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THE ACID-CATALYZED HYDROLYSIS OF β-D-XYLOFURANOSIDES

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ABSTRACT

The rate constants for the hydrolysis of six alkyl and four aryl β-D-xylofuranosides in aqueous perchloric acid at various temperatures have been measured. The effects of varying the aglycon structure on the hydrolysis rate are interpreted in terms of two concurrent reactions. Either, the substrate, protonated on the glycosidic oxygen atom, undergoes a rate-limiting heterolysis to form a cyclic oxocarbonium ion, or, an initial rapid protonation of the ring oxygen is followed by a unimolecular cleavage of the five-membered ring, all subsequent reactions being fast. It is suggested that xylofuranosides having strongly electron-attracting aglycon groups react mainly by the former pathway, whereas the latter is more favourable for substrates having electron-repelling aglycon groups. The negative entropies of activation obtained with the latter compounds are attributed to the rate-limiting opening of the five-membered ring. The rate variations of the hydrolyses of alkyl β-D-xylofuranosides in aqueous perchloric acid–methyl sulfoxide mixtures are interpreted as lending further support for the suggested change in mechanism.

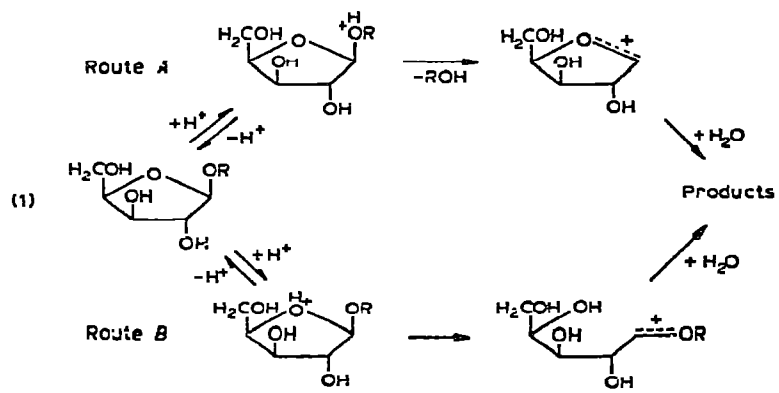
INTRODUCTION

It is generally accepted that the acid-catalyzed hydrolysis of glycopyranosides proceeds by initial rapid protonation of the glycosidic oxygen atom followed by rate-limiting heterolysis of the resulting conjugate acid to give a cyclic oxocarbonium ion[1,2]. In contrast, the hydrolysis of glycofuranosides has been much less extensively studied, and little is definitely known about the mechanisms of these reactions. Several lines of evidence suggest that ketofuranosides react analogously to glycopyranosides, *i.e.*, by formation of a furanosyl carbonium ion[1,3]. The hydrolysis of aldofuranosides has also been shown to involve a pre-equilibrium protonation of the substrate and cleavage of the glycosyl–oxygen bond in one of the subsequent steps[4], but the site of protonation and rate-limiting bond-rupture cannot be deduced on the basis of the available data. To elucidate these aspects, the effects of varying the aglycon structure on the hydrolysis rates of alkyl and aryl β-D-xylofuranosides have been studied in this work.

The hydrolyses of one ethyl and several methyl aldofuranosides have been shown to exhibit negative entropies of activation[4,5], in striking contrast to the positive values obtained with ketofuranosides[3]. This finding has led to the conclusion that water participates as a nucleophilic reagent in the transition states for the former reactions. The rate variations of many acid-catalyzed hydrolyses in binary solvent mixtures composed of water and methyl sulfoxide have been shown to be strongly dependent on the molecularity of the rate-limiting step. Thus, A-1 reactions undergo a marked retardation as the content of methyl sulfoxide is increased from zero to ~30 mole per cent[6], whereas the rate constants for A-2 hydrolyses remain almost unchanged in this range[7]. To acquire further information about the molecularity of the rate-limiting stage for the hydrolysis of aldofuranosides, the effects of solvent composition on the hydrolysis rates of some alkyl β-D-xylofuranosides have been investigated.

