

THE ACID HYDROLYSIS OF ALKYL β -D-GALACTOPYRANOSIDES

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ABSTRACT

Twenty-one alkyl β -D-galactopyranosides were synthesised and hydrolysed in hydrochloric acid. Application of the Hammett-Zucker criterion indicates a unimolecular (A-1) mechanism. The activation parameters indicate an isoenthalpic reaction series. Galactosides having secondary-alkyl aglycon groups belong to the same series, but the rate of hydrolysis is slightly increased by the entropy factor. The influence of the aglycon group can be correlated with the Robinson-Matheson Φ parameter.

INTRODUCTION

In previous papers^{1,2}, we described the acid-catalysed hydrolysis of series of alkyl and aryl β -D-glycosides and the influence³ of the acid concentration on the rate coefficients. It was the purpose of this work to investigate, in a similar manner, the hydrolysis of a series of alkyl β -D-galactopyranosides, and to compare the results with those of our own previous series, and with analogous series investigated by other authors^{4,5}. For further details on the acid-catalysed hydrolysis of glycosides, the recent review of BeMiller⁶ may be consulted.

RESULTS AND DISCUSSION

Twenty-one alkyl β -D-galactopyranosides were hydrolysed in M aqueous hydrochloric acid at five different temperatures. The pseudo-first-order reaction coefficients at three temperatures and the activation parameters are presented in Table I.

Influence of the acid concentration

For five of the alkyl β -D-galactopyranosides, the pseudo-first-order rate coefficient was determined at constant temperature and various concentrations of hydrochloric acid (Table II). If the reaction proceeds *via* a slow, rate-limiting, unimolecular heterolysis of the glycoside conjugate acid (as is generally accepted⁶), $\log k_1$ should show a linear dependence (slope -1) on the Hammett acidity function

TABLE I

PSEUDO-FIRST-ORDER RATE COEFFICIENTS AND ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF ALKYL β -D-GALACTOPYRANOSIDES IN M HYDROCHLORIC ACID

Glycoside	Alkyl group	$10^5 k_1$ (sec $^{-1}$)			ΔS^\ddagger (cal.deg. $^{-1}$ mole $^{-1}$)	ΔG^\ddagger (kcal.mole $^{-1}$)	ΔH^\ddagger (kcal.mole $^{-1}$)
		60°	70°	80°			
1	Methyl	1.28	5.38	20.9	+14.9	27.0	32.0 \pm 0.2
2	Ethyl	1.43	5.97	23.0	+14.5	27.0	31.8 \pm 0.1
3	Propyl	1.56	6.57	25.5	+15.1	26.9	31.9 \pm 0.3
4	Butyl	1.67	6.99	27.0	+14.2	27.1	31.9 \pm 0.1
5	Pentyl	1.57	6.53	25.0	+14.3	26.9	31.7 \pm 0.1
6	Hexyl	1.64	6.80	26.0	+14.3	26.9	31.6 \pm 0.3
7	Heptyl	1.59	6.60	25.3	+14.4	26.9	31.7 \pm 0.3
8	Octyl	1.65	6.81	26.0	+14.2	26.9	31.6 \pm 0.3
9	2-Methyl-1-propyl	1.94	8.11	31.3	+14.4	27.0	31.8 \pm 0.3
10	4-Methyl-1-pentyl	1.58	6.62	25.7	+15.2	26.9	32.0 \pm 0.1
11	2-Methyl-1-pentyl	1.84	7.67	29.5	+15.0	26.8	31.8 \pm 0.3
12	2-Butyl	3.16	13.3	51.3	+16.5	26.4	31.9 \pm 0.2
13	3-Pentyl	4.00	16.6	63.6	+16.2	26.3	31.7 \pm 0.2
14	2-Pentyl	3.29	13.8	53.5	+16.6	26.4	31.9 \pm 0.1
15	2-Hexyl	3.32	14.0	54.1	+16.6	26.4	32.0 \pm 0.2
16	2-Heptyl	3.27	13.7	52.7	+16.3	26.4	31.8 \pm 0.1
17	2-Octyl	3.06	12.8	49.4	+16.3	26.5	31.9 \pm 0.3
18	Benzyl	1.35	5.59	21.4	+14.0	27.0	31.7 \pm 0.1
19	3-Phenylpropyl	1.28	5.38	20.9	+14.9	27.0	31.9 \pm 0.1
20	Cyclopentyl	2.19	9.02	34.2	+14.3	26.7	31.5 \pm 0.1
21	Cyclohexyl	2.85	11.7	44.3	+14.8	26.5	31.4 \pm 0.3

H_0 (Zucker–Hammett criterion⁷⁻⁹). Experimentally, it was found that, in all of the cases, $\log k_1$ indeed showed a linear dependence on H_0 , but that the slopes deviated from unity. A least-squares fit of the data yielded the values given in Table III, where b represents the slope, a the intercept, s_b the estimated standard error on b , $s_{y/x}$ the standard error on the estimate, and r the correlation coefficient. Although, in most of the cases, the deviation from unity is statistically significant (t -test), these small deviations do not invalidate the Zucker–Hammett criterion, and thus the hydrolysis should proceed by the unimolecular A-1 mechanism, without participation of water in the rate-limiting step. We did not use the Bunnett¹⁰ and Bunnett–Olsen¹¹ criteria to obtain further evidence for this mechanism, because we have shown³ that, in cases of glycoside hydrolysis where the Hammett slope b remains constant (linear function), these criteria are of little mechanistic value.

