Acta Chemica Scandinavica A 31 (1977) 306—312

Mechanisms for the Acid-catalyzed Hydrolysis of Some Alkyl Aldofuranosides with *trans*-1,2-Configuration

HARRI LÖNNBERG and ANTERO KULONPÄÄ

Department of Chemistry and Biochemistry, University of Turku, SF-20500 Turku, Finland

The rate constants for the hydrolysis of several alkyl α-D-arabino-, α-D-lyxo-, and β-D-ribofuranosides in aqueous perchloric acid have been measured at different temperatures. The effects of varying the aglycon structure on the hydrolysis rates are interpreted to indicate that α-arabinosides and α-lyxosides are usually hydrolyzed by rate-limiting formation of cyclic oxo-carbenium ions. However, if the aglycon group is strongly electropositive a mechanism involving rate-limiting opening of the five-membered ring may occur. Alkyl β-D-ribofuranosides, with the exception of those carrying highly electronegative substituents in the aglycon group, probably utilize the latter route. The values for the entropy of activation and the rate variations in aqueous perchloric acid – dimethyl sulfoxide solutions of different compositions are interpreted to lend further support for the suggested difference in mechanism.

Whereas the acid-catalyzed hydrolysis of aldopyranosides has been extensively studied in recent years,[1] there have been only a few mechanistic investigations of the corresponding reactions of aldofuranosides.[2,3] Capon showed that the hydrolysis of methyl aldofuranosides consists of an initial rapid protonation of the substrate and glycosyl-oxygen bond rupture in one of the subsequent steps, but drew no firm conclusions concerning the details of the mechanism.[3] In a previous paper one of us suggested that alkyl β-D-xylofuranosides usually react by protonation of the ring-oxygen followed by a unimolecular cleavage of the five-membered ring in the rate-limiting step.[4] However, a pathway involving protonation of the glycosidic oxygen atom and rate-limiting formation of a cyclic oxo-carbenium ion is probably only slightly less favorable and becomes the major one on going to substrates with markedly electronegative aglycon groups. On this basis it does not seem unreasonable that in the hydrolysis of alkyl glycosides of other aldofuranoses the latter mechanism might be followed even when the aglycon group is electropositive. To elucidate the influence of varying the glycon moiety configuration on the relative rates of the reactions described above the hydrolyses of alkyl α-D-arabino-, α-D-lyxo-, and β-D-ribofuranosides have been studied in this work.

EXPERIMENTAL

The alkyl aldofuranosides used in this investigation were obtained by ion exchange chromatography[5] (Dowex 1X2 resin, mesh 200 – 400, OH^- form) of furanoside-rich syrups prepared by Fischer glycosidation.[6] The purity of the separated anomers was checked by ^1H NMR spectroscopy (a 60 MHz Perkin-Elmer Model R 10 spectrometer). In each case only one signal in the anomeric proton region (δ 4.7 – 5.1) was observed indicating the homogeneity of the separated anomers. Many of the products crystallized from ethyl acetate. The melting points and ^1H NMR data are listed in Table 1 together with the specific optical rotations. The kinetic measurements were performed as described earlier.[4]

RESULTS AND DISCUSSION

Scheme 1 describes the mechanism suggested in a previous paper[4] for the acid-catalyzed hydrolysis of alkyl β-D-xylofuranosides with electropositive or weakly electronegative aglycon groups. The substrate protonated on the ring-oxygen undergoes a rate-limiting heterolysis to form an acyclic oxo-carbenium ion.

Scheme 1.

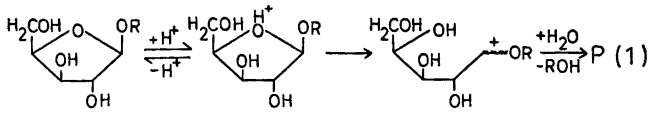


Table 1. Specific optical rotations (measured in water at 293 K), melting points and ^1H NMR spectra (D_2O; 306.7 K) for the alkyl aldofuranosides prepared.

