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Note

Effect of axial hydroxyl groups upon the hydration of glycopyranosides: evidence from mechanistic studies of acid hydrolysis*

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From studies of the thermodynamic properties of aqueous solutions of D-glucose and sucrose, Taylor and Rowlinson[1] concluded that "... there is strong hydrogen bonding between the sugars and the surrounding water molecules. This binding is apparently stronger, or more abundant, than that between the water molecules themselves." This statement has since been corroborated by an impressive variety of independent evidence. Measurements of intrinsic viscosities and diffusion coefficients[2], apparent molal volumes and compressibilities[3], heats of solution, heat capacities and dielectric constants[4], and ^{17}O-n.m.r. and dielectric relaxation[5], all support the idea that sugar molecules, in aqueous solution, are surrounded by a fairly well-defined, solvational sheath of water molecules. This structure is more ordered than that of pure water, and it breaks down with increasing temperature, but, even at 80°, a remnant of it is still demonstrable[5]. In the acid hydrolysis of sucrose, it may explain the extraordinary temperature-dependence[6] of the activation energy between 0 and 40°.

This idea leads automatically to the question of how the stability of the solvational sheath varies with the proportion of axial hydroxyl groups on a pyranose ring. Many authors have recognised that equatorial groups are, in principle, more accessible to solvation than axial ones, and an apparent solvent-dependence of the conformational energy of the hydroxyl group[7] has been interpreted in these terms[8]. From thermodynamic studies of the anomerisation of several reducing sugars in water[9], Kabayama and Patterson[10] inferred that HO-1 was less hydrated when axial than when equatorial. By ^{17}O-n.m.r. relaxation, Tait *et al.*[5] were unable to detect any difference in the extent of hydration of D-glucose, D-mannose, and D-galactose, but D-ribose was clearly less-hydrated than these three hexoses. In his pioneering work on the conformational analysis of pyranoses in aqueous solution, Angyal[11] was unable to detect any difference between an $O_{eq}:O_{eq}$ and an $O_{eq}:O_{ax}$ interaction, and assigned a value of 0.35 kcal.mol^{-1} to both. Recent calculations by Rees and Smith[12] suggest, however, that when a conformer contains at least two, and especially three,

*Dedicated to Professor Stephen J. Angyal on the occasion of his retirement.

$O_{eq}:O_{eq}$ interactions, it is significantly more stable than Angyal's value would predict.

We have recently discussed[13] the significance of the hydration phenomenon in mechanistic studies of the acid hydrolysis of glycopyranosides[14]. The difficulties that arise when the Zucker–Hammett[15] and Bunnett[16] criteria are used to distinguish between the A-1 and A-2 mechanisms of hydrolysis[14] are generally acknowledged[13,14,17–20]. Although independent evidence[13,14,18–21] strongly indicates that the mechanism is actually A-1, the slopes of the Zucker–Hammett plots are usually different from the expected[17] value of unity, and they vary with the identity of the acid[13,17,20]. For some acids, but apparently not for others, the plots are curved, as if to suggest an A-2 mechanism[13,18,19]. The Bunnett ω-parameter, which should be close to zero for an A-1 mechanism, varies chaotically from -5 to $+3$, depending upon the identity of the acid and the range of acid-concentrations used[16–19].

These criteria depend for their validity upon the explicitly stated[16] (but sometimes forgotten) assumption that water can participate in the reaction only as the initial, proton-transferring agent, or as a nucleophile[15–17]. Their significance in the present context lies in the fact that the ω-parameter is believed, on empirical[16] and theoretical[13] grounds, to be correlated with the *change* in the number of water molecules closely associated with the substrate molecule, when it passes through the transition state. If the molecule is already strongly hydrated in its ground state, it is obvious that the criteria must lose their original significance, unless the transition state is hydrated to the same extent, and in the same way. Bunnett explicitly recognised[16] that his criterion appeared to be disturbed by "unusual hydration", implying that the latter condition generally is not fulfilled*.

This situation would be too complicated to be useful, were it not for recent evidence[13] which suggests that, at least for pyranosides, the transition states may not be "unusually hydrated" at all. For the methyl D-glucopyranosides in sulphuric acid at 70°, it was found that increasing the acid concentration (namely, decreasing the activity of water, a_w) led to a rather small decrease in $\Delta H^{\ddagger}$, and a much larger decrease in $T\Delta S^{\ddagger}$. This depressed the rate of reaction, giving slopes of considerably less than unity for the Zucker–Hammett plots (corresponding to positive values for the Bunnett ω-parameter).

