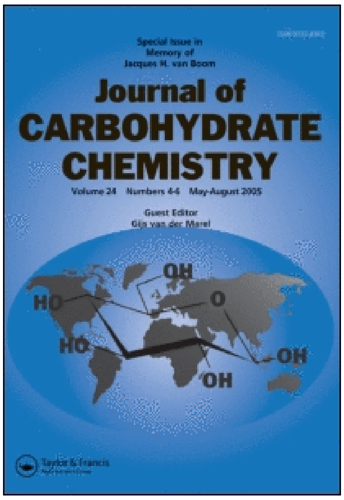

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THE ACID-CATALYZED HYDROLYSIS OF ANOMERIC ALKYL FRUCTOFURANOSIDES

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ABSTRACT

The rate constants for the hydrolysis of some alkyl α- and β-D-fructofuranosides in aqueous perchloric acid have been determined at various temperatures. The effects of varying the aglycon structure on the hydrolysis rate suggest, together with the markedly positive entropies of activation, that the substrate, protonated on the glycosidic oxygen atom, undergoes a rate-limiting unimolecular heterolysis to form a glycosyl oxocarbenium ion. The rate variations in mixtures of aqueous perchloric acid and dimethyl sulfoxide are interpreted as lending further support for the proposed mechanism.

INTRODUCTION

The hydrolytic cleavage of the glycosidic bond has been the object of considerable interest ever since the early investigations of Armstrong[1-3] and Fischer.[4] It is now generally accepted that the acid-catalyzed hydrolysis of glycopyranosides consists of rapid initial protonation of the glycosidic oxygen atom followed by

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rate-limiting rupture of the glycosyl-oxygen bond with formation of a cyclic oxocarbenium ion.[5-7] However, if the aglycon group is capable of forming a particularly stable alkyl cation then alkyl-oxygen fission may take place.[8-10]

The mechanisms for the hydrolysis of glycofuranosides have been less extensively studied than those of glycopyranosides. We have previously[11-14] suggested that the acidic hydrolysis of aldofuranosides proceeds by two concurrent pathways. Either the reaction involves a rapid initial protonation of the ring-oxygen and a rate-limiting opening of the five-membered ring, all subsequent steps being fast, or the route described for glycopyranosides is utilized. The latter mechanism becomes more favorable with the increasing electron-attracting nature of the aglycon group. Participation of water as a nucleophilic reagent in the transition state for the hydrolysis of aldofuranosides has been repeatedly suggested[15-18] on the basis of the negative entropies and volumes of activation obtained with some methyl derivatives.

The hydrolysis of ketofuranosides exhibits positive $\Delta \underline{S}^{\ddagger}$ and $\Delta \underline{V}^{\ddagger}$ values,[19-23] in contrast to the hydrolysis of methyl aldofuranosides. Accordingly, rate-limiting formation of a glycosyl oxocarbenium ion, as in the cleavage of glycopyranosides, has been considered to be the most probable mechanism.[6,22] The aim of the present report is to obtain further evidence for this assumption by examining the effects that varying the polar nature of the aglycon group exerts on the hydrolysis rates of anomeric alkyl fructofuranosides. For the same reason the rate variations in binary mixtures of water and DMSO have been studied.

RESULTS AND DISCUSSION

The kinetic data for the hydrolysis of alkyl α- and β-D-fructofuranosides in aqueous perchloric acid at different temperatures are given in Tables 1 and 2, respectively. The values obtained for the entropy of activation are all considerably positive, indicating that the rate-limiting stage is unimolecular. Three different pathways consistent with this requirement can a priori be written for the hydrolysis of fructofuranosides (Scheme 1). Either the substrate, protonated on the ring-oxygen, undergoes a rate-limiting ring-opening (Route A), or protonation of the glycosidic oxygen atom leads to rupture of the glycosyl-oxygen or alkyl-oxygen bonds (Routes B and C). The last mechanistic possibility appears highly unlikely, since a primary alkyl cation can hardly be more stable than a resonance stabilized tertiary furanosyl cation. Routes A and B can be distinguished by examining the influences of the struc-