TABLE II

INFLUENCE OF THE ACID CONCENTRATION ON THE RATE COEFFICIENT $10^5 k_1$ (SEC⁻¹) AT 60°

Aglycon group	HCl (M) H ₀ ^a	1	2	32.5	3	4	5
		-0.20	-0.69	-0.87	-1.05	-1.40	-1.76
Methyl		1.26	3.98	6.10	10.4	22.4	48.2
Hexyl		1.59	5.25	8.55	13.6	30.9	68.4
3-Pentyl		4.66	15.2	24.0	37.5	86.1	209
2-Butyl		3.22	10.7	18.1	27.9	65.8	152
Benzyl		1.41	4.34	6.84	10.3	22.3	47.2

^aFrom Ref. 22.

TABLE III

SLOPES OF THE ZUCKER–HAMMETT PLOTS

Aglycon group	a	-b	s_b	-r	$s_{y/x}$
Methyl	-0.085	1.016	0.019	0.9989	0.027
Hexyl	0.010	1.044	0.015	0.9995	0.021
3-Pentyl	0.458	1.057	0.004	0.9999	0.006
2-Butyl	0.303	1.074	0.012	0.9997	0.012
Benzyl	-0.034	0.981	0.014	0.9996	0.017

Isokinetic relationship

According to the theory of Exner^{12,13}, a relation between the activation enthalpy and entropy can be proved by plotting two values of $\log k$, obtained at two different temperatures, against each other. Using the k_1 values of Table I, a plot of $\log 10^5 k_1$ at 80° (T_1) versus $\log 10^5 k_1$ at 60° (T_2) shows a linear relationship. Regression analysis, using all derivatives, yields the equation:

$$\log 10^5 k_1(80^\circ) = 1.26 + 0.9977 \log 10^5 k_1(60^\circ),$$

with $s_{y/x} = 0.0066$, $s_b = 0.009$, $r = 0.9992$, and $n = 21$.

A *t*-test on the value of the slope $b=0.9977$ indicates that it is not significantly different from unity. Moreover, notwithstanding the high correlation and the small standard error on b , this error causes a large uncertainty in the calculation^{12,13} of the isokinetic temperature β . The only possible conclusion seems to be that b approaches unity, and thus that β approaches zero. In the Exner classification, this represents case 2, with ΔH^\ddagger constant and a rate controlled by changes of ΔS^\ddagger . From Table I, it can be seen that ΔH^\ddagger is indeed constant throughout the whole series, which thus represents an isoenthalpic series. An analysis according to the original Leffler¹⁴ procedure naturally gives the same $\beta=0$ value.

It is possible that the isokinetic relationship should be separately⁵ determined for glycosides of primary and secondary alcohols, respectively. Thus, we calculated the following regression lines for primary and secondary (without cyclohexyl and cyclopentyl) alkyl groups:

$$\begin{aligned} \text{primary, } \log 10^5 k_1(80^\circ) &= 1.212 + 0.969 \log 10^5 k_1(60^\circ), \\ &\text{with } s_{y/x} = 0.005, s_b = 0.03 \text{ and } r = 0.995; \end{aligned}$$

$$\begin{aligned} \text{secondary, } \log 10^5 k_1(80^\circ) &= 1.247 + 0.927 \log 10^5 k_1(60^\circ), \\ &\text{with } s_{y/x} = 0.003, s_b = 0.03, \text{ and } r = 0.997. \end{aligned}$$

It is clear that the slopes do not differ significantly from each other, and thus there is no proof that the two series have different isokinetic temperatures. Hence, we believe that all derivatives hydrolyse *via* the same mechanism, and belong to the same isoenthalpic reaction series.

Linear free energy relationship

It is evident from the values in Table I that there is no simple relation between the $\log k_1$ values and the electronic (Taft polar σ^*) or steric (E_s) effects of the aglycon group. However, Robinson, and Matheson¹⁵ introduced a new parameter Φ , based on the alkaline hydrolysis of alkyl-substituted 3,5-dinitrobenzoates as the standard reaction. Since the substituent variation is in the alcohol portion of the ester, there is some resemblance to the variation of the aglycon part in alkyl glycosides, and thus we tested this parameter. Using the $\log 10^5 k_1$ at 60° of the derivatives for which a Φ value was available (and thus derivatives **7**, **10**, **11**, **15**, and **19** are not included), we calculated:

$$\log 10^5 k_1(60^\circ) = 0.054 - 0.211 \Phi,$$

$$\text{with reaction constant } \rho' = -0.211 \pm 0.016, s_{y/x} = 0.04, r = 0.966, \text{ and } n = 16.$$

