenoxy)tetrahydropyrans correlate with σ rather than with σ^- values.[12] The high positive value of 1.8 for the reaction constant, ϱ^-, also argues against mechanism (9). Protonation of the *exo* cyclic oxygen atom concerted with the cleavage of the glycosidic bond would diminish the negative charge developed at this site in the activated complex. Consequently, a lower susceptibility to inductive effects than that observed would be expected.

Mechanisms (8) and (10) cannot be rigorously distinguished with the data indicated above. The fact that 2-aryloxytetrahydrofurans undergo under alkaline conditions a spontaneous decomposition makes the latter possibility more attractive, however.[13] The rate constants for these reactions are smaller by a factor of 10 – 100 than those for the 2-oxyanions of the corresponding β-D-xylofuranosides. A reactivity difference of this order is of what would be expected on the basis of polar inductive effects. When the phenoxy group begins to depart a partial positive charge will develop at the anomeric carbon. The strong electron-donating ability of the ionized hydroxyl group at C-2 increases the electron density at this site leading to a marked stabilization of the transition state. It should be noted, however, that the mechanism involving neighboring group participation by this group has not been rigorously excluded. Moreover, the aim of the preceding discussion is by no means to suggest that mechanism (10) would operate for aldofuranosides with poorer leaving-groups.

EXPERIMENTAL

The aryl β-D-xylofuranosides used in this investigation were obtained in their fully acetylated forms by fusing tetra-*O*-acetyl-D-xylofuranose with appropriate phenols in the presence of *p*-toluenesulfonic acid.[14] Deacetylation of the products with sodium methoxide in methanol gave crude furanoside syrups which were purified by successive crystallizations from ethyl acetate. The melting points, ^{1}H NMR spectra and elemental analyses for the phenyl, 4-chlorophenyl, and 4-acetylphenyl derivatives are given in Ref. 15. 4-Cyanophenyl β-D-xylofuranoside melted at 383-385 K and gave the following ^{1}H NMR signals (D_2O): δ 3.6 – 3.8 (m, 2 H), 4.2 – 4.5 (m, 3 H), 5.59 (s, 1 H), 6.99 (d, 2 H), 7.50 (d, 2 H). 3-Chlorophenyl β-D-xylofuranoside failed to crystallize. ^{1}H NMR (D_2O): δ 3.7 – 3.8 (m, 2 H), 4.3 – 4.5 (m, 3 H), 5.55 (s, 1 H), 6.9 – 7.2 (m, 4 H).

Hydrolyses were followed spectrophotometrically at the absorption maxima of the liberated phenoxide ions. The measurements were performed on a Unicam SP 800 spectrophotometer equipped with a scale expansion accessory. The temperature of the cell housing block was kept at 343.15 ± 0.10 K with water circulation from a Lauda thermostat and controlled with a thermoelement. The initial substrate concentration was in the range of $10^{-5} - 10^{-4}$ mol dm^{-3}. The first-order rate constants were calculated by the method of Guggenheim.

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