SCHEME 1

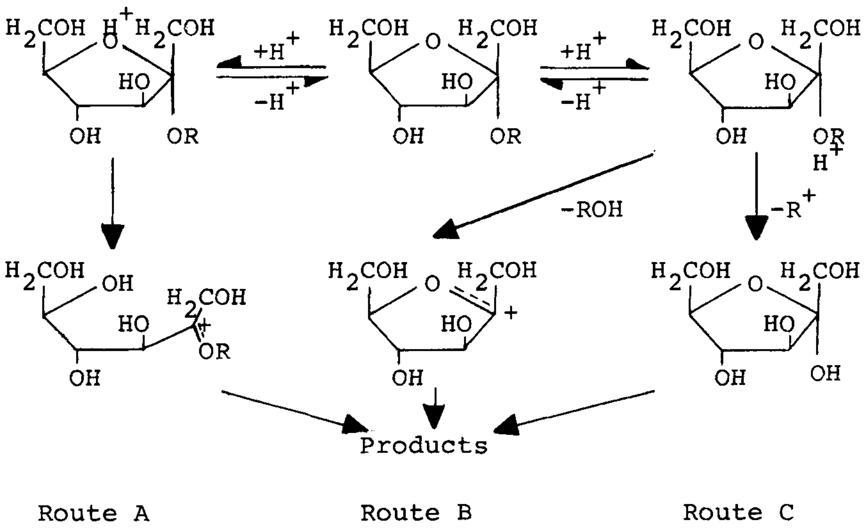

TABLE 1

Second-order Rate Constants at Different Temperatures, and the Enthalpies and Entropies of Activation for the Acidic Hydrolysis of Alkyl α-D-Fructofuranosides.

Aglycon	T / K	k[a] / 10^{-3} M^{-1} s^{-1}	k(298.2 K)[b] / 10^{-3} M^{-1} s^{-1}	$\Delta H^{\ddagger}$ [c] / kJ mol^{-1}	$\Delta S^{\ddagger}$ [c] / J K^{-1} mol^{-1}
Isopropyl	293.2	3.12 ±0.06	6.34 ±0.51	104.3±4.2	63±14
	303.2	13.4 0.6			
	312.2	38.0 0.2			
	323.2	193 2			
Ethyl	293.2	0.708±0.012	1.54 ±0.09	104.6±2.6	52± 8
	303.2	3.35 0.03			
	313.2	12.6 0.2			
	323.2	37.9 1.3			
	333.2	153 8			
Methyl	293.2	0.450±0.013	0.883±0.081[d]	106.5±3.6[d]	54±12[d]
	303.2	1.71 0.07			
	313.2	7.38 0.28			
	323.2	22.3 0.8			
	333.2	103 2			
2-Methoxyethyl	293.2	0.648±0.009	1.38 ±0.04	104.4±1.3	50± 4
	303.2	2.74 0.04			
	313.2	11.6 0.2			
	323.2	39.4 0.8			
	333.2	122 7			

[a] The first-order rate constants obtained in 0.1 M aqueous perchloric acid. [b] By the Arrhenius equation. [c] At 298.2 K. [d] In Ref. 19: k(298.2 K) = (0.96±0.10)x10^{-3} M^{-1} s^{-1}, $\Delta H^{\ddagger}$ = (109.4±5.1) kJ mol-1, and $\Delta S^{\ddagger}$ = (64±16) J K^{-1} mol-1.

TABLE 2

Second-order Rate Constants at Different Temperatures, and the Enthalpies and Entropies of Activation for the Acidic Hydrolysis of Alkyl β-D-Fructofuranosides.

Aglycon	T K	k[a] $10^{-3}\ M^{-1}\ s^{-1}$	k(298.2 K)[b] $10^{-3}\ M^{-1}\ s^{-1}$	ΔH‡ [c] $kJ\ mol^{-1}$	ΔS‡ [c] $J\ K^{-1}\ mol^{-1}$
Isopropyl	293.2	2.42 ±0.05	5.21 ±0.34	106.0±3.5	67±11
	303.2	10.4 0.2			
	312.2	41.7 2.3			
	323.2	144 7			
Ethyl	293.2	0.392±0.006	0.854±0.008	110.6±0.4	67± 2
	303.2	1.81 0.02			
	313.2	7.70 0.13			
	323.2	28.6 0.5			
	333.2	104 5			
Methyl	293.2	0.308±0.005	0.631±0.030[d]	109.9±1.9[d]	62± 6[d]
	303.2	1.31 0.04			
	313.2	5.10 0.06			
	323.2	20.4 0.3			
	333.2	79.1 2.9			
2-Methoxyethyl	293.2	0.353±0.004	0.741±0.026	107.1±1.4	54± 4
	303.2	1.52 0.02			
	313.2	6.30 0.17			
	323.2	21.0 0.5			
	333.2	80.6 2.5			