RESULTS AND DISCUSSION

The second-order rate constants for the acid-catalyzed hydrolysis of several alkyl β-D-xylofuranosides are listed in Table I, together with their standard mean deviations. The hydrolysis rate decreases considerably with increase in the electron-attracting ability of the aglycon group on going from the isopropyl to 2-chloroethyl derivative. If these compounds were hydrolyzed *via* a cyclic oxocarbonium ion (Route *A* in Scheme 1), as are the corresponding glycopyranosides[1,2], a much lower susceptibility to the polar properties of the aglycon group would be expected.



Scheme 1 Alternative pathways of hydrolysis

Electron-repelling substituents, for example, increase the basicity of the glycosidic oxygen atom and thus the standing concentration of the protonated substrate, but at the same time they retard the rupture of the exocyclic carbon–oxygen bond. Accordingly, the effect on the observed rate constants should remain slight. For example, in the hydrolyses of 2-alkoxytetrahydro-furans and -pyrans[8] and of several

TABLE I

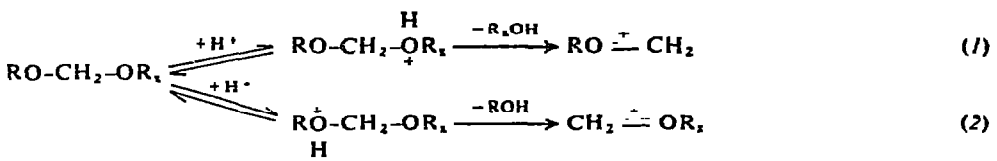
SECOND-ORDER RATE CONSTANTS AT DIFFERENT TEMPERATURES, AND THE ENTROPIES AND ENTHALPIES OF ACTIVATION FOR THE ACID-CATALYZED HYDROLYSIS OF ALKYL β-D-XYLOFURANOSIDES

Aglycon group	*T* (*K*)	k[a] ($10^{-3}.dm^3.mol^{-1}.sec^{-1}$)	k (298.15 K)[b] ($10^{-4}.dm^3.mol^{-1}.sec^{-1}$)	$\Delta S^{\ddagger}$ (298.15 K) ($J.K^{-1}.mol^{-1}$)	$\Delta H^{\ddagger}$ (298.15 K) ($kJ.mol^{-1}$)
Isopropyl	288.05	0.610 ±0.011	19.7 ±0.5	−26 ±6	80.6 ±1.8
	297.95	1.972 0.018			
	307.85	5.33 0.07			
	317.85	16.24 0.10			
Ethyl	297.95	0.647 ±0.006	6.6 ±0.2	−27 ±4	83.1 ±1.1
	307.85	1.899 0.026			
	317.85	5.76 0.05			
	327.85	14.80 0.20			
Methyl	317.85	1.607 ±0.012	1.56 ±0.06	−15 ±3	90.4 ±1.1
	322.85	2.68 0.03			
	327.85	4.74 0.03			
	332.85	7.81 0.10			
	337.75	12.54 0.11			
2-Methoxyethyl	332.85	2.15 ±0.02	0.36 ±0.02	−11 ±3	95.1 ±1.0
	342.65	6.01 0.04			
	352.45	15.79 0.15			
	362.45	38.1 0.2			
2-Chloroethyl	337.75	1.252 ±0.008	0.079 ±0.013	+11 ±7	105.1 ±2.7
	347.55	3.91 0.04			
	357.45	11.26 0.09			
	367.35	27.1 0.1			
2,2,2-Trichloroethyl	332.85	1.191 ±0.039	0.105 ±0.015	+30 ±9	110.3 ±3.1
	342.65	4.03 0.08			
	352.45	11.48 0.22			

[a]Calculated from the first-order rate constants measured in 0.1 $mol.dm^{-3}$ aqueous perchloric acid. [b]Calculated by the Arrhenius equation.

