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THE ACID HYDROLYSIS OF SUBSTITUTED PHENYL α-D-GALACTOPYRANOSIDES

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ABSTRACT

Rate coefficients and activation parameters were determined for the hydrochloric acid-catalysed hydrolysis of substituted phenyl α-D-galactopyranosides. Application of the Hammett–Zucker and the Bunnett criteria leads to contradictory conclusions about the mechanism. Substituents have only a small influence on the reaction. Under comparable conditions, the phenyl α-D-galactopyranosides hydrolyse faster than the corresponding β anomers. Most probably, these α anomers hydrolyse *via* the cyclic mechanism with protonation of the exocyclic oxygen atom.

INTRODUCTION

In recent years, the acid-catalysed hydrolysis of β-D-glycopyranosides has been extensively investigated and the general mechanism seems to be well established. It involves a fast, equilibrium-controlled protonation of the exocyclic oxygen atom, followed by the unimolecular, rate-limiting heterolysis of the conjugate acid to a glycosyl oxonium–carbonium ion (A-1 mechanism, without ring-opening). With α-D-glycopyranosides, in which the aglycon group is axially attached, much less work has been done. Some studies[1–4] indicate that the α anomers might be hydrolysed by a more-complex mechanism. For further details on this subject, the review by BeMiller[5] may be consulted.

In a previous paper[6], we described the acid-catalysed hydrolysis of a series of substituted phenyl β-D-galactopyranosides. We now report on a parallel study of the hydrolysis of substituted phenyl α-D-galactopyranosides.

RESULTS AND DISCUSSION

Influence of the acid concentration. For a number of substituted phenyl α-D-galactosides, the pseudo-first-order rate coefficient k_1 (ln e; sec^{-1}) was determined at constant temperature and various concentrations of hydrochloric acid (Table I). These values clearly show that there exists no linear relation between k_1 and the stoichiometric concentration of the acid. Moreover, and in contrast to aryl β-D-galactosides[6,7]

no linear relationship between log k_1 and the Hammett[8,9] acidity function H_0 could be found for acid concentrations higher than ~2M. For the lower concentrations, the plot of log k_1 *versus* H_0 was approximately linear. A least-squares fit of the data (0.1 to 2M) yielded the values given in Table II, where b represents the slope and its estimated standard error, and r the correlation coefficient. The deviation of the slope from the theoretical value −1 is statistically significant, and thus the requirement of unit slope is only approximately fulfilled. This deviation is still too small to invalidate the Zucker–Hammett criterion, and therefore the hydrolysis should proceed *via* a unimolecular A-1 mechanism, without participation of water in the rate-limiting step.

TABLE I

INFLUENCE OF THE ACID CONCENTRATION ON THE RATE COEFFICIENT $10^5 k_1$ (SEC^{-1})

Substituent	*Temp.* (*degrees*)	*HCl* (M) H_0[a]	*0.1* *+0.98*	*0.25* *+0.55*	*0.50* *+0.20*	*1.00* *−0.20*	*2.00* *−0.69*	*3.00* *−1.05*	*4.00* *−1.40*	*5.00* *−1.76*
None	60		—	9.3	16.5	38.4	108	231	445	825
p-Bromo	50		—	2.07	4.2	8.7	25.2	54.3	103	193
p-Nitro	61		3.0	8.0	14.8	34.9	97	196	373	609
p-Ethoxy	74		11.8	31.0	68.9	163	444	—	—	—
	60		—	—	10.3	25.7	101	174	309	550

[a]From Ref. 9, p. 39.

TABLE II

COEFFICIENTS OF THE ZUCKER–HAMMETT PLOT

Substituent	*Temp* (*degrees*)	b	−r	*A*	*−B*	*C*	*D*	$s_{y/x}$	*R*
None	60	0.874 ±0.018	0.9995	1.402	0 900	+0.602	+0.048	0.005	0.9999
p-Bromo	50	0.869 ±0.022	0.9990	0.743	0.982	−0 014	+0.026	0.008	0.9999
p-Nitro	61	0.860 ±0.091	0.9871	1.382	1.044	−0.232	−0.052	0.037	0.9987
p-Ethoxy	60	0.945 ±0.013	0.9997	1.212	1.040	+0.024	+0.071	0 057	0.9984