[a,b,c] See the corresponding footnotes in Table 1. [d] In *Ref*. 23: *k*(298.2 K) = (0.720±0.019)×$10^{-3}\ M^{-1}\ s^{-1}$, Δ*H*‡ = (101.5±2.1) kJ mol^{-1}, Δ*S*‡ = (35±7) J $K^{-1}\ mol^{-1}$.

ture of the aglycon group on the hydrolysis rate. Reaction A is markedly susceptible to the polar nature of the aglycon moiety, because both the basicity of the ring-oxygen and the stability of the acyclic oxocarbenium ion are decreased with the increasing electronegativity of this group, the latter factor being more decisive. For example, the rate of reaction (1) of acyclic acetals is continuously diminished with the in-

$$R^1OCH_2OR^2 \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} R^1OCH_2\overset{H}{\overset{+}{O}}R^2 \xrightarrow{-HOR^2} R^1O\overset{+}{=}CH_2 \qquad (1)$$

creasing electron-attracting ability of the nondeparting alkyl group, R^1.[24] The relative rate constants for the isopropyl, ethyl, methyl and 2-methoxyethyl derivates have been shown to be 22.1, 4.48, 1.00 and 0.201, respectively.[24] Alkyl β-D-xylofuranosides, suggested to react by Route A, exhibit a similar dependence of reactivity on the structure of the aglycon group.[11] In contrast, the polar nature of the aglycon moiety does not markedly affect the rate of reaction B, since the effects on the pre-equilibrium protonation and the rate-limiting heterolysis are opposite. For example, in the hydrolysis of alkyl glycopyranosides,[25-27] and 2-alkoxytetrahydrofurans and -pyrans[28] these two influences almost completely cancel each other. As seen from Table 3, with each series of compounds the hydrolysis rate goes through a minimum on going from the isopropyl to ethyl, methyl and 2-methoxyethyl derivatives.

Table 3 also records the relative rate constants for the hydrolysis of anomeric alkyl fructofuranosides. The structural effects closely resemble those reported for glycopyranosides. In fact, the only significant difference is the slightly greater rate-enhancing effect of the isopropyl group with fructofuranosides. The latter finding can possibly be accounted for by

TABLE 3

Comparison of the Structural Effects in the Acid-Catalyzed Hydrolysis of Anomeric Alkyl Fructofuranosides with Those in the Hydrolysis of Some Hemicyclic Acetals Proceeding *via* Cyclic Oxocarbenium Ions (Route B in Scheme 1).

Series of Compounds	Exocyclic Alkyl Group				Ref.
	$(CH_3)_2CH-$	CH_3CH_2-	CH_3-	$CH_3OCH_2CH_2-$	
Alkyl α-D-Fructofuranosides	7.2	1.7	1.0	1.6	[a]
Alkyl β-D-Fructofuranosides	8.3	1.4	1.0	1.2	[a]
2-Alkoxytetrahydrofurans	3.4	1.5	1.0	1.4	28
2-Alkoxytetrahydropyrans	2.1	1.3	1.0	1.5	28
Alkyl β-D-Xylopyranosides	3.3	1.5	1.0	1.6	26
Alkyl β-D-Glucopyranosides	1.9	1.1	1.0	1.3	25
Acyclic Acetals[b]	2.3	1.2	1.0	1.5	24

[a] This work.

[b] For the partial reaction $R^1OCH_2OR^2 \underset{}{\overset{+H^+}{\rightleftharpoons}} R^1\overset{+}{\underset{}{O}}HCH_2OR^2 \xrightarrow{-R^1OH} CH_2\overset{+}{=}OR^2$, when R^1 is varied.

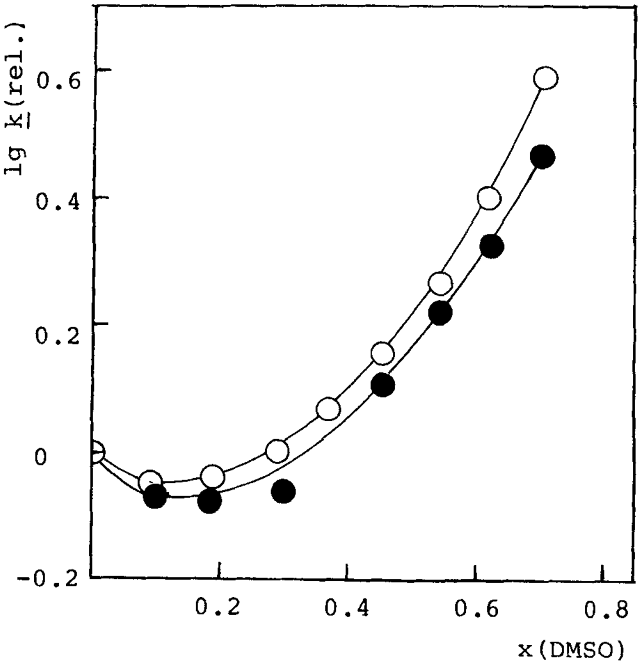

FIG. 1: Rate variation for the acid-catalyzed hydrolysis of methyl α- (filled circles) and β-D-fructofuranosides (open circles) in binary mixtures of water and DMSO at 313.2 K.