TABLE II

THE EFFECTS OF THE DEPARTING (REACTION *1*) AND NONDEPARTING ALKOXYL GROUPS (REACTION *2*) ON THE RATE CONSTANTS FOR THE ACID-CATALYZED HYDROLYSIS OF DIALKOXYMETHANES[11] AT 298.15 K



R_1	k (*rel., Reaction* 1)	k (*rel., Reaction* 2)
Isopropyl	2.27	22.1
Ethyl	1.21	4.48
Methyl	1	1
2-Methoxyethyl	1.53	0.201
2-Chloroethyl	1.96	0.048

glycopyranosides[9,10], shown to react by this mechanism, these two influences almost cancel. With each reaction series investigated, the structural effects of the exocyclic alkoxyl group are similar to the influence of the leaving alkoxyl group on the hydrolysis rates of dialkoxymethanes[11] (Reaction *1* in Table II). Since this is not the situation with alkyl β-D-xylofuranosides, it seems highly improbable that Route *A* is followed in their hydrolysis.

In contrast, the relative reactivities of the alkyl β-D-xylofuranosides considered above can be accounted for by a mechanism involving a pre-equilibrium protonation of the endocyclic oxygen atom followed by rate-limiting ring-opening (Route *B* in Scheme 1). The rate of this reaction is quite sensitive to the polar character of the aglycon group. Electropositive substituents, for example, greatly facilitate cleavage of the five-membered ring by stabilizing the acyclic oxocarbonium ion. Owing to the relatively long distance between the aglycon group and the ring-oxygen, the equilibrium constant for the initial protonation remains, in turn, almost unchanged. The gross effect of these two factors would be expected to be comparable to the influence that the nondeparting alkoxyl group exerts on the hydrolysis rates of dialkoxymethanes[11] (Reaction *2* in Table II). To facilitate a comparison of structural effects in the xyloside hydrolysis with those in this partial reaction of dialkoxymethanes, the logarithms of the relative rate-constants of these two reaction series are plotted in Fig. 1. A fairly good, linear, correlation line with a slope close to unity is obtained as long as β-D-xylofuranosides having electropositive or slightly electronegative aglycon groups are concerned, suggesting that mechanism *B* is the major route for their hydrolysis.

The entropies of activation obtained for isopropyl, ethyl, methyl, and 2-methoxyethyl β-D-xylofuranosides are negative (Table I). Values of this magnitude have been reported for the hydrolyses of several methyl and ethyl aldofuranosides,

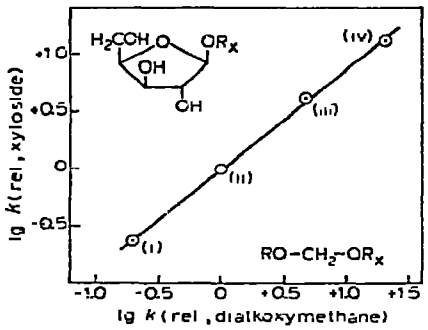


Fig. 1. Comparison of structural effects in the acid-catalyzed hydrolysis of alkyl β-D-xylofuranosides with those in Reaction (*2*) of dialkoxymethanes (see Table II) at 298.15 K. Notation: (i) 2-methoxyethyl, (ii) methyl, (iii) ethyl, and (iv) isopropyl derivatives.

and attributed to the participation of water as a nucleophilic reagent in the transition states[4,5]. Either, water attacks at the anomeric carbon atom concerted with the rate-limiting ring-opening, or, a bimolecular displacement of the protonated alkoxyl group by water takes place. Although these mechanisms cannot be rigorously excluded, they seem less probable on the basis of the structural effects indicated above. If the former pathway were followed, the oxocarbonium-ion character would be poorly developed in the transition state, and the hydrolysis rate would thus be relatively insensitive to changes in the polar nature of the aglycon group. The latter reaction would also be expected to exhibit a low susceptibility to inductive effects of the aglycon group. Electron donation from polar substituents facilitates the pre-equilibrium protonation, but at the same time both the nucleophilic attack of water and the departure of the protonated alkoxyl group are retarded. For example, the hydrolysis rates of those esters reacting *via* rate-limiting attack of water at the carbonyl carbon are not markedly affected by the polar nature of the leaving alcohol moiety[12].

