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THE ACID HYDROLYSIS OF PHENYL α-D-MANNOPYRANOSIDES

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ABSTRACT

The influence of the acid concentration and of the substituent group on the hydrolysis of substituted phenyl α-D-mannopyranosides has been investigated. Most probably, these derivatives are hydrolysed *via* a unimolecular (A-1) mechanism. Application of the Hammett–Zucker, Bunnett, and entropy criteria leads to contradictory results. Substituent groups have practically no influence on the activation parameters.

INTRODUCTION

In previous papers[1–5], the acid-catalysed hydrolysis of series of alkyl and aryl D-glycopyranosides and the influence of the acid concentration on the rate coefficients have been described. The results of these studies indicated that the hydrolysis proceeds *via* the generally accepted, unimolecular, A-1 mechanism[6]. This mechanism involves a rapid, equilibrium-controlled protonation of the glycosidic oxygen atom to give the conjugate acid. This acid decomposes, in a slow, rate-limiting, unimolecular heterolysis, to a glycosyl carbenium–oxonium ion which then adds water. In all of the cases studied, the Zucker–Hammett criterion[7,8] and the magnitude of the entropies of activation were in accordance with the A-1 mechanism. However, the Bunnett criteria[9,10] suggested that the hydrolysis should proceed *via* a mechanism in which the rate-controlling step should involve the participation of water.

Having synthesized a number of substituted phenyl α-D-mannopyranosides in order to study their enzymic hydrolysis by α-D-mannosidases, we also used these compounds to study their acid-catalysed hydrolysis. Sufficient data were collected to test the Hammett and Bunnett criteria, and to calculate the activation parameters, in particular the entropy of activation.

RESULTS AND DISCUSSION

Influence of the acid concentration

For the unsubstituted and two substituted phenyl α-D-mannopyranosides, the pseudo-first-order rate coefficient k_1 (ln e; sec^{-1}) was determined at constant temperature (60°) and various concentrations of hydrochloric acid (Table I). The values show that there exists no linear relation between k_1 and the stoichiometric concentration of the acid. However, a plot of log k_1 *versus* the Hammett acidity function[7,8] H_0 is approximately linear. A least-squares fit of the data of Table I yielded the values given in Table II, where b represents the slope and r the correlation coefficient. In each case, the deviation of the slope from the theoretical value —1 is statistically significant, and thus the requirement of unit slope is only approximately fulfilled. Because the plot of log k_1 *versus* H_0 is slightly curved, the data of Table I were fitted to an equation of the form: $\log 10^5 k_1 = A + BH_0 + C(H_0)^2$. The coefficients A–C, together with the standard error of the estimate $s_{y/x}$ and the multiple correlation coefficient R, are gathered in Table II. They can be used to calculate k_1 (60°) at any acid concentration in the range 0.5–5M hydrochloric acid. The value (>0.9) of the partial correlation coefficient for C indicates that the inclusion of the quadratic term significantly improves the equation, and thus that the curvature is real. The value of B shows that the slope approaches the theoretical value of —1 at low concentrations of acid, but deviates at higher concentrations of hydrochloric acid. However, such small deviations do not invalidate the Zucker–Hammett criterion, and therefore the hydrolysis should proceed *via* the generally accepted, unimolecular, A-1 mechanism, without participation of water in the rate-limiting step.

Plots of $H_0 + \log 10^5 k_1$ *versus* log A (where A is the activity of water) are slightly curved. A graphical estimation of the slopes yields values from +1.4 to +2.7. As these slopes represent the Bunnett *w*-parameter[9], the positive values should mean that water reacts as a nucleophile in the rate-limiting step and, thus, that the reaction proceeds *via* a bimolecular mechanism.