TABLE III

w AND Φ PARAMETERS

HCl (M)	*−Log A*	$H_0+log[HCl]$	$H_0+log\ 10^5 k_1$			
			Phenyl (*60°*)	p-*Bromophenyl* (*50°*)	p-*Nitrophenyl* (*61°*)	p-*Ethoxyphenyl* (*60°*)
1	0.017	−0.200	1.384	0.734	1.382	1.220
2	0.039	−0.389	1.347	0.715	1.318	1.230
3	0.070	−0.573	1.310	0.678	1.231	1.197
4	0.107	−0.798	1.252	0.618	1.129	1.119
5	0.155	−1.061	1.156	0.524	1.020	0.968

Since, for the higher concentrations of acid, the linear equations are no longer valid, the data of Table I were fitted to an equation of the form: $\log 10^5 k_1 = A+BH_0+C(H_0)^2+D(H_0)^3$. The coefficients A–D, together with the standard error of the estimate $s_{y/x}$ and the multiple correlation coefficient R, are shown in Table II. The coefficients can then be used to calculate the rate constant k_1 at any acid concentration, and were so used in the application of the Bunnett[10,11] criteria.

By plotting $H_0+\log 10^5 k_1$ (Table III) *versus* log A (where A is the activity of water), the w parameter, defined by the equation $H_0+\log 10^5 k_1 = a+w \log A$, can be calculated. However, since the plots are distinctively curved, the slopes are dependent on the acid concentration and the exact calculation of w is impossible. A rough, graphical estimate of w yields values from +1.7 to +2.7. Since the w-values are positive, the application of the Bunnett criterion should mean that water reacts as a nucleophile in the rate-limiting step and thus that the reaction proceeds *via* a bimolecular mechanism.

The second Bunnett parameter[10], w^*, can be calculated by plotting $\log k_1 - \log$ [HCl] (Table IV) *versus* log A (Table III). Again, the plots are curved and calculation of w^* is impossible. Graphical estimates show that w^* changes from −10 at low concentrations of acid to −4 at high concentration. Since $w^* < -2$ indicates the participation of water in the rate-limiting step, the criterion is incompatible with an A-1 mechanism.

TABLE IV

w^* PARAMETER

HCl (M)	*Log HCl*	*Log* $10^5 k_1 - log$ [*HCl*]			
		Phenyl (60°)	p-*Bromophenyl* (50°)	p-*Nitrophenyl* (61°)	p-*Ethoxyphenyl* (60°)
1	0	1 584	0.939	1.582	1.420
2	0.301	1.736	1.104	1.707	1.616
3	0 477	1.883	1 251	1.804	1.770
4	0.602	2.050	1.416	1.927	1.917
5	0.699	2.217	1.585	2.081	2.029

The third Bunnett parameter[11], ϕ, is defined by the equation: $H_0+\log 10^5 k_1 = \text{constant}+\phi(H_0+\log$ [HCl]). Except for the *p*-ethoxy derivative, the plots of $H_0+\log 10^5 k_1$ (Table III) *versus* $H_0+\log$ (HCl] give nearly straight lines, with slope values (ϕ) ranging from +0.29 to +0.57. On the basis of the Bunnett calibration reactions[11], $0.22 < \phi < 0.56$ indicates an A-2 mechanism. Consequently, the Bunnett criteria lead to the conclusion that water participates as a nucleophile in the rate-limiting step. However, in previous communications[7,12], it was shown that the mechanistic interpretation of the Bunnett criteria, at least in the case of hydrolysis of glycosides, can lead to contradictory conclusions. On the other hand, the Hammett criterion points out that, at least in low concentrations of acid, the reaction proceeds

via carbonium ions, generated unimoleculary from the conjugate acid. But, since the Hammett plots are curved and the slopes deviate from -1 even at low concentrations of acid, the mechanistic interpretation of the Hammett criterion is rather doubtful.

The possibility exists that the reaction proceeds *via* an A-1 mechanism in dilute acid, and *via* a mixture of unimolecular and bimolecular pathways at higher concentrations of the acid. If this were true, the change to the A-2 mechanism should be reflected in the standard entropy of activation ($\Delta S^{\ddagger}$). For a bimolecular mechanism, involving the addition of water in the rate-limiting step, one can expect that $\Delta S^{\ddagger}$ will be less positive than for the unimolecular cleavage reaction. Accordingly, we determined the activation parameters for the *p*-nitrophenyl and *p*-ethoxyphenyl derivatives in 0.5 and 5M hydrochloric acid. In each case, ln k_1 was a linear function of 1/T. As can be seen from the data in Table V, the activation parameters remained constant within the experimental error. Consequently, there is no indication for a change of mechanism. Moreover, none of the other $\Delta S^{\ddagger}$ values is negative, and thus a bimolecular mechanism seems very improbable.