Several, specific, acid-catalyzed hydrolyses involving cleavage of a five-membered ring in the rate-limiting stage exhibit negative entropies of activation, though all other experimental results agree with the A-1 mechanism. For example, the $\Delta S^{\ddagger}$ values obtained with a series of 2-substituted 1,3-dioxolanes are invariably more-negative by 30 to 40 $J.K^{-1}.mol^{-1}$ than those reported for exactly analogous diethyl acetals[13]. Similarly, the hydrolyses of 1,3-dioxolones, shown to proceed by the A-1 mechanism, exhibit[14] entropies of activation ranging from -15 to -40 $J.K^{-1}.mol^{-1}$, as does the hydrolysis of 4-ethoxy-4-butyrolactone[15], although the corresponding reactions of acyclic acyl–alkyl acetals are characterized by slightly positive $\Delta S^{\ddagger}$ values[16]. On this basis, it does not seem unreasonable that the negative entropies of activation for the hydrolyses of isopropyl, ethyl, methyl, and 2-methoxyethyl β-D-xylofuranosides would reflect the rate-limiting ring-opening, and not the A-2 nature of these reactions.

It seems probable, however, that mechanism *B* is not followed for the compounds carrying highly electronegative substituents in the aglycon group. 2,2,2-Tri-

TABLE III

SECOND-ORDER RATE CONSTANTS AT DIFFERENT TEMPERATURES, AND THE ENTROPIES AND ENTHALPIES OF ACTIVATION FOR THE ACID-CATALYZED HYDROLYSIS OF 4-SUBSTITUTED-PHENYL β-D-XYLOFURANOSIDES

Aglycon group	*T* (*K*)	k[a] ($10^{-3}.dm^3.mol^{-1}.sec^{-1}$)	k (*333.15 K*)[b] ($10^{-3}\ dm^3.mol^{-1}.sec^{-1}$)	$\Delta S^{\ddagger}$ (*298.15 K*) ($J.K^{-1}.mol^{-1}$)	$\Delta H^{\ddagger}$ (*298.15 K*) (*kJ* mol^{-1})
4-Methylphenyl	313.15	0.275 ±0.002	3.17 ±0.17	+8 ±12	100 8 ±3.8
	323.15	1.117 0 007			
	333.15	3.19 0.02			
	343.15	8.98 0.06			
Phenyl	308.15	0.1694 ±0.0021	3.88 ±0.19	+25 ±9	105.6 ±2.8
	318.15	0.570 0.005			
	328.15	2.26 0.02			
	338.15	6.85 0.05			
4-Chlorophenyl	313.15	0.270 ±0.003	2.99 ±0.09	+7 ±7	100.4 ±2.2
	323.15	1.010 0.015			
	333.15	2.89 0.03			
	343.15	8.83 0.09			
4-Acetylphenyl	318.15	0.700 ±0.008	4.13 ±0.13	+15 ±8	102.0 ±2.6
	328.15	2.39 0.04			
	338.15	6.70 0.09			
	348.15	21.8 0.2			

[a]Calculated from the first-order rate constants measured in 0.1mol.dm^{-3} aqueous perchloric acid. [b]Calculated by the Arrhenius equation.