$[\alpha]_D$ (°)	M.p. (K)	^1H NMR (δ)
Isopropyl α-D-arabinofuranoside		
+102	syrup	1.09 [d,$(CH_3)_2CH$], 3.6–3.7 (m, H-5), 3.8–4.0 [m, H-2, H-3, H-4 and $(CH_3)_2CH$], 4.99 (d, H-1)
Ethyl α-D-arabinofuranoside		
+110	syrup	1.10 (t, CH_3CH_2), 3.4–3.7 (m, H-5 and CH_3CH_2), 3.8–4.0 [m, H-2, H-3 and H-4], 4.90 (d, H-1)
Methyl α-D-arabinofuranoside		
+119[a]	335–338 (hygr.)	3.32 (s, CH_3), 3.6–3.7 (m, H-5), 3.8–4.0 (m, H-2, H-3 and H-4), 4.83 (d, H-1)
2-Methoxyethyl α-D-arabinofuranoside		
+99	syrup	3.29 (s, $CH_3OCH_2CH_2$), 3.5–3.7 (m, H-5 and $CH_3OCH_2CH_2$), 3.8–4.0 (m, H-2, H-3 and H-4), 4.93 (d, H-1)
2-Chloroethyl α-D-arabinofuranoside		
+77	syrup	3.6–3.8 (m, H-5 and $ClCH_2CH_2$), 3.8–4.0 (m, H-2, H-3 and H-4), 4.99 (d, H-1)
Isopropyl α-D-lyxofuranoside		
+113	362–365	1.11 [d, $(CH_3)_2CH$], 3.6–3.8 (m, H-5), 3.9–4.3 [m, H-2, H-3, H-4 and $(CH_3)_2CH$], 5.03 (d, H-1)
Methyl α-D-lyxofuranoside		
+130[b]	365–367[b]	3.35 (s, CH_3), 3.6–3.8 (m, H-5), 3.9–4.3 (m, H-2, H-3, and H-4), 4.86 (d, H-1)
2-Methoxyethyl α-D-lyxofuranoside		
+90	syrup	3.27 (s, $CH_3OCH_2CH_2$), 3.5–3.8 (m, H-5 and $CH_3OCH_2CH_2$), 3.9–4.3 (m, H-2, H-3 and H-4), 4.94 (d, H-1)
Isopropyl β-D-ribofuranoside		
−50	342–343	1.08 [d, $(CH_3)_2CH$], 3.6–3.7 (m, H-5), 3.8–4.0 [m, H-2, H-3, H-4 and $(CH_3)_2CH$], 4.99 (s, H-1)
Methyl β-D-ribofuranoside		
−46	syrup[c]	3.30 (s, CH_3), 3.6–3.7 (m, H-5), 3.8–4.0 (m, H-2, H-3 and H-4), 4.81 (s, H-1)
2-Methoxyethyl β-D-ribofuranoside		
−45	syrup	3.28 (s, $CH_3OCH_2CH_2$), 3.5–3.7 (m, H-5 and $CH_3OCH_2CH_2$), 3.8–4.1 (m, H-2, H-3 and H-4), 4.91 (s, H-1)
2-Chloroethyl β-D-ribofuranoside		
−40	syrup	3.6–3.8 (m, H-5 and $ClCH_2CH_2$), 3.8–4.1 (m, H-2, H-3 and H-4), 4.98 (s, H-1)

[a] Lit.:[7] $[\alpha]_D$ +123°, m.p. 338–340 K (hygr.). [b] Lit.:[8] $[\alpha]_D$ +131°, m.p. 368–370 K. [c] Lit.:[9] $[\alpha]_D$ −50°, m.p. 353 K.

Table 2. Second-order rate constants at different temperatures and the entropies of activation for the acid-catalyzed hydrolysis of alkyl β-D-ribofuranosides.

T / K	k [a] / 10^3 dm^3 mol^{-1} s^{-1}	k(333.15 K) [b] / 10^3 dm^3 mol^{-1} s^{-1}	$\Delta S^{\ddagger}$(298.15 K) / J K^{-1} mol^{-1}
Isopropyl			
312.85	8.38(9)	59.5(24)	−23(9)
317.85	12.85(20)		
322.85	23.3(2)		
327.85	37.6(4)		
332.85	56.3(5)		
Methyl			
312.85	1.034(12)	8.16(7)	−29(2)
317.85	1.768(38)		
322.85	2.99(4)		
327.85	4.93(7)		
332.85	7.84(6)		
2-Methoxyethyl			
332.85	2.83(3)	2.84(11)	−20(9)
337.75	4.53(5)		
342.65	6.93(11)		
347.55	11.08(21)		
352.45	19.12(22)		
2-Chloroethyl			
342.65	3.34(3)	1.189(84)	−14(10)
347.55	5.05(7)		
352.45	7.92(6)		
357.45	13.05(17)		
362.45	22.0(2)		

[a] Calculated from the first-order rate constants obtained in 0.10 mol dm^{-3} aqueous perchloric acid. [b] Calculated by the Arrhenius equation from the rate constants at other temperatures.

