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Short Communications

The Effect of Glycon Moiety Configuration on the Alkaline Cleavage of Aryl Aldofuranosides

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In a previous discussion[1,2] the alkaline hydrolysis of substituted phenyl β-D-xylofuranosides was shown to proceed *via* a rapid initial formation of a 2-oxyanion of the substrate followed by rate-limiting unimolecular heterolysis of this intermediate. For the latter partial reaction two alternative mechanisms were suggested.[1] Either the anionic intermediate is decomposed spontaneously to a phenoxide and a cyclic oxocarbenium ion, or the ionized hydroxyl group at C-2 acts as an intramolecular nucleophilic catalyst, analogous to the hydrolysis of aryl aldopyranosides with *trans*-1,2-configuration.[3] To distinguish between these two possibilities, the effect of varying the glycon moiety configuration on the hydrolysis rate is considered in this communication.

In intramolecular displacement reactions, as in their intermolecular counterparts, the attacking nucleophile must approach the reaction center from the side opposite to the departing group. This requirement can be fulfilled in aryl aldofuranosides with the hydroxyl group at C-2 *trans* to the aglycon group, but not in their *cis* anomers. Accordingly, the former compounds should be cleaved under alkaline conditions considerably more readily than the latter, assuming that neighboring group participation plays a dominant role in their hydrolysis. Table 1 records the first-order rate constants obtained for the hydrolyses of anomeric 4-chlorophenyl D-ribofuranosides. In both reactions the dependence of the rate constants on the base concentration seems to be similar to that presented for the alkaline cleavage of phenyl β-D-xylofuranosides.[1] In other words, the observed first-order rate constant, k(obs), can be expressed by eqn. (1), where K stands for the equilibrium

$$k(\text{obs}) = kK[\text{OH}^-]/(1+K[\text{OH}^-]) \quad (1)$$

Table 1. First-order rate constants for the hydrolysis of 4-chlorophenyl α- and β-D-ribofuranosides in aqueous sodium hydroxide solutions of various concentrations[a] at 363.15 K.

$[\text{OH}^-]$/mol dm^{-3}	$k/10^{-6}$ s^{-1}	
	α-Riboside	β-Riboside
0.10	0.37(2)	200(5)
0.20	0.69(3)	390(5)
0.30	1.00(4)	438(6)
0.40	1.21(6)	590(9)
0.50	1.25(6)	633(7)

[a] The ionic strength was adjusted to 0.50 mol dm^{-3} with sodium chloride.

constant for the initial ionization and k denotes the rate constant for the subsequent heterolysis. As previously stated,[1] parameters K and k can be evaluated from the slope and intercept of the plot $[\text{OH}^-]/k$(obs) *vs.* $[\text{OH}^-]$. Application of this method to the data in Table 1 gives values of $K=(1.3\pm0.4)$ dm^3 mol^{-1} and $k=(3.3\pm0.7)\times10^{-6}$ s^{-1} for the hydrolysis of 4-chlorophenyl α-D-ribofuranoside, and values of $K=(1.8\pm0.5)$ dm^3 mol^{-1} and $k=(1.34\pm0.25)\times10^{-3}$ s^{-1} for the cleavage of the β-anomer. In other words, the extent of the pre-equilibrium ionization is with both substrates nearly the same, but the anionic form of the β-anomer decomposes several hundred times faster than that of the α-anomer. The reactivity difference of this magnitude strongly suggests that the hydrolysis of the β-anomer, having *trans*-1,2-configuration, proceeds by intramolecular displacement of the 4-chlorophenoxy group by the C-2 oxyanion. The present data do not allow any firm conclusions concerning the mechanism for the cleavage of the α-anomer, but for the reasons presented earlier[1,4] a spontaneous decomposition of the anionic substrate to a phenoxide and a cyclic oxocarbenium ion seems reasonable.

