Reactions at High Pressure. Part 8.† The Mechanisms of Acid-catalysed Hydrolyses of Glycosides

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Rates of acid-catalysed hydrolysis for 19 glycosides, both furanosides and pyranosides, have been measured at pressures between 1 and 1 500 bar.‡ Volumes of activation have been determined for these reactions and were found to show a markedly parallel trend to the entropies of activation for the same reactions. In particular, alkyl furanosides have $\Delta\bar{V}$ − 2 to −10 cal K^{-1} mol^{-1} § while the corresponding pyranosides have $\Delta\bar{V}$ = 10—17 cal K^{-1} mol^{-1}. It is inferred that the former react by an $A2$ mechanism and the latter by an $A1$ type.

THE hydrolyses of acetals under acid-catalysed conditions normally proceed by the $A1$ mechanism;[1,2] electron release in the aldehyde moiety greatly facilitates reaction (ρ −3.5) consistent with stabilisation of a cationic intermediate. There is a substantial solvent isotope effect (k_{H_2O}/k_{D_2O} *ca.* 2.6) indicating that the acidic properties of the solvent are more important than nucleophilic properties, and entropies of activation are positive ($\Delta S^{\ddagger}$ *ca.* 5—20 cal K^{-1} mol^{-1}) consistent with release of an alcohol molecule in the rate-determining step.[3] Glycopyranosides appear to fit into this generalisation [4] but some years ago it was shown [5] that the corresponding furanosides differ in exhibiting negative hydrolytic entropies of activation, $\Delta S^{\ddagger}$ −2.5 to −10 cal K^{-1} mol^{-1}. This result presumably signals a mechanistic change but several possibilities must be considered as the possible origins of this difference.

(a) There may be change of mechanism to an $A2$ type in the furanoside series. (b) Glycosides are unsymmetrical acetals and either the anomeric oxygen or the ring oxygen may in principle act as the leaving group. That is, ring-opening may occur in one case but not the other. It might be predicted that $\Delta S^{\ddagger}$ would be less positive for ring-opening than for release of a free alcohol molecule. Solvation differences, however, might make prediction unreliable. (c) There may be differences in the degree of reversibility of the slow step, the C–O bond fission. Return of this type might be more important in a ring-opening reaction since the alcoholic group and the carbocation remain attached. (d) Differences in solvation may exist in the two series, either in the glycosides or in the transition states. An increase in solvation during activation would be associated with a negative contribution to $\Delta S^{\ddagger}$. (e) A combination of two or more of these factors may be operating.

In order to try and resolve this problem further, we have applied a further variable, pressure, in order to determine the volumes of activation of these reactions and have also measured part of the volume profile for an isomeric pair of glycosides. The physical interpretation of volume changes is often easier than that of entropy changes and, moreover, absolute volume measurements may be readily made so that differences in initial state quantities may be seen.

EXPERIMENTAL

Preparations of the glycopyranosides and glycofuranosides which were studied, have previously been published.[5] Hydrolytic studies were carried out in 2M-perchloric acid in the sampling cell previously described, contained in a vessel of polytetrafluoroethylene.[6] The progress of the reaction was monitored by polarimetry. In general, rate measurements were made at 1 bar and at one high pressure between 1 200 and 1 500 bar, measurements being made in duplicate. In one case (for methyl β-D-galactofuranoside) rate measurements were made at eight pressures up to 2 000 bar in order to examine the curvature of a plot of ln k with pressure. Since this latter relationship was almost linear, volumes of activation were calculated according to equation (1). Results are presented in Table 1 and Figure 1.

$$\Delta V^{\ddagger} = -RT(\ln k_p - \ln k_1)/(P - 1) \qquad (1)$$

TABLE 1

Entropies and volumes of activation for acid-catalysed hydrolyses of some glycosides

	Pyranosides		Furanosides	
Glycoside	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}	$\Delta V^{\ddagger}$/ cm^3 mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}	$\Delta V^{\ddagger}$/ cm^3 mol^{-1}
Methyl α-D-galacto-	+17.7	+5.4	−9.4	−3.6
Methyl β-D-galacto-	+13.3	+4.9	−8.7	−3.9
Ethyl β-D-galacto-	+11.2	+5.0	−7.1	−4.4
Phenyl β-D-galacto-	+4.1	0	+6.7	+1.3
Methyl β-D-gluco-	+16.5	+6.2	−9.0	−3.5
Phenyl β-D-gluco-	+10.8	+2.9	+14.7	+3.8
Methyl α-D-manno-	+10.4	+3.6		
Methyl β-L-arabino-	+15.2	+6.1	−2.8	−2.0
Methyl α-D-xylo-	+15.7		−8.3	−4.6
p-Cresyl α-D-gluco-			+12.0	+3.4
p-Anisyl β-D-gluco-			+15.2	+3.5

† Part 7, ref. 9.
‡ 1 bar = 10^5 Pa.
§ 1 cal = 4.184 J.

Partial molar volumes were measured from the densities of standard solutions of the solutes in the concentration range $10^{-2} < M < 10^{-1}$. Densities were obtained by means of a pyknometer of *ca.* 80 ml capacity, thermostatting at 25 ± 0.002 °C. The partial molar volume $\bar{V}$ was obtained using equation (2) where ρ, ρ_0 are densities of solution and solvent

$$\bar{V} = \frac{1\,000(\rho_0 - \rho)}{\rho_0 c} + \frac{M}{\rho_0} \qquad (2)$$

respectively, c the concentration, and M the molecular weight of the solute. Values are shown in Table 2.