TABLE V

PSEUDO-FIRST-ORDER RATE COEFFICIENTS AND ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF SUBSTITUTED PHENYL α-D-GALACTOPYRANOSIDES IN 0.5 AND 5M HYDROCHLORIC ACID

Substituent	*HCl* (M)	$10^5 k_1$ (sec^{-1})		$\Delta S^{\ddagger}$ (*cal deg.*$^{-1}$*mole*$^{-1}$)	$\Delta G^{\ddagger}$ (*kcal.mole*$^{-1}$)	$\Delta H^{\ddagger}$ (*kcal.mole*$^{-1}$)
		60°	*80°*			
None	0.5	16.3	191	+ 9.7	24.9	28.1 ±0.2
p-Chloro	0.5	14 0	169	+10.4	25.0	28 5 ±0.2
p-Methyl	0 5	11.0	150	+14.0	25.2	29.8 ±0.3
p-Ethoxy	0.5	10.2	107	+ 4.8	25 2	26.8 ±0.4
p-Ethoxy	5	540	—	+ 3.8	25.7	26.9 ±0.8
p-Bromo	0.5	14.7	163	+ 7.5	25.0	27.5 ±0.3
p-Nitro	0.5	12.5	126	+ 3.9	25.1	26.3 ±0.2
p-Nitro	5	601	—	+ 0.3	25.7	25.8 ±0.4
m-Nitro	0.5	13.1	133	+ 4.1	25.0	26.4 ±0.2

The results of this investigation of the influence of the concentration of the acid are in full agreement with those of our previous, analogous studies. Again, the application of the Hammett, the Bunnett, and the entropy criteria leads to contradictory conclusions as to the nature of the rate-limiting step. But, for aryl α-D-galactopyranosides, the uncertainty becomes so large that a choice between the A-1 and A-2 mechanism, on the basis of these criteria, would hardly be justified.

Effects of the substituent. Inspection of the data in Table V indicates that the substituent has practically no influence on the reaction rate. This is in agreement with the results of Hall *et al.*[1], who found that the rate of hydrolysis of a series of substituted phenyl α-D-glucopyranosides by acid is unaffected by the nature of the substituent. For phenyl β-D-galactopyranosides, we found[6] that electronic effects of

the substituent had an influence on the rate, and that there existed a linear free-energy relationship ($\rho = -0.6$ at 60°) between $\log k_1$ and the Hammett substituent constant σ.

The reason for the low value of the reaction constant ρ in the β series is 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. It is possible that the absence of substituent effects in the α series is due to a chance, exact cancellation of the two opposing effects, and thus that the same reaction mechanism as in the β series is operative. However, since the aglycon group in the α series is axially attached, the possibility of another mechanism cannot be, *a priori*, excluded.

Whereas alkyl β-D-glucopyranosides are hydrolysed more rapidly than the α anomers[4], the reverse is true for aryl D-glucopyranosides[1]. From the data of Table VI, it can be seen that, under comparable conditions, phenyl α-D-galactopyranosides are hydrolysed by acid 3 to 16 times more rapidly than the corresponding β anomers, and that the difference becomes greater when the substituent is an electron-withdrawing group.

TABLE VI

RATE COEFFICIENTS AND ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF SUBSTITUTED PHENYL D-GALACTOPYRANOSIDES IN 0.5M HCl[a]

Substituent	$10^5 k_1$ (sec^{-1}; 60°)		$\Delta H^{\ddagger}$ ($kcal.mole^{-1}$)		$\Delta S^{\ddagger}$ ($cal.mole^{-1}.degree^{-1}$)		$k_1(\alpha)/k_1(\beta)$
	α	β	α	β	α	β	
None	16.3	3.44	28.1	27.7	9.7	5.2	4.7
p-Chloro	14.0	2.50	28 5	27.8	10.4	5 9	5 6
p-Methyl	11.0	3.75	29.8	28.7	14.0	8.5	2.9
p-Ethoxy	10.2	3.45	26 8	29.5	4.8	10.9	3.0
p-Bromo	14.7	2.15	27.5	29.1	7.5	8.5	6.8
p-Nitro	12.5	0.75	26.3	29.3	3.9	7.1	16.7
m-Nitro	13.1	1.16	26 4	29.0	4.1	7.0	11.3

[a]Data for the β anomers were recalculated for 0 5M HCl from the values given in Ref. 6.