To ascertain that the rate-retarding effect of changing the 1,2-configuration from *trans* to *cis* far exceeds the influences that the other configurational variations exert, and is thus mechanistically

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Table 2. First-order rate constants for the hydrolysis of 4-acetylphenyl α-D-arabino- and β-D-ribofuranosides in aqueous sodium hydroxide solutions of various concentrations[a] at 343.15 K.

$[OH^-]$/mol dm^{-3}	$k/10^{-4}$ s^{-1}	
	α-Arabinoside	β-Riboside
0.02	4.24(5)	2.44(2)
0.04	7.79(6)	4.66(2)
0.06	11.24(11)	6.11(3)
0.08	12.96(13)	7.60(4)
0.10	14.44(9)	9.02(4)
0.12	15.87(15)	10.28(8)
0.14	17.70(19)	11.32(4)
0.16	19.21(23)	12.59(4)
0.18	19.57(24)	13.58(7)
0.20	21.4(2)	14.22(9)

[a] The ionic strength was adjusted to 0.20 mol dm^{-3} with sodium chloride.

Table 3. Equilibrium constants, K, for the formation of an anionic intermediate in the alkaline hydrolysis of some 4-acetylphenyl aldofuranosides at 343.15 K, and first-order rate constants, k, for the heterolysis of this species.

Furanoside	K/dm^3 mol^{-1}	$k/10^{-3}$ s^{-1}
β-D-Xyloxide	6.7(0.9)[a]	16.3(1.6)[a]
α-D-Arabinoside	6.8(0.5)	3.6(0.1)
β-D-Riboside	4.2(0.3)	3.1(0.1)

[a] See Ref. 1.

relevant, the rates for the alkaline hydrolysis of 4-acetylphenyl α-D-arabino-, β-D-ribo-, and β-D-xylofuranosides were compared. The kinetic data obtained for these compounds, all having the C-2 hydroxyl group *trans* to the aglycon, are collected in Tables 2 and 3. α-Arabinoside and β-xyloside exhibit almost equal values for the equilibrium constant, K, of the initial ionization, while β-riboside shows slightly reduced acidity. The differences in the heterolysis rates are more marked, but still quite small compared to those due to a change in the 1,2-configuration. The reason for the higher reactivity of the anionic β-xyloside, compared to the other aldofuranosides studied, remains obscure.

Some further support for the neighboring group participation of C-2 oxyanion in the hydrolysis of *trans*-1,2-aldofuranosides comes from the fact that methyl β-D-ribofuranoside was found to be the only detectable product, besides 4-acetylphenol, in the sodium methoxide catalyzed methanolysis of 4-acetylphenyl β-D-ribofuranoside. This kind of retention of anomeric configuration can be accounted for by a mechanism involving rate-limiting formation of a 1,2-epoxy intermediate and a subsequent nucleophilic attack of methoxide ion at the anomeric carbon. In contrast, if the reaction would proceed *via* a cyclic oxocarbenium ion both methyl α- and β-D-ribofuranosides would be expected.

Experimental. Anomeric 4-chlorophenyl D-ribofuranosides were prepared by stannic chloride catalyzed glycosidation of peracetylated ribofuranose[5] followed by deacetylation with sodium methoxide in methanol. Equal amounts (5 mmol) of stannic chloride, 4-chlorophenol and tetra-*O*-acetyl-β-D-ribofuranose were shaken for half an hour in benzene solution (100 cm^3) at room temperature. Besides traces of ribofuranose tetraacetate, two spots with R_F values of 0.53 and 0.64 were detected on the thin layer chromatogram of the product (Silica gel F-254, chloroform – diethyl ether 9:1 [6]). This finding together with the observation of two ^{1}H NMR signals in the anomeric proton region (s at δ 5.56 and d at δ 5.77 in CCl_4) indicated the presence of both furanoid anomers. Anomerically pure 4-chlorophenyl α- and β-D-ribofuranosides were obtained by preparative TLC of the deacetylated glycoside mixture (Silica gel 60, ethyl acetate – methanol 9:1). The α-anomer melted, after crystallization from chloroform, at 107 – 109 °C (*lit.*[7] 107 – 110 °C), and exhibited the following ^{1}H NMR signals in D_2O (Jeol FX60 spectrometer): δ(C5-*H*) m 3.7 – 3.8, δ(C2,3,4-*H*) m 4.2 – 4.4, δ(C1-*H*) d 5.77, δ(C1-OC$_6H_4$Cl) q 7.26. 4-Chlorophenyl β-D-ribofuranoside had a melting point of 143 – 144 °C (*lit.*[7] 111 – 113 °C). The following ^{1}H NMR signals were observed: δ(C5-*H*) m 3.5 – 3.8, δ(C2,3,-4-*H*) m 4.3 – 4.4, δ(C1-*H*) s 5.69, δ(C1-OC$_6H_4$Cl) q 7.23. Elemental analysis of the compound gave: C 49.2; H 4.8; Cl 13.1 (calc. C 50.7, H 5.0, Cl 13.6).