To determine whether the same pathway is followed in the hydrolysis of the corresponding glycosides of other aldopentoses, the dependences of their hydrolysis rates on the polar properties of the aglycon group were studied. Table 2 records the kinetic data obtained with alkyl β-D-ribofuranosides. The reactivity is considerably decreased with the increasing electron-attracting character of the aglycon group on going from the isopropyl to 2-chloroethyl derivative. This is just what would be expected on the basis of mechanism (1). Electron withdrawal by polar substituents greatly retards the cleavage of the five-membered ring by destabilizing the developing acyclic oxo-carbenium ion, and, owing to the long distance between the ring-oxygen and the aglycon group, exerts only a slight effect on the extent of protonation. As seen from Fig. 1, plotting the logarithms of the rate constants obtained with β-ribosides against the corresponding

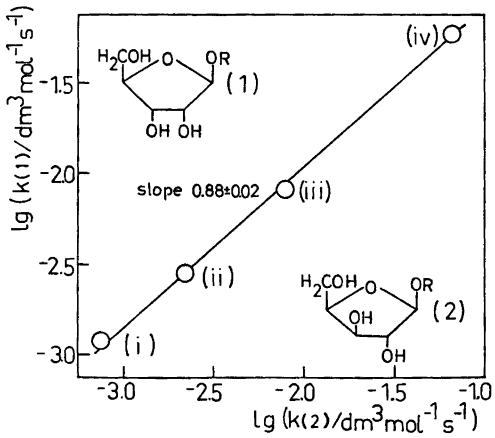


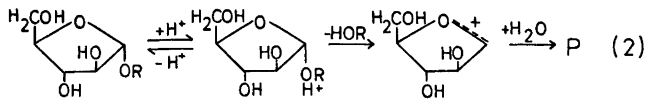
Fig. 1. Comparison of the structural effects in the acid-catalyzed hydrolysis of alkyl β-D-ribofuranosides (1) with those in the hydrolysis of the corresponding β-D-xylosides (2) at 333.15 K. Notation: (i) 2-chloroethyl, (ii) 2-methoxyethyl, (iii) methyl, and (iv) isopropyl derivatives.

Table 3. Second-order rate constants at different temperatures and the entropies of activation for the acid-catalyzed hydrolyses of alkyl α-D-arabino- and α-D-lyxofuranosides.

T / K	k [a] / 10^3 dm^3 mol^{-1} s^{-1}	k(333.15 K) [b] / 10^3 dm^3 mol^{-1} s^{-1}	$\Delta S^{\pm}$(298.15 K) / J K^{-1} mol^{-1}
α-D-Arabinosides Isopropyl			
347.55	9.75(16)	2.34(15)	−15(8)
352.45	16.12(27)		
357.45	24.1(1)		
362.45	39.0(5)		
Ethyl			
347.55	3.63(4)	0.715(52)	+15(9)
352.45	6.26(6)		
357.45	10.92(10)		
362.45	17.05(33)		
Methyl			
337.75	0.682(8)	0.386(17)	+ 7(8)
342.65	1.119(8)		
347.55	1.915(19)		
352.45	3.19(3)		
357.45	5.77(6)		
2-Methoxyethyl			
347.55	1.595(23)	0.272(36)	+24(16)
352.45	2.47(3)		
357.45	4.61(6)		
362.45	8.02(11)		
2-Chloroethyl			
347.55	1.822(25)	0.332(7)	+22(3)
352.45	3.18(5)		
357.45	5.38(5)		
362.45	9.27(9)		
α-D-Lyxosides Isopropyl			
317.85	2.13(4)	11.89(42)	−1(9)
327.85	7.15(6)		
337.75	20.0(4)		
347.55	47.6(8)		
Methyl			
322.85	0.571(6)	2.05(2)	+31(4)
327.85	1.049(8)		
332.85	1.981(14)		
337.75	3.56(3)		
2-Methoxyethyl			
332.85	2.18(3)	2.29(4)	+50(4)
337.75	4.17(3)		
342.65	7.47(5)		
347.55	12.98(9)		
352.45	23.8(2)		

[a,b] See the footnotes in Table 2.

Scheme 2.



values for β-xylofuranosides yields a straight line with a slope close to unity. In other words, the susceptibility to polar inductive effects is in both reactions nearly the same, indicating a constancy of mechanism. As in the xyloside hydrolysis, the values for the entropy of activation are slightly negative in an apparent conflict with the proposed A-1 mechanism. In a previous discussion [4] we, however, presented evidence for the suggestion that this would be the result of rate-limiting opening of the five-membered ring rather than of the bimolecular nature of the slow step.

