THE INFLUENCE OF ACIDS ON THE HYDROLYSIS OF SUBSTITUTED PHENYL β-D-GALACTOPYRANOSIDES

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ABSTRACT

The influence of the acid concentration on the hydrolysis of substituted phenyl β-D-galactopyranosides has been investigated. Application of the Hammett–Zucker and the Bunnett criteria leads to contradictory conclusions about the mechanism of the reaction. The real meaning and possible intercorrelation of these criteria are discussed. It is concluded that, at least for glycosides, the mechanistic value of these criteria is doubtful.

INTRODUCTION

In a previous communication[1], the influence of hydrochloric and sulphuric acids on the hydrolysis of phenyl and methyl D-glucopyranosides was investigated, mainly in order to see if the Hammett[2] and Bunnett[3,4] criteria had sufficient mechanistic value to prove either the generally accepted unimolecular A-1 mechanism, or the bimolecular A-2 mechanism. The results of this study, especially the rather-complex behaviour of the w, w^*, and ϕ parameters, which produced contradictory conclusions, indicated that the mechanistic value is doubtful, at least in the case of glycosides.

Firstly, there seemed to be an *a priori* correlation between the slope in the Hammett plot and the w and ϕ parameters, so that the fundamental question still remained the deviation of the slope in the Hammett plot. Secondly, the w^* parameter seemed to be correlated with the number of water molecules liberated on protonation of the substrate, rather than to indicate a hydration change in the rate-limiting step to the transition complex. In a study[5] of the acid hydrolysis of a series of substituted phenyl β-D-galactopyranosides, we also observed a very complex behaviour of the w, w^*, and ϕ parameters.

In this work, we have investigated the influence of the acid concentration on these derivatives, in order to see if our previous assumptions could also explain the results of the galactoside series. In this series, only the substituent on the phenyl group is changed, and thus a change in mechanism is highly improbable.

RESULTS AND DISCUSSION

Hammett criterion

For a number of β-D-galactopyranosides, the pseudo-first-order rate constant k_1 was determined at constant temperature and various concentrations of hydrochloric acid (Table I). In each case, a plot of log 10^5k_1 *versus* H_0 indicates a nearly linear function of the form: log $10^5k_1 = a+bH_0$. The coefficients a and b were calculated by regression analysis, together with the standard deviation on b (s_b), the standard error of the estimate ($s_{y/x}$), and the correlation coefficient r (Table II). Although the lines are nearly straight, the mean slopes deviate significantly from unity in both directions. These deviations are still too small to invalidate the Zucker–Hammett criterion and thus, according to this criterion, the hydrolysis should proceed by a unimolecular A-1 mechanism without participation of water in the rate-limiting step.

TABLE I

FIRST-ORDER RATE CONSTANT (10^5k_1, sec^{-1})

Substituent	t (*degrees*)	*HCl* (M) H_0[a]	*1* *−0.20*	*2* *−0.69*	*3* *−1.05*	*4* *−1.40*	*5* *−1.76*
None	70		32.8	95.5	214	442	1016
p-Nitro	70		8.46	24.2	50.4	97.7	180
p-Bromo	60		6.08	18.7	40.7	83.7	162
p-Ethyl	60		10.2	30.7	69.5	146	285
o-Acetyl	40		3.02	10.5	31.2	85.3	210

[a]From ref. 9.

TABLE II

SLOPES OF THE ZUCKER–HAMMETT PLOTS

Substituent	a	−b	s_b	$s_{y/x}$	r	A	−B	C	$s_{y/z}$	R
None	1.325	0.952	0.007	0.009	0.9999	1.329	0.937	−0.007	0.007	0.9999
p-Nitro[a]	0.781	0.854	0.023	0.027	0.9989	0.739	0.945	0.004	0.0002	0.9999
p-Bromo	0.625	0.916	0.023	0.028	0.9990	0.570	1.079	−0.084	0.003	0.9995
p-Ethyl	0.840	0.933	0.020	0.025	0.9993	0.796	1.065	−0.068	0.008	0.9996
o-Acetyl	0.226	1.199	0.023	0.028	0.9994	0.229	1.190	0.004	0.025	0.9998

[a]D = 0.0289.

The slight departure from linearity, however, will have a definite influence on the determination of the Bunnett parameters. Accordingly, the data of Table I were fitted to a quadratic equation of the form: log $10^5k_1 = A+BH_0+C[H_0]^2$. For the *p*-nitrophenyl galactoside, where the curvature is more pronounced, a term $D[H_0]^3$ was included in the calculations. The coefficients A, B, C, and D, together with $s_{y/x}$ and the correlation coefficient R, are shown in Table II. It follows from these data

that, since inclusion of the $[H_0]^2$ term does not significantly improve the fit in the case of phenyl and *o*-acetylphenyl galactosides, the Hammett plots are practically linear. The most-severe curvature occurs with the *p*-nitro derivative, where a $[H_0]^3$ term was needed, whereas the other two derivatives show only a moderate curvature and thus a $[H_0]^2$ term was sufficient.