Due to the reverse anomeric effect[13], protonation of the exocyclic oxygen atom should be more difficult for the α-D-galactopyranosides (axial aglycon group) than for the corresponding β anomers. Hence, the concentration of the conjugate acid should be lowered, and, since in all previous studies[6,14,15] this was found to be the dominant factor, the reverse anomeric effect should lead to a decrease of the reaction rate. Consequently, the reason for the higher rate of hydrolysis of the phenyl α-D-galactopyranosides must be a lowering of the free energy of activation of the heterolysis step. A possible explanation might be the greater release of strain in going from the initial conformation, destabilized by the positive charge on the axial, exocyclic oxygen atom, to the carbonium–oxonium-like transition state. The greater

loss of molecular order, in comparison with the β anomers, on passing to the transition state should be reflected in the entropy of activation of the heterolysis step. From the data in Table VI, it follows that there is neither a systematic nor a significant increase in the experimental $\Delta S^{\ddagger}$. However, this $\Delta S^{\ddagger}$ value includes the standard entropy change for the protonation as well as for the heterolysis. Consequently, these experimental entropy values cannot be used to prove that the generally accepted, cyclic mechanism is impossible.

A second possible mechanism[5,16] for the hydrolysis of glycopyranosides involves protonation of the ring-oxygen atom[13], after which the ring is opened in a slow, rate-limiting, unimolecular, heterolysis step. The carbonium–oxonium ion then adds water and releases the aglycon group (open-chain mechanism). Although currently available evidence is in favour of the cyclic mechanism, the open-chain mechanism cannot be entirely excluded, especially for aryl α-D-galactopyranosides. Firstly, the base-weakening effect of the phenyl ring (in contrast to alkyl groups) on the glycosidic oxygen atom, and secondly, the destabilization by the reverse anomeric effect may result in a more readly protonation of the endocyclic oxygen atom[13]. However, the small effect of the substituents on the hydrolysis indicates that this mechanism is very improbable. Since the heterolysis step generates an ion with a positive charge on the oxygen atom next to the phenyl ring, an electron-releasing substituent, by stabilizing this ion, must favour the heterolysis step. Because such substituents will also promote the protonation (at least if they have any effect), one can expect a linear free-energy relationship between log k_1 and the Hammett substituent constant σ. Since there is no cancelling effect, a large negative ρ-value should be found and this is not the case. Moreover, if the slight decrease of the rate by the electron-donating substituents methyl and methoxyl is real, this constitutes a severe objection to the open-chain mechanism, because such substituents must increase, not decrease, the rate of the reaction.

The absence of substituent effects in the acid-catalysed hydrolysis of aryl α-D-glucopyranosides led Hall *et al.*[1] to propose a third mechanism, in which protonation of the ring-oxygen atom, in the axial position, is followed by trans elimination of two axially placed groups, without ring opening. As pointed out by Hall[1], this trans elimination should occur under steric, rather than electronic, control. Since, in our series (para and meta substituents), relative steric effects are unimportant, this mechanism could possibly explain the absence of electronic effects. However, as suggested by Capon and Rees[17], the protonation of the ring-oxygen atom, and thus the generation of a positive charge on this atom, should hinder, and not facilitate, the departure of the leaving group. Consequently, this mechanism cannot explain the positive catalysis by the acid.

Since, in all possible mechanisms, the rate-limiting step is a unimolecular heterolysis, without participation of water, neither the Hammett nor the Bunnett criterion will permit differentiation between the alternatives.

In conclusion, the results reported here seem to indicate that the acid-catalysed hydrolysis proceeds by the generally accepted, cyclic mechanism with