In contrast, alkyl α-D-arabino- and α-D-lyxofuranosides exhibit structure-reactivity relationships quite different from that observed for β-xylosides. The second-order rate constants for the hydrolyses of these compounds are given in Table 3 together with the entropies of activation. In both series the reactivity decreases appreciably on going from the isopropyl to methyl derivative but changes little thereafter with the increasing electronegativity of the aglycon group. The latter kind of behavior argues strongly against mechanism (1). In contrast, it suggests that a mechanism involving rate-limiting formation of a cyclic oxo-carbenium ion (Scheme 2) is followed, as in the hydrolysis of alkyl aldopyranosides.[1] The rate of this reaction would be expected to be relatively insensitive to the polar nature of the aglycon group. Electron-attracting substituents, for example, tend to decrease the basicity of the glycosidic oxygen atom and hence the concentration of the protonated substrate, but at the same time they facilitate the departure of the protonated alkoxy group. For instance, in the hydrolyses of 2-alkoxytetrahydrofurans,[10] 2-alkoxytetrahydropyrans,[10] and several alkyl aldopyranosides,[11] shown to proceed *via* a cyclic oxo-carbenium ion, these two influences almost cancel. On this basis it seems probable that of the alkyl α-D-arabino- and α-D-lyxofuranosides studied only isopropyl derivatives would react mainly by mechanism (1), while the others utilize preferably route (2). Mechanisms involving a rate-limiting nucleophilic attack of water at the anomeric

Table 4. First-order rate constants for the hydrolysis of alkyl β-D-ribo- and α-D-arabinofuranosides in water – DMSO mixtures of different compositions containing perchloric acid 0.1 mol dm^{-3}.

	Isopropyl β-D-riboside	Methyl β-D-riboside	2-Chloroethyl β-D-riboside	Isopropyl α-D-arabinoside	Methyl α-D-arabinoside	2-Chloroethyl α-D-arabinoside
x(DMSO)	k(342.65 K) / 10^{-4} s^{-1}	k(352.45 K) / 10^{-4} s^{-1}	k(352.45 K) / 10^{-4} s^{-1}	k(352.45 K) / 10^{-4} s^{-1}	k(352.45 K) / 10^{-4} s^{-1}	k(352.45 K) / 10^{-4} s^{-1}
0	138.8(89) [a]	46.4(9) [a]	8.32(19) [a]	15.65(26) [b]	3.30(7) [b]	3.16(2) [b]
0.13	55.4(7)		2.81(4)			
0.20		12.97(13)		4.54(6)	1.059(8)	1.045(12)
0.26	26.1(4)		1.470(28)			
0.46		4.29(7)		1.908(3)	0.867(10)	0.878(14)
0.48	14.48(14)		0.896(17)			
0.62	9.10(9)		1.055(17)	2.37(3)	0.930(9)	0.951(13)
0.66		3.13(3)				
0.73	7.66(9)	2.74(5)	1.067(18)	2.68(3)	1.064(13)	1.240(5)
0.87	5.11(7)	2.42(4)	1.168(26)	2.83(3)	1.550(17)	1.767(26)

[a] Calculated from the rate constants given in Table 2. [b] Calculated from the rate constants given in Table 3.

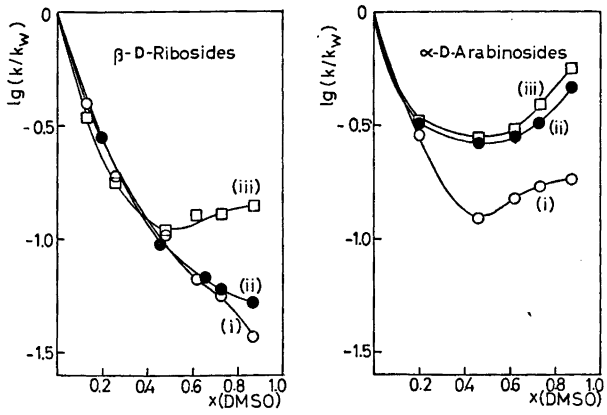


Fig. 2. Rate variations of the acid-catalyzed hydrolyses of alkyl β-D-ribo- and α-D-arabinofuranosides in binary mixtures of water and dimethyl sulfoxide. The values for the first-order rate constants, k and k_w, are given in Table 4. Notation: (i) isopropyl, (ii) methyl, and (iii) 2-chloroethyl derivatives.

carbon concerted with the cleavage of either the *exo* or *endo* cyclic acetal bond would also be expected to exhibit a relatively low susceptibility to the nature of polar substituents in the aglycon group. The fact that the hydrolyses of alkyl α-arabinosides and α-lyxosides are characterized by positive entropies of activation makes, however, these routes less probable.