Further, in two of the cases (*p*-bromophenyl and *p*-ethylphenyl), the slope *b* in the Hammett plot (calculated line) has an absolute value >1 at low concentrations of acid, takes the value 1 at intermediate concentrations, and then further decreases. For the phenyl and *p*-nitrophenyl aglycon groups, *b* never exceeds 1 but decreases at higher concentrations of acid. For the *o*-acetylphenyl derivative, the *b*-value remains always greater than 1 and practically constant.

w *Parameter*

The values of $\log(k_1 \times 10^5)$ at 1–5M hydrochloric acid were recalculated from the power series in H_0, with the aid of the coefficients *A*, *B*, *C*, and *D*. These values were then used to construct the Bunnett plots. By plotting $H_0 + \log 10^5 k_1$ (Table III) *versus* $\log A$ (where *A* is the activity of water), the *w* parameter[3], defined by the equation $H_0 + \log 10^5 k_1 = a + w \log A$, can be determined. However, if this is done, it is found that the lines are curved and that the exact calculation of *w* is impossible. Moreover, there are fundamental differences between the various galactosides. For the phenyl derivative, the *w* parameter changes from ~ 1 to zero (at 4M HCl) but remains positive; for the *o*-acetylphenyl galactoside, it is always negative and changes from -8 to -1. The line for the *p*-nitrophenyl galactoside is practically straight, and *w* takes the value $+1.7$. For the *p*-bromophenyl and *p*-ethylphenyl derivatives, *w* is negative at low concentrations of the acid, becomes zero at $\sim$2M HCl, and takes the value $+1$ at higher concentrations. According to Bunnett, the unimolecular A-1 mechanism requires a *w* value of -2.5 to 0, which means that only the *o*-acetylphenyl derivative hydrolyses *via* the A-1 mechanism. The other galactosides should hydrolyse *via* a bimolecular mechanism with participation of water in the rate-limiting step, or even *via* a combination of the two mechanisms. This is, however, highly improbable, and thus another explanation should be sought.

TABLE III

w PARAMETER

HCl (M)	$-\log A^a$	$H_0 + \log[HCl]$	$H_0 + \log 10^5 k_1$				
			Phenyl	p-*Nitro-phenyl*	p-*Bromo-phenyl*	p-*Ethyl-phenyl*	o-*Acetyl-phenyl*
1	0.017	−0.200	1.315	0.7282	0.5827	0.8062	0.2673
2	0.039	−0.389	1.292	0.6936	0.5852	0.8087	0.3627
3	0.070	−0.573	1.275	0.6521	0.5613	0.7898	0.4341
4	0.107	−0.798	1.250	0.5901	0.5174	0.7546	0.5047
5	0.155	−1.061	1.240	0.4926	0.4508	0.7011	0.5784

[a]From Ref. 9.

In our previous[1] communication, we showed that, where the Hammett function is nearly linear, the Bunnett function must be curved, and that w is correlated with the slope b of the Hammett plot by the equation:

$$w = \frac{(H_0)\,(b+1)}{\log [A/A_0]} = P(b+1),$$

where A_0 is the *a priori* known value of A at the acid concentration where $H_0 = 0$. In this formula, P is always positive and the sign of w is thus determined by the absolute value of b, which is always negative. Moreover, since P is a function of the concentration of the acid, w can be constant only if the Zucker–Hammett plot itself is severely curved, which is not the case for the phenyl galactosides under discussion. These conclusions easily explain the changes in the w parameter. For the *o*-acetylphenyl derivative, the Hammett slope (absolute value) is always >1, and thus w must be negative. For the phenyl and *p*-nitrophenyl derivatives, the b value is always <1 and w must be positive. For the *p*-bromophenyl and *p*-ethylphenyl derivatives, $b>1$ at low concentrations of acid, takes the value 1 at intermediate concentrations, and then becomes <1 (*cf.* Table II). Thus, w must change from a negative to a positive value.

Furthermore, since all of the Hammett plots are nearly straight (b remains constant), the w parameter cannot be constant. The most-severe curvature in the Bunnett plot occurs with the *o*-acetylphenyl and the phenyl derivative, for which the Hammett plot is linear (*cf.* inclusion of the $[H_0]^2$ term). On the other hand, w is practically constant for the *p*-nitrophenyl derivative, which shows the most-severe curvature in the Hammett plot. Therefore, the mechanistic meaning of the w parameter as a new criterion seems rather limited, since it is correlated with the Hammett slope. The fundamental question is thus neither the sign nor the value of w, but the deviation of the slope b from unity.

w* *Parameter*

By plotting $\log 10^5 k_1 - \log[\mathrm{HCl}]$ (Table IV) *versus* $\log A$, an attempt was made to calculate the w^* parameter[3], defined by the equation $\log k_1 - \log[\mathrm{HCl}] = a + w^* \log A$. However, in each case, the line is curved and an exact calculation is impos-

TABLE IV

w^* PARAMETER

HCl (M)	*log* $10^5 k_1 - log[HCl]$				
	Phenyl	p-*Nitrophenyl*	p-*Bromophenyl*	p-*Ethylphenyl*	o-*Acetylphenyl*
1	1.515	0.9282	0.7827	1.0062	0.4673
2	1.681	1.0826	0.9742	1.1977	0.7517
3	1.848	1.2251	1.1343	1.3628	1.0071
4	2.056	1.3881	1.3154	1.5526	1.3027
5	2.301	1.5536	1.5118	1.7621	1.6394

sible. A rough graphical estimate of w^* ranges from ~ -8 to -4 at higher concentrations of acid. This should mean that a bimolecular mechanism operates at all of the concentrations.