As it is nonsensical to infer that the mechanism changes from A-1 to A-2 as a_w *decreases*, the dramatic decrease in $\Delta S^{\ddagger}$ must mean that *water of hydration is released in passing through the transition state*. This would imply that the degree of hydration of the transition state is comparatively invariant and low, whereas the changes in $\Delta S^{\ddagger}$, and their effect upon the Zucker–Hammett slope, reflect changes in the degree of solvation of the *ground* state.

A relevant, incidental finding in this work[13] was that decreasing a_w led to an increase in the magnitude of the anomeric effect[24], and, hence, to different Zucker–Hammett slopes for α and β anomers.

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*Salt effects[22] can also cause anomalies[16], and may be important for glycosides with such bulky, non-polar aglycons as *tert*-butyl[23]. They do not, however, appear to be significant for methyl glycopyranosides[13].

Exactly why the hydrates should decompose in the transition state is a matter for conjecture. The collision theory implies, of course, that activation is a "molecule-battering" process, and it could scarcely occur without some disturbance of the solvational sheath. More particularly, the transition state for a glycopyranoside is probably close to a half-chair[25], in which the distances between *all* the ring-substituents have changed. Kabayama and Patterson[10] have pointed out that, for *vic*-diols, the distance between two oxygen atoms in a true *gauche* conformation is almost identical with that between two hydrogen-bonded oxygen atoms in ordinary ice or liquid water (~2.8 Å)[26]. It is therefore possible that the solvational sheath around a glycopyranoside molecule bears some structural resemblance to ice, and this sheath cannot be maintained when the chair conformation is distorted.

Regardless of the explanation, we have inferred that measurements of Zucker–Hammett slopes and activation parameters provide a novel way of studying the hydration of glycopyranosides in their ground states. The new findings in Table I are reported in this context. Sulphuric acid was chosen because of its strong capacity to dehydrate glycosides*. Values of H_0 were corrected for temperature[17]. At 70°, the Zucker–Hammett plots were linear, within experimental error, in the measured range of acid-concentrations (0.5–6.0M), and the reported slopes (*S*) were measured at this temperature. Rate coefficients were also measured at 60, 80, and 90° in 0.5M acid, and at 30, 40, 50, and 60° in 6.0M acid, to obtain the activation parameters, which are calculated for a temperature of 70°. The experimental details were otherwise as described previously[13].

Because of the anomeric effect, the results for the β-D-gluco- and β-D-galacto-pyranosides must be considered separately. The others may be compared directly. In every case, it may be seen that an axial hydroxyl group brings the Zucker–Hammett slope closer to unity, and reduces the extent to which $\Delta S^{\ddagger}$ decreases with increasing acid-concentration. It should perhaps be noted that $\Delta S^{\ddagger}$ is made up, in part, of the entropy change associated with the initial protonation. This is usually positive[27],

TABLE I

ZUCKER–HAMMETT SLOPES (*S*) AND ACTIVATION PARAMETERS[a] FOR HYDROLYSIS OF METHYL GLYCOPYRANOSIDES IN SULPHURIC ACID AT 70°

Glycoside	S	*0.5M H_2SO_4*		*6.0M H_2SO_4*	
		$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Methyl α-D-glucopyranoside	0.68	34.1	17.4	33.8	7.7
Methyl α-D-mannopyranoside	0.87	31.2	11.2	30.7	7.9
Methyl α-D-galactopyranoside	0.77	32.4	15.7	31.5	10.5
Methyl β-L-arabinopyranoside	0.89	30.8	13.1	30.2	10.0
Methyl β-D-glucopyranoside	0.82	33.8	17.6	31.0	7.8
Methyl β-D-galactopyranoside	0.88	31.4	12.5	29.7	6.3

[a]Limits of error are estimated to be ±0.5 kcal.mol^{-1} for $\Delta H^{\ddagger}$, and ±1.0 cal.mol^{-1}.K^{-1} for $\Delta S^{\ddagger}$.

*The formation constants of the hydrates are very different in different acids at the same H_0. Possible reasons for this have been discussed[13].

probably because proton-transfer is itself solvent-releasing. Some decrease in $\Delta S^{\ddagger}$ with decreasing a_w might therefore be expected for any acid-catalysed reaction. The notorious anomalies that occur with "unusually hydrated" substrates, together with the clear effect of configuration now reported, nevertheless indicate that it is correct to interpret the activation parameters in the way described.

In conclusion, the results support the idea that axial hydroxyl groups destabilise, but do not completely eliminate, the solvational sheath of pyranose rings in aqueous solution. The effect of this upon conformational energies is evidently rather small, and the results serve mainly to illustrate the sensitivity of kinetic methods for studying solvation.

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