The influences of solvent composition on the hydrolysis rates of alkyl α-D-arabino- and β-D-ribofuranosides lend some further support for the suggested change in mechanism. Table 4 summarizes the rate constants obtained in binary water-dimethyl sulfoxide mixtures containing perchloric acid 0.10 mol dm^{-3}. The same data are presented in Fig. 2 in terms of the logarithms of the relative rate constants, k/k_w, against the mol fractions of DMSO in reaction solutions. Here k and k_w stand for the first-order rate constants in a given solvent mixture and in water, respectively. Of the compounds studied isopropyl and methyl β-D-ribofuranosides exhibit solvent effects analogous to those reported for the alkyl β-D-xylofuranosides reacting with rate-limiting ring opening.[4] The relative rate constants, k/k_w, decrease monotonously over the whole range studied. In contrast, the hydrolysis rates of methyl and 2-chloroethyl α-D-arabinofuranosides pass through broad minima in solutions containing approximately equal amounts of water and organic component. In other words, these reactions respond to changes in solvent composition in roughly the same manner as the hydrolyses of β-xylosides suggested to occur by route (2). The solvent effect curves for isopropyl α-D-arabino- and 2-chloroethyl β-D-ribofuranoside also show broad minima, but the rate-retarding effect of DMSO is in these cases more marked than with methyl and 2-chloroethyl arabinosides. This kind of behavior can be rationalized by assuming that although mechanism (1) prevails in water, the route through a cyclic ion is only slightly less favorable. On the basis of the structure-reactivity relationships indicated above this seems quite feasible for the hydrolyses of these two compounds. Accordingly, route (2) may become the major one in DMSO-rich solutions. The hydrolysis rates would thus experience sharp decreases at low DMSO concentrations, a property suggested to be characteristic for reactions occurring *via* acyclic intermediates, and still go through minima.

In summary, the preceding discussion suggests that the mechanism for the acid-catalyzed hydrolysis of alkyl aldofuranosides depends not only on the polar nature of the aglycon group, but also on the configuration of the glycon moiety. A detailed understanding of the latter factor would, however, require exact knowledge of the conformations of aldofuranosides in water solution.

REFERENCES

1. a. Capon, B. *Chem. Rev. 69* (1969) 407; b. BeMiller, J. N. *Adv. Carbohydr. Chem. 22* (1967) 25.
2. a. Blom, J. *Acta Chem. Scand. 15* (1961) 1667: b. Overend, W. G., Rees, C. W. and Sequeira, J. S. *J. Chem. Soc.* (1962) 3429; c. Capon, B. and Thacker, D. *J. Am. Chem. Soc. 87* (1965) 4199.
3. Capon, B. and Thacker, D. *J. Chem. Soc. B* (1967) 185.
4. Lönnberg, H., Kankaanperä, A. and Haapakka, K. *Carbohydr. Res. In press.*
5. Austin, P. W., Hardy, F. E., Buchanan, J. G. and Baddiley, J. *J. Chem. Soc.* (1963) 5350.
6. Fischer, E. *Ber. Dtsch. Chem. Ges. 47* (1914) 1980.
7. Montgomery, E. M. and Hudson, C. S. *J. Am. Chem. Soc. 59* (1937) 992.
8. Bhattacharya, A. K., Ness, R. K. and Fletcher, H. G., Jr. *J. Org. Chem. 28* (1963) 428.
9. Augestad, I. and Berner, E. *Acta Chem. Scand. 10* (1956) 911.
10. Kankaanperä, A. and Miikki, K. *Suom. Kemistil. B 41* (1968) 42.
11. a. Timell, T. E. *Can. J. Chem. 42* (1964) 1456; b. DeBruyne, C. K. and Van Wijnendaele, F. *Carbohydr. Res. 6* (1968) 367; c. BeMiller, J. N. and Doyle, E. R. *Carbohydr. Res. 20* (1971) 23; d. DeBruyne, C. K. and van der Groen, G. *Carbohydr. Res. 25* (1972) 59.

Received November 12, 1976.