chloroethyl β-D-xylofuranoside, for example, reacts somewhat more rapidly than the corresponding 2-chloroethyl derivative. This effect is just the opposite of that to be expected on the basis of the mechanism involving rate-limiting ring-opening. In contrast, the observed reactivity order suggests that these compounds are hydrolyzed *via* a cyclic oxocarbonium ion. For instance, in the hydrolysis of alkyl β-D-glucopyranosides proceeding by this pathway, a comparable rate-enhancement is found on going from the 2-chloroethyl derivative to glucosides having more-electronegative aglycon groups[9]. The studies with 4-substituted-phenyl β-D-xylofuranosides lend further support to this claim. As seen from Table III, the hydrolysis rates of these compounds, each having a strongly electron-attracting aglycon group, are almost independent of the polar nature of the 4-substituent. This trend can be interpreted, in accord with Route *A*, in terms of the opposing effects of the aglycon group on initial protonation and rate-limiting heterolysis. Consistent with the assumed A-1 mechanism, the entropies of activation obtained for 2-chloroethyl, 2,2,2-trichloroethyl, and phenyl xylosides are positive and of the same magnitude as those reported for ketofuranosides, the hydrolysis of which has been suggested to proceed *via* a cyclic oxocarbonium ion[3].

On the basis of inductive effects, it does not seem unreasonable that the hydrolysis mechanism of β-D-xylofuranosides would change from Route *B* to Route *A* on replacing an electropositive aglycon group by a strongly electronegative group. As mentioned above, electron-attracting substituents retard the former reaction, but

TABLE IV

FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF ALKYL β-D-XYLOFURANOSIDES IN WATER–METHYL SULFOXIDE MIXTURES OF DIFFERENT COMPOSITIONS CONTAINING PERCHLORIC ACID (0.1mol dm^{-3})

Mole fraction of Me_2SO	*Isopropyl β-D-xylofuranoside*		*Ethyl β-D-xylofuranoside*		*Methyl β-D-xylofuranoside*		*2-Chloroethyl β-D-xylofuranoside*	
	k (*332.85 K*) ($10^{-4}.sec^{-1}$)		k (*332.85 K*) ($10^{-4}.sec^{-1}$)		k (*352.45 K*) ($10^{-4}.sec^{-1}$)		k (*352.45 K*) ($10^{-4}.sec^{-1}$)	
0	64.8	±4.5[a]	24.0	±0.7[a]	50.2	±1.5[a]	6.41	±0.17[a]
0.051	47.9	0.6	16.99	0.07	32.7	0.5		
0.16					13.40	0.26	2.41	0.02
0.18	18.86	0.19	6.75	0.04				
0.31					6.38	0.14	1.499	0.016
0.33	8.32	0.09	3.11	0.02				
0.43					4.08	0.05	1.224	0.014
0.46	4.90	0.06	1.817	0.035				
0.54					3.20	0.06	1.278	0.013
0.59	3.33	0.03	1.376	0.014				
0.72	2.95	0.04	1.187	0.010				
0.76					2.66	0.03	1.578	0.020
0.87	1.904	0.013	0.829	0.011	1.921	0.02	1.952	0.034

[a]Calculated by the Arrhenius equation from the rate constants given in Table I.

exert only a slight influence on the rate of the latter. When the aglycon group is sufficiently electronegative, Route *A* may become predominant, although the compounds having electropositive aglycon groups were hydrolyzed *via* the acyclic intermediate.

Table IV records the rate constants for the hydrolyses of isopropyl, ethyl, methyl, and 2-chloroethyl β-D-xylofuranosides in aqueous perchloric acid–methyl sulfoxide mixtures of different compositions. In Fig. 2, the observed data are presented in terms of the logarithms of the relative constants, k/k_w, where k_w is the first-order rate constant in aqueous 0.1 mol.dm^{-3} perchloric acid, and k is the rate constant in a given water–methyl sulfoxide mixture having the same acid concentration. For each investigated compound, a considerable rate-retardation is found as the mole fraction of methyl sulfoxide is increased from zero to 0.3. This kind of behaviour is characteristic for the A-1 mechanism[6]. Solvent effects thus lend mild, additional support to the claim that the rate-limiting step in the hydrolysis of aldofuranosides is unimolecular.