TABLE VII

SUBSTITUTED PHENYL α-D-GALACTOPYRANOSIDES

Substituent	*Yield* (%)	*M.p.* (*degrees*)	*Solvent*[a]	$[\alpha]_{5890}^{23}$ (*degrees*)	$[\alpha]_{4360}^{23}$	*Found* (%) *C*	*H*	*Formula*	*Calc.* (%) *C*	*H*
Acetylated Phenyl α-D-Galactopyranosides										
None	23	82–83	A	+163	+332	56.6	5.7	$C_{20}H_{24}O_{10}$	56.6	5.7
p-Chloro	24	99–100	B	+183	+373	52.3	5.0	$C_{20}H_{23}ClO_{10}$	52.3	5.1
p-Bromo	20	108–110	B	+155	+317	47.7	4.6	$C_{20}H_{23}BrO_{10}$	47.7	4.6
p-Iodo	40	119–120	A	+152	+322	43.7	4.3	$C_{20}H_{23}IO_{10}$	43.6	4.2
p-Methyl	33	141–143	B	+164	+330	57.2	5.9	$C_{21}H_{26}O_{10}$	57.5	5.9
p-Ethyl	35	118–120	A	+175	+357	58.3	6.3	$C_{22}H_{28}O_{10}$	58.4	6.2
p-Ethoxy	39	121–122	B	+174	+353	56.5	6.0	$C_{22}H_{28}O_{11}$	56.4	6.0
m-Nitro	15	124–125	B	+185	+371	50.9	5.1	$C_{20}H_{23}NO_{12}$	51.1	4.9
3,4-Dimethyl	43	107–108	C	+176	+358	58.3	6.3	$C_{22}H_{28}O_{10}$	58.4	6.2
p-tert-Butyl	36	97–98	A	+160	+332	59.9	6.7	$C_{24}H_{32}O_{10}$	60.0	6.7
Phenyl α-D-Galactopyranosides										
None	78	141–142	D	+202	+406	56.2	6.3	$C_{12}H_{16}O_6$	56.2	6.3
p-Chloro	75	147–148	D	+198	+402	49.3	5.3	$C_{12}H_{15}ClO_6$	49.5	5.2
p-Bromo	79	159–160	D	+179	+365	43.0	4.6	$C_{12}H_{15}BrO_6$	43.0	4.5
p-Iodo	82	165–166	D	+165	+337	37.6	4.2	$C_{12}H_{15}IO_6$	37.7	3.9
p-Methyl	79	147–148	D	+203	+409	57.7	6.7	$C_{13}H_{18}O_6$	57.8	6.7
p-Ethyl	98	144–145	D	+206	+413	59.0	7.0	$C_{14}H_{20}O_6$	59.1	7.1
p-Ethoxy	70	155–156	D	+197	+399	56.0	6.7	$C_{14}H_{20}O_7$	56.0	6.7
m-Nitro	73	160–161	D	+217	+466	47.7	5.0	$C_{12}H_{15}NO_8$	47.8	5.0
3,5-Dimethyl	—	222–223	E	+ 78	+156	58.9	7.1	$C_{14}H_{20}O_6$	59.1	7.1

[a]Crystallisations from A, ethanol; B, methanol; C, methanol saturated with hexane; D, water–methanol (1:1); E, 2-methoxyethanol.

protonation of the exocyclic oxygen atom. The absence of electronic effects must then be due to a chance, exact cancellation of the two opposing effects on the protonation and the heterolysis.

EXPERIMENTAL

The synthesis of the aryl α-D-galactopyranosides was performed by a slightly modified Helferich[18] reaction. Freshly molten zinc chloride (70 mmoles) and penta-*O*-acetyl-α-D-galactopyranose[19] (100 mmoles) in acetic acid (200 ml) were heated *in vacuo* at 125°, and the acetic acid was distilled off. A small amount of zinc powder and the appropriate phenol (150 mmoles) were added, and the mixture was further heated *in vacuo* at 125–130° for 1 h. After cooling, the resulting syrup (or solid residue) was dissolved in chloroform (200 ml), the solution was thoroughly washed with ice-cold, 5% aqueous sodium hydroxide and water, dried (Na_2SO_4), and evaporated *in vacuo*, and the residue was crystallized from the appropriate solvent (Table VII). Catalytic deacetylation with sodium methoxide[19] yielded the corresponding phenyl α-D-galactopyranosides (Table VII).

Melting points were determined with a Mettler FP2 instrument and are uncorrected. Optical rotations were measured on 0.5% solutions in chloroform (acetates) or methanol (galactosides) with a Perkin–Elmer Model 141 photoelectric polarimeter. The purity of the products was tested by t.l.c. on Silica Gel G (Merck), using acetic acid–water–ethyl acetate (1:1:3) for the galactosides, and ethyl acetate–benzene (3:7) for the acetates. Detection was effected with 5% sulphuric acid in ethanol (10 min at 120°).

The polarimetric measurements of reaction velocity were carried out with a Perkin–Elmer Model 141 polarimeter, and the calculations of the first-order rate coefficients and of the activation parameters were performed as described in previous[12,14,15] publications.

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