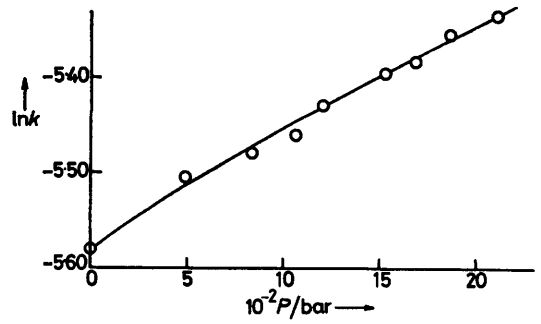

FIGURE 1 Rates of hydrolysis of methyl β-D-galactofuranoside in 2M aqueous perchloric acid at 38.7 °C as a function of pressure

TABLE 2

Partial molar volumes of some substrates in water at 25 °C

	$\bar{V}$/cm³ mol⁻¹
Methyl β-D-glucofuranoside	117.7
Methyl β-D-glucopyranoside	133.6
Glucose (α-D ⇌ β-D)	111.2
Methanol	38.0

DISCUSSION

The most striking observation (Figure 2) is the considerable correlation between volumes and entropies of activation. If one considers only the alkyl glycosides, the pyranosides and furanosides fall into two well separated groups of points. Adding in the aryl glycosides, the correlation is enhanced but the latter compounds do not seem to fall within the same groups. The values of $\Delta V^{\ddagger}$ are, in reality, composite quantities and contain the volume of protonation of the glycoside, $\Delta\bar{V}$, in addition to the volume of activation of the rate-determining step. It is likely that $\Delta\bar{V}$ is negligible since proton transfer is between two oxygen bases with no additional creation of charge. In any event its value should not differ significantly for the two series. The parallel variation of $\Delta V^{\ddagger}$ and $\Delta S^{\ddagger}$ in a series of related reactions has been noted before [6] and clearly points to a common origin of the two effects. The interpretation favoured assumes there is a gradation in the pattern of solvation change along the series, an increase of solvent co-ordination bringing about both a decrease in the entropy and the volume of the system and *vice versa*. The same may be true of the present case. On the other hand, an alternative explanation, that changes of both $\Delta V^{\ddagger}$ and $\Delta S^{\ddagger}$ for furanosides might be in the opposite sense to those for pyranosides due to differences in the initial state solvation of the substrates, may be tested.[7] Solvation differences in the two series of glycosides should show up in their partial molar volumes. If those for furanosides were generally greater than those for pyranosides and if the volume of the products, glucose and methanol, were in between the two then the observed values might result. However, in one case for which a volume profile has been measured, this possibility is not found to hold. The partial molar volume of the furanoside appears to be less than that of the pyranoside so that their respective volume changes diverge initially (Figure 3). We take this as indicative of a distinctly different mechanism of hydrolysis for the two isomers. The mechanism of pyranoside hydrolysis may be assumed to be *A*1 by the criteria mentioned above and, additionally, an oxygen primary kinetic isotope effect associated with the anomeric oxygen (k_{16}/k_{18} 1.03 [8]) in the hydrolysis of methyl α-D-glucopyranoside shows the rate-determining expulsion of methanol rather than ring-opening to be occurring. This type of evidence is not available for the corresponding furanoside for which the evident difference in mechanism is open to speculation. Either an *A*1 mechanism with ring-opening or an *A*2 mechanism might be considered. While the former might conceivably lead to more negative values of both $\Delta V^{\ddagger}$ and $\Delta S^{\ddagger}$, the latter should certainly do so. Therefore we tend to favour this interpretation.

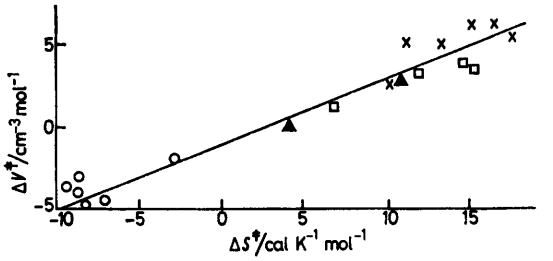

FIGURE 2 Correlation between entropies and volumes of activation for the acidic hydrolysis of some glycosides: ×, alkyl pyranosides; ▲, aryl pyranosides; ○, alkyl furanosides; □, aryl furanosides

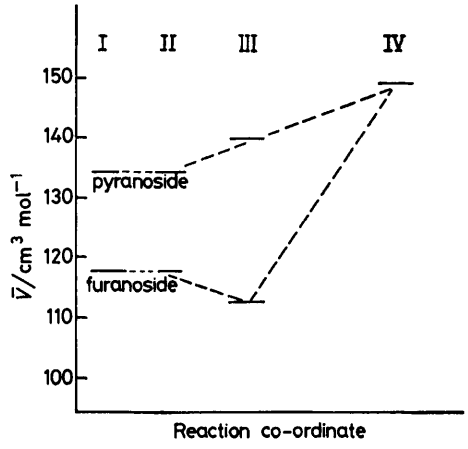

FIGURE 3 Volume profile for the hydrolyses of methyl α-D-glucopyranoside and -furanoside: I, glycoside; II, protonated glycoside; III, transition state; IV, glucose + methanol

The mechanistic interpretation of the activation volumes and entropies for the hydrolyses of aryl glycosides is less clear-cut. The limited amount of data seems to indicate there is not a clear mechanistic change between furanosides and pyranosides and it is possible that solvation changes are uniformly reduced as a result of the bulky aryl group near the reaction centre. There should be more incentive for ring-opening in these cases since the oxocation produced intermediately is capable of further stabilisation by the aromatic ring so it may be that these compounds react by yet another mechanism.

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