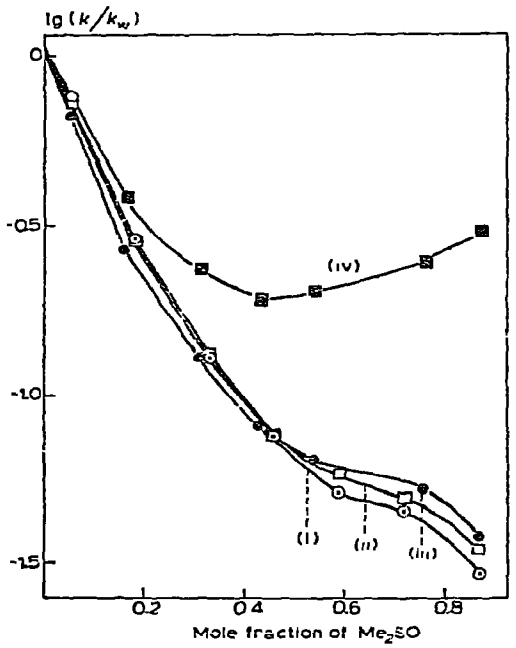


Fig. 2. Rate variations for the acid-catalyzed hydrolyses of alkyl β-D-xylofuranosides in binary water–methyl sulfoxide mixtures containing perchloric acid (0.1mol.dm^{-3}). Notation: (i) isopropyl, (ii) ethyl, (iii) methyl, and (iv) 2-chloroethyl xyloside.

In solutions rich in methyl sulfoxide, the kinetic medium-effects for the hydrolyses of alkyl β-D-xylofuranosides fall into two distinct groups. The rate constants obtained for isopropyl, ethyl, and methyl derivatives decrease mono-

tonously with the increasing concentration of methyl sulfoxide, whereas the hydrolysis rate of the 2-chloroethyl xyloside passes through a broad minimum in solutions containing approximately equal amounts of water and organic component. Assuming that these compounds react by A-1 mechanisms, the relative rate constants, k/k_w, can be expressed by equation (*1*). Here, y(S), $y(H^+)$, and $y(^{\ddagger})$ denote the

$$\frac{k}{k_w} = \frac{y(S).y(H^+)}{y(^{\ddagger})} \qquad (1)$$

concentration activity coefficients for the substrate, hydrogen ion, and transition state, respectively. By definition, these coefficients are unity in dilute aqueous solutions. It has been shown that moderate variations in the structures of acyclic acetals change the values of y(S) and $y(^{\ddagger})$ in any given water–methyl sulfoxide mixture by about the same proportion, leaving their ratio unchanged[17]. In other words, the hydrolyses of closely related compounds proceeding by the same pathway would be expected to exhibit similar kinetic medium-effects. However, as mentioned above, two different types of solvent effect have been demonstrated for the hydrolyses of alkyl β-D-xylofuranosides. It is probable that, for all the substrates studied, the activity coefficients, y(S), respond in roughly the same manner to changes in solvent composition. Consequently, the most obvious explanation for the sudden change in solvent effects on going from isopropyl, ethyl, and methyl xylosides to the 2-chloroethyl derivative seems to be that these two groups of compounds react *via* two different types of transition states, the solvation requirements of which differ appreciably. Although the solvent effects in themselves would not be sufficient evidence for a change in hydrolysis mechanism, they, in part, corroborate the conclusions drawn on the basis of structural effects and the values for the entropy of activation.

EXPERIMENTAL

Preparation and identification of materials. — The alkyl xylofuranosides, except the 2,2,2-trichloroethyl derivative, were prepared by Fischer glycosidation[18] under mild conditions. The furanoside-rich syrups obtained were fractionated by ion-exchange chromatography[19] on a strongly basic resin (Dowex 1 X2, mesh 200–400, HO^- form). In each case, xylopyranosides, formed in small proportions, were eluted more rapidly than the furanoid glycosides, the α anomers of which appeared first, as deduced from optical rotations. The fractions with negative rotation, containing the β anomers, were concentrated to syrups, the purity of which was checked by p.m.r. spectroscopy (60 MHz, Perkin–Elmer Model R-10 spectrometer). All β-D-xylofuranosides prepared by this method showed, in deuterium oxide, a broad singlet in the anomeric-proton range δ 4.5–5.5, as would be expected for 1,2-trans glycosides[20], whereas the corresponding α anomers gave a doublet (J ~4 Hz) in this field. The absence of signals for the α anomers was interpreted as indicating that the β anomers were sufficiently pure for kinetic purposes. The fact that first-order kinetics were strictly obeyed in their hydrolyses lends further support for this argument.