In our previous communication, we argued that the w^* value, although it indicates a participation of water, does not necessarily prove that this occurs in the rate-limiting step. Another alternative appeared to be that w^* reflects the variable hydration change on protonation of the glycoside, according to the reaction scheme:

$$S + H^+(H_2O)_n \rightleftharpoons SH^+ + nH_2O$$

$$SH^+ \rightleftharpoons SH^{\ddagger} \rightarrow \text{products}$$

If this is accepted, the lines necessarily will be curved, and w^* $(=n)$ will not be constant, since the number of water molecules liberated is a function of the concentration of water, and will diminish at higher concentrations of acid. According to Perrin[6], the relative concentration of the proton-tetrahydrate reaches a maximum near 6.5M perchloric acid. Experimentally, the w^* parameter approaches the value 4–5 near 5M HCl for the galactosides under study and for all of the glycosides previously tested[1,7,8]. Even if this is a coincidence, it seems very probable that w^* reflects more than a participation of water in the formation of a transition complex, and thus cannot prove and A-2 mechanism, especially when other criteria indicate an A-1 mechanism.

ϕ Parameter

A plot of $H_0 + \log 10^5 k_1$ *versus* $H_0 + \log[HCl]$ (Table III), which defines the third Bunnett parameter[4] (ϕ), shows severe curvature in each case, except for the phenyl derivative. It goes through a maximum at ~2M HCl for the *p*-ethyl and *p*-bromo galactoside, and thus ϕ changes its sign from negative to positive at higher concentrations of acid. The *o*-acetylphenyl derivative behaves exceptionally, in that its ϕ-value remains negative. Thus, there is a perfect parallelism between the behaviour of the w and ϕ parameters. The calculation of the mean value of ϕ yields: phenyl, +0.10; *p*-ethylphenyl, +0.13; *p*-bromophenyl, +0.18; *p*-nitrophenyl, +0.29; and *o*-acetylphenyl, −0.36. Since a ϕ value of 0.22 to 0.56 indicates a bimolecular, and a ϕ value <0 a monomolecular, mechanism, the conclusion should be that only the *o*-acetylphenyl galactoside hydrolyses *via* the A-1 mechanism. But the w and w^* parameters indicate that even this derivative hydrolyses *via* the A-2 mechanism. These contradictory results clearly make conclusions about the mechanism rather doubtful. The parallelism between w and ϕ suggests an analogue explanation, and, indeed, it can be shown[1] in the same way as for the w parameter:

$$\phi = \frac{H_0(b+1)}{H_0 + \log[H^+]/[H^+]_0} = Q(b+1),$$

where $[H^+]_0$ is the concentration of the acid at which H_0 becomes zero. The sign of Q will always be positive, and thus the sign of ϕ will be determined by the absolute value of b. Moreover, Q is a function of the concentration of the acid, and thus, if b is constant (linear Hammett plot), ϕ cannot be constant. The same reasoning as was

used in the case of w then explains the curvature in the ϕ plot, and the signs and the change of signs of the ϕ values. Again, the fundamental question remains the deviation in the Zucker–Hammett plot.

CONCLUSIONS

The results of this study are in full agreement with our previous analogous investigation on the influence of the acid concentration on the hydrolysis of glycopyranosides. The real mechanistic meaning of some acidity functions is too uncertain to allow clear-cut conclusions. Moreover, some may be correlated, and thus each is dependent on the numerical value of the other. This is especially true in the cases where the Hammett criterion is fulfilled (slope approaches -1), since then, even small experimental errors can determine the sign and thus the mechanistic meaning of w and ϕ. Even if the slope deviates significantly from unity, the sign of these parameters is *a priori* determined by the real deviation of the Hammett slope. Therefore, the Hammett criterion, notwithstanding its shortcomings, remains the fundamental one.

EXPERIMENTAL

The substituted phenyl β-D-galactopyranosides were synthesized as described previously[10]. The polarimetric measurements were carried out at 436 nm, with a Perkin–Elmer model 141 photoelectric polarimeter, in jacketed tubes, connected to an ultrathermostat bath. The first-order rate coefficients (ln e; sec^{-1}) were calculated[11] from least-squares, straight-line plots of $\log(\alpha_t \pm \alpha_\infty)$ *versus* time. The α_∞ values were determined experimentally for corresponding solutions of D-galactose, and for each temperature and concentration of acid. As a check, some rate coefficients were also determined by the Guggenheim[12] method. These duplicate runs agreed within the estimated error.

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