different sensitivities to the steric properties of the aglycon group. The anomeric carbon atom bears a hydroxymethyl group in fructofuranosides and a hydrogen atom in glycopyranosides. Consequently, the reaction center of the hydrolysis of the former compounds is more crowded, and the rate-limiting departure or the relatively bulky isoporoxy group may be an exceptionally facile process.

We have shown previously that the rate variations of the acid-catalyzed hydrolysis of alkyl aldofuranosides in binary mixtures of water and DMSO fall into two distinct groups.[11,12] The reactions suggested to occur by Route A undergo continuous rate-retardations with the increasing concentration of the organic component. In contrast, the hydrolysis rates of the compounds assumed to utilize Route B pass through broad minima in solutions containing approximately equal mole fractions of water and DMSO. As seen from Fig. 1, the hydrolyses of anomeric fructofuranosides respond to changes in the solvent composition in a manner that closely resemble the latter kind of behavior. However, the rate-acceleration in DMSO-rich solutions are larger than those in the hydrolysis of aldofuranosides. Although qualitative similarities of the solvent effects cannot be regarded as convincing evidence for the similarity of mechanisms, it is reassuring that this approach does not argue against the conclusions drawn on the basis of structural effects.

In summary, the preceding discussion lends some additional support for the suggestion that alkyl ketofuranosides are hydrolyzed by rate-limiting formation of glycosyl oxocarbenium ions.

EXPERIMENTAL

The alkyl fructofuranosides employed in kinetic measurements were obtained by ion exchange chromatography[29] (Dowex 1X2 resin, mesh 200-400, OH^- form) of furanoside-rich syrups prepared by Fischer glycosidation. The purity of the furanoid anomers was checked by TLC on silica gel 60 ($CHCl_3$-CH_3OH 7:3, v/v) and ^{13}C NMR spectroscopy. These data are presented in Table 4 together with the results of the elemental analyses.

The kinetic measurements were performed as described earlier[11] with the exception that aliquots of 1 cm^3 were withdrawn.

TABLE 4

^{13}C NMR Chemical Shifts, Elemental Compositions and TLC Data for the Alkyl D-Fructofuranosides Prepared.

Compound	^{13}C NMR Shifts[a]							Composition[b]		R_F[c]
	δ(C1)	δ(C2)	δ(C3)	δ(C4)	δ(C5)	δ(C6)	δ(R)	C%	H%	
Isopropyl α	62.2	110.1	83.2	78.5	84.1	63.1	25.4, 25.5, 67.6	48.37 (48.65)	8.14 (8.17)	0.69
Isopropyl β	62.7	106.0	77.9	76.9	82.6	64.9	25.5, 25.7, 67.1	48.65 (48.65)	8.23 (8.17)	0.58
Ethyl α	58.4	109.0	81.7	78.2	83.7	62.3	15.8, 60.1	45.87 (46.15)	7.74 (7.75)	0.62
Ethyl β	61.2	104.8	77.6	76.2	82.2	63.8	15.7, 58.3	45.69 (46.15)	7.81 (7.75)	0.51
Methyl α	58.7	109.0	80.9	78.2	84.1	62.1	49.1[d]	43.48 (43.30)	7.27 (7.27)	0.53
Methyl β	60.7	104.7	77.8	76.0	82.2	63.6	49.8[d]	43.40 (43.30)	7.47 (7.27)	0.40
2-Methoxy-ethyl α	59.2	109.2	81.7	78.3	84.1	62.3	60.0, 61.0, 72.4	45.07 (45.38)	7.46 (7.62)	0.65
2-Methoxy-ethyl β	61.2	104.7	77.9	75.7	82.2	63.4	59.0, 61.2, 72.5	45.50 (45.38)	7.64 (7.62)	0.55

[a] In D_2O as ppm from DSS. [b] Calculated values in parentheses. [c] On Silica gel 60 (Merck), eluent $CHCl_3$-CH_3OH 7:3 (v/v). [d] Consistent with the data in Ref.30.

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