2,2,2-Trichloroethyl and 4-substituted-phenyl β-D-xylofuranosides were synthesized by the procedure described by Börjeson *et al.*[21]. The products were purified by recrystallization from ethyl acetate to constant melting-points. Phenyl β-D-xylofuranoside exhibited almost the same value as that reported in the literature[21]. Data for new compounds are recorded in Table V.

TABLE V

ANALYTICAL DATA FOR SOME β-D-XYLOFURANOSIDES

Aglycon group	*M.p.* (*degrees*)	$[\alpha]_D$ (*degrees*)	*Formula*	*Found*		*Calc.*	
				C	*H*	*C*	*H*
Ethyl	Syrup	−82 (W)[a]	$C_7H_{14}O_5$	47.1	7.9	47.2	7.9
Isopropyl	Syrup	−81 (W)	$C_8H_{16}O_5$	49.7	8.5	50.0	8.4
2-Methoxyethyl	Syrup	−70 (W)	$C_8H_{16}O_6$	45.7	7.8	46.1	7.8
2-Chloroethyl	87–90	−71 (W)	$C_7H_{13}ClO_5$	39.9	6.3	39.5	6.2
2,2,2-Trichloroethyl	109–111	−53 (E)	$C_7H_{11}Cl_3O_5$	30.1	4.2	29.9	3.9
4-Methylphenyl	110–113	−118 (E)	$C_{12}H_{16}O_5$	59.7	6.9	60.0	6.7
4-Chlorophenyl	132–135	−124 (E)	$C_{11}H_{13}ClO_5$	50.2	5.3	50.7	5.0
4-Acetylphenyl	132–135	−147 (E)	$C_{13}H_{16}O_6$	57.8	6.1	58.2	6.0

[a]W, water; E, ethanol.

Kinetic measurements. — Hydrolyses of alkyl β-D-xylofuranosides were carried out in stoppered tubes immersed in a thermostated bath, the temperature of which was kept constant within 0.05 K (electronically controlled Lauda thermostat). Reactions were started by adding the substrates (1.5×10^{-4} mol) into pre-thermostated reaction media (3 cm^3). Samples were withdrawn at appropriate intervals with a 100-mm^3 micropipette, and the progress of the hydrolysis was followed by determining the concentration of the liberated reducing-sugar by the method of Sumner[22]. First-order rate constants were calculated from the integrated first-order rate equation. 2,2,2-Trichloroethyl β-D-xylofuranoside decomposed markedly in the alkaline 3,5-dinitrosalicylate reagent employed in the method of Sumner. To determine the rate constants for the acid-catalyzed hydrolysis of this compound, the following modification of the procedure was used. The reaction was started by mixing the substrate (2×10^{-4} mol) with the pre-thermostated acid solution (40 cm^3). Samples were withdrawn with a 2-cm^3 semiautomatic pipette, and the unreacted substrate was removed by immediate extraction with ethyl acetate (20 cm^3). After the phases had been separated, 1-cm^3 of the water layer was used for the colorimetric determination of the sugar.

Hydrolyses of 4-substituted-phenyl β-D-xylofuranosides were followed spectrophotometrically at the absorption maxima of the liberated phenols. The measurements were performed on a Unicam SP-800 spectrophotometer equipped with a scale-expansion accessory. The temperature of the cell-housing block was adjusted with water circulating from a Lauda thermostat and controlled with a thermoelement.

Reactions were started by injecting 5% solutions of the substrates in methyl sulfoxide (2–3 mm^3) into the thermostated reaction-media (3 cm^3). The first-order rate constants were calculated by the method of Guggenheim.

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