Another Bunnett parameter[9], w^*, can be calculated by plotting $\log k_1 - \log [\mathrm{HCl}]$ *versus* log A. Again, the plots are slightly curved. Graphical estimation

TABLE I

INFLUENCE OF THE ACID CONCENTRATION ON 10^5 k_1 (SEC^{-1}) AT 60°

Substituent	*HCl* (M) H_0[a]	0.5 +0.20	1.0 −0.20	2.0 −0.69	3.0 −1.05	4.0 −1.40	5.0 −1.76
None		5.1	12.0	33.4	74	143	274
p-Nitro		3.3	8.6	22.6	45	86	151
p-Ethyl		4.0	10.4	27.5	60	119	226

[a] From Ref 8, p. 39.

TABLE II

COEFFICIENTS OF THE ZUCKER–HAMMETT PLOT (60°)

Substituent	*b*	$-r$	*A*	*B*	*C*	$s_{y/x}$	*R*
None	−0.89 ± 0.02	0.999	0.893	−0.963	−0.0463	0.01	0.9999
p-Nitro	−0.85 ± 0.03	0.998	0.726	−0.983	−0.0896	0.01	0.9999
p-Ethyl	−0.91 ± 0.02	0.999	0.788	−0.980	−0.0480	0.02	0.9998

yields w^* values from -3.5 to -4.1. Since $w^* < -2$ indicates the participation of water in the rate-limiting step, the value of w^* is incompatible with an A-1 mechanism. The same conclusion is reached when the third Bunnett parameter[10], Φ, defined by the equation $H_0 + \log 10^5 k_1 = \text{constant} + \Phi\,(H_0 + \log[\text{HCl}])$, is calculated. Graphical estimation yields Φ values from $+0.23$ to $+0.36$. As $0.22 < \Phi < 0.56$ indicates[10] an A-2 mechanism, the A-1 mechanism is incompatible with the Φ-values.

The results of this investigation on the influence of the concentration of the acid are in full agreement with those of our previous studies[1-5, 11, 12]. Again, the application of the Hammett, the Bunnett, and the entropy (see further) criteria leads to contradictory conclusions as to the nature of the rate-limiting step. However, in our previous studies[11], we have shown that, in those cases where the plots of $\log k_1$ against H_0 yield nearly straight lines, the sign of w and Φ are *a priori* determined by the value of the slope b in the Hammett plot. When $b > -1$ (*e.g.*, -0.9), then w and Φ become positive. Thus, the experimentally found values for w and Φ are a necessary consequence of the slope values (*ca.* -0.9) of the Hammett plots. Because of this *a priori* correlation, the mechanistic meaning of the w and Φ parameters is uncertain. The fundamental question is whether a deviation of the slope b from unity invalidates the Zucker–Hammett criterion. Since it is generally accepted that this is not the case, the Hammett criterion remains the fundamental one.

Influence of the substituents

For eleven substituted phenyl α-D-mannopyranosides, k_1 was determined in M aqueous hydrochloric acid at five temperatures. All of the reactions were pseudo-first-order, and $\ln k_1$ was a linear function of $1/T$. Inspection of the rate coefficients and activation parameters (Table III) reveals that the substituent has practically no influence on the reaction rate or on the activation parameter. These findings are in agreement with previous results for aryl α-D-glucopyranosides[13] and aryl α-D-

TABLE III

INFLUENCE OF THE SUBSTITUENT ON THE REACTION PARAMETERS IN M HCl

Substituent	$10^5 k_1$ *(sec^{-1})*			E_A *(kJ mol^{-1})*	$\Delta H^\ddagger$ *(kJ mol^{-1})*	$\Delta S^\ddagger$ *(60°) (J K^{-1} mol^{-1})*	$\Delta G^\ddagger$ *(60°) (kJ mol^{-1})*
	60°	*70°*	*80°*				
None	12.0	44.9	157	126 ± 0.4	119	49 ± 5	107
p-Ethyl	10.4	39.1	136	125 ± 1.0	118	47 ± 2	107
p-Methyl	9.6	36.7	130	128 ± 0.4	125	53 ± 2	108
p-Bromo	8.8	34.4	123	129 ± 3.0	127	58 ± 9	107
p-Chloro	9.4	35.5	125	127 ± 2.0	124	49 ± 5	108
p-Methoxy	9.1	34.4	121	127 ± 0.9	124	49 ± 2	108
p-Nitro	8.6	29.7	103	125 ± 1.6	122	42 ± 5	108
m-Methyl	11.4	45.7	170	132 ± 3.1	130	68 ± 9	107
m-Bromo	10.0	37.8	133	127 ± 1.2	124	49 ± 4	107
m-Nitro	7.5	26.7	88	121 ± 0.4	119	32 ± 4	107
p-Nitro-*o*-chloro	10.3	35.7	115	119 ± 0.9	116	25 ± 4	107