4-Acetylphenyl α-D-arabino- and β-D-ribofuranosides were obtained in their peracetylated forms by fusing the furanoid sugar acetates with 4-acetylphenol in the presence of *p*-toluenesulfonic acid. Deacetylation with sodium methoxide in methanol gave crude furanoside syrups which were purified by successive crystallizations from ethyl acetate. Of the sugar acetates employed, tetra-*O*-acetyl-D-arabinofuranoside was prepared as described earlier.[8] The corresponding ribose derivative was a commercial product. 4-Acetylphenyl α-D-arabinofuranoside melted at 102 – 104 °C and had and $[\alpha]_D$ value of 113° in methanol. The following ^{1}H NMR signals were observed in D_2O (Perkin-Elmer R 10 spectrometer): δ(C1-OC$_6$H$_4$COCH_3) s 2.42, δ(C5-*H*) m 3.7 – 3.8, δ(C2,3,4-*H*) m 4.1 – 4.4,

δ(C1-*H*) d 5.73, δ(C1-OC$_6$*H*$_4$COCH$_3$) q 7.40. Elemental analysis yielded: C 57.5, H 5.9 (calc. C 58.2, H 6.0). 4-Acetylphenyl β-D-ribofuranoside had a melting point of 157–159 °C and an $[\alpha]_D$ value of −119° in methanol. For the ^{1}H NMR signals the following shifts were obtained: δ(C1-OC$_6$H$_4$COC*H*$_3$) s 2.45, δ(C5-*H*) m 3.5–3.8, δ(C2,-3,4-*H*) m 4.2–4.4, δ(C1-*H*) s 5.67, δ(C1-OC$_6$*H*$_4$-COCH$_3$) q 7.40. Elemental analysis gave: C 57.7, H 5.8 (calc. C 58.2, H 6.0).

The kinetic measurements concerning the hydrolysis of 4-acetylphenyl derivatives were performed as described earlier.[1] Hydrolyses of anomeric 4-chlorophenyl D-ribofuranosides were carried out in sealed tubes immersed in a thermostated bath. At appropriate intervals tubes were removed and the progress of the reaction was determined by measuring the absorbance of the cooled solution at the absorption maximum of 4-chlorophenoxide ion. The final values were obtained through incubation at higher temperatures.

The product analysis of the base-catalyzed methanolysis of 4-acetylphenyl β-D-ribofuranoside was carried out by TLC of the reaction solution.[9] The substrate (20 μmol) was dissolved in a 1 mol dm^{-3} solution of sodium methoxide in methanol (0.5 cm^3). After 4 h incubation at 60 °C TLC on Silica gel 60 (ethyl acetate – 2-propanol – water 65:25:12) revealed the presence of 4-acetylphenol (R_F 0.95), methyl β-D-ribofuranoside (R_F 0.64) and traces of the starting material (R_F 0.84). No sign of methyl α-D-ribofuranoside (R_F 0.43) or methyl α- or β-D-ribopyranoside (R_F 0.37 and 0.60) could be detected. The R_F values given above were determined by standard compounds prepared as described earlier.[10,11]

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