galactopyranosides[5], and indicate that the rate of hydrolysis of phenyl α-D-glycopyranosides is unaffected by the nature of the substituent group. For substituted phenyl β-D-glucopyranosides[14], β-D-glucosiduronic acids[15], β-D-galactopyranosides[4], and β-D-xylopyranosides[2], it was found that there exists a linear free-energy relationship between log k_1 and the Hammett substituent constant σ. The reaction constant ρ was always a small (but significant) negative value. The low value of the experimental reaction constant ρ is explained by the fact that the substituent has an influence on both the formation of the conjugate acid and its subsequent heterolysis, but affects these two processes in opposing manners, thus partially cancelling each other. The above findings suggest that the cancelling is more complete for α-D-glycopyranosides than for β-D-glycopyranosides.

Although the positive values of $\Delta S^\ddagger$ cannot be regarded as *proof* of the A-1 unimolecular mechanism, they make an A-2 bimolecular mechanism very improbable. Both $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values are of the same order of magnitude as found for other aryl (α and β) glycopyranosides.

For three substituted phenyl α-D-mannopyranosides, we determined k_1 in 5M HCl at five temperatures. In each case, ln k_1 was a linear function of 1/T. Assuming a linear dependence of log k_1 on H_0 (*cf.* influence of the concentration of acid), the activation parameters were then calculated. From the data in Table IV, in comparison with those in Table III, it can be seen that the activation parameters remain constant within experimental error, and that none of the $\Delta S^\ddagger$ values becomes negative. Consequently, there is no indication of a change to the A-2 bimolecular mechanism at higher concentrations of the acid.

TABLE IV

ACTIVATION PARAMETERS IN 5M HCl

Substituent	*$10^5 k_1$ (sec^{-1})*			E_A *(kJ.mol^{-1})*	$\Delta H^\ddagger$ *(kJ mol^{-1})*	$\Delta S^\ddagger$ *(60°) (J K^{-1}.mol^{-1})*	$\Delta G^\ddagger$ *(60°) (kJ mol^{-1})*
	40°	*50°*	*60°*				
None	15.2	66.0	262	124 ± 1.6	121	42.0 ± 5.3	107
p-Nitro	9.8	40.3	153	119 ± 2.3	116	24.5 ± 3.5	108
p-Ethyl	12.6	57.7	241	128 ± 2.1	125	54.3 ± 5.3	107

CONCLUSION

The evidence available indicates that aryl α-D-mannopyranosides are hydrolysed *via* the generally accepted, unimolecular (A-1) mechanism, without participation of water in the rate-limiting step. Again, the Bunnett criteria are not in accordance with this mechanism. The substituent group has practically no effect on the reaction parameters. The results of this study are thus in full agreement with our previous[1–5, 11, 12], analogous investigations.

EXPERIMENTAL

The synthesis of the substituted phenyl α-D-mannopyranosides was performed as described previously[16]. The hydrolysis of the mannosides was followed at 436 nm with a Perkin–Elmer 141 photoelectric polarimeter, and jacketed polarimeter tubes connected to an ultrathermostat bath. The pseudo-first-order rate coefficients (ln e; $\sec^{-1}$) were calculated from least-squares fits of plots: log $(\alpha \pm \alpha_\infty)$ *versus* time. The values of α_∞ were determined experimentally for corresponding solutions of D-mannose. Some rate coefficients (especially those in 5M HCl) were also determined by the Guggenheim[17] method. These duplicate runs agreed within the estimated error. Calculations of the thermodynamic activation parameters were based on the absolute reaction-rate theory[17]. H_0 and log A values were taken from Ref. 8.

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