Although a linear relationship probably exists, the correlation coefficient r is not as high as those listed by Robinson and Matheson¹⁵. In order to prove that the relation is more than a coincidence, we also analysed, in the same way, the reaction series of BeMiller and Doyle⁵, and our own series of alkyl β -D-xylopyranosides¹. For alkyl D-gluc-

pyranosides in 0.5M sulphuric acid at 80° (see ref. 5, Table II, and ref. 4, Table VI), the following calculations were made:

$$\alpha\text{-series, } \log 10^6 k_1 (80^\circ) = 0.903 - 0.217 \Phi, \\ \text{with } \rho' = -0.217 \pm 0.05, s_{y/x} = 0.09, r = -0.82, \text{ and } n = 10;$$

$$\beta\text{-series, } \log 10^6 k_1 (80^\circ) = 1.401 - 0.160 \Phi, \\ \text{with } \rho' = -0.160 \pm 0.04, s_{y/x} = 0.06, r = -0.84, \text{ and } n = 8.$$

For alkyl β -D-xylopyranosides in 0.5M hydrochloric acid at 60° (see ref. 1, Table I), calculation yields:

$$\log 10^6 k_1 (60^\circ) = 0.793 - 0.297 \Phi, \\ \text{with } \rho' = -0.297 \pm 0.029, s_{y/x} = 0.06, r = -0.958, \text{ and } n = 11.$$

It is noteworthy that *tert*-butyl β -D-xylopyranoside is the only derivative of the xyloside series which does not fit the relationship ($\log 10^6 k_1 = 2.887$; $\Phi = -3.34$). However, it is known¹⁶ that glycosides of tertiary alcohols hydrolyse with heterolysis of the exocyclic oxygen-aglycon bond, and thus the mechanism is different.

Although the correlation coefficients of the glucoside series are not very significant, we believe that the Φ parameter does have some mechanistic value for these glycoside series. In particular, the fact that the reaction constants ρ' are of the same magnitude, and thus that the influence of the aglycon group is more or less the same in each of these very similar series, seems to corroborate the value of Φ .

The interpretation of Φ , which contains a steric as well as an electrical factor, is more difficult than the interpretation of the more-classical Taft or Hammett substituent constants. However, because of the absence of steric effects^{1,4,5}, in accordance with the unimolecular nature of the rate-limiting step, it can be assumed that Φ reflects predominantly the polar effects of the aglycon group. All derivatives of our galactoside series have aglycon groups with negative Φ value (electron sources). The fact that the reaction constant ρ' has a negative value then means that the reaction constant is increased by electron-donating groups, and thus that the influence on the protonation (and concentration of the conjugate acid) is dominant^{1,4}.

Activation parameters

The isokinetic relationship indicated an isoenthalpic reaction series. Inspection of the data in Table I indicates that this is true, and that the reason for the small increase in reaction velocity in the case of secondary alkyl groups is the entropy factor ΔS^\ddagger . The rate enhancement by these strong electron-donors is in accordance with the linear free-energy relationship. As was put forward by BeMiller and Doyle⁵, these electron-donating groups stabilise the conjugate acid because of their ability to disperse the positive charge on the oxygen atom. But, since there is less separation of like charges, the bond has to be stretched farther in the transition state, and thus there is a greater increase in entropy.

TABLE IV
 β -D-GALACTOPYRANOSIDES

Aglycon group	Crystallisation solvent	M.p. (degrees)	[α] _D ²² (degrees)	[α] _D ²² (degrees)	Found (%)		Calc. (%)	
					C	H	C	H
Methyl	Ethanol	175-176	-16.9	-34.7	43.2	7.0	43.3	7.2
Ethyl	Ethanol	157-159	-20.5	-42.4	46.0	7.6	46.2	7.7
Propyl	Acetone	110-112	-20.3	-40.9	48.7	8.1	48.7	8.1
Butyl	Acetone	104-105	-20.6	-41.1	50.8	8.4	50.9	8.5
Pentyl	Acetone	114-116	-18.4	-38.0	52.7	8.8	52.8	8.8
Hexyl	Acetone	116-117	-17.5	-37.0	54.5	9.0	54.6	9.1
Heptyl	Acetone	98-99	-17.1	-34.2	56.1	9.4	56.1	9.4
Octyl	Acetone	99-100	-16.5	-33.3	57.5	9.5	57.5	9.6
2-Methyl-1-propyl	Ethyl acetate	117-118	-20.6	-40.1	50.8	8.5	50.9	8.5
4-Methyl-1-pentyl	Acetone	126-127	-17.7	-36.9	54.7	9.1	54.6	9.1
2-Methyl-1-pentyl	Acetone	141-143	-18.7	-37.6	54.6	9.2	54.6	9.1
2-Butyl	Acetone	121-123	-21.1	-43.9	50.8	8.5	50.9	8.5
3-Pentyl	Acetone	145-146	-24.6	-46.3	52.8	8.8	52.8	8.8
2-Pentyl	Acetone	155-156	-16.6	-34.6	52.9	8.7	52.8	8.8
2-Hexyl	Acetone	144-145	-17.7	-37.5	54.4	9.1	54.6	9.1
2-Octyl	Acetone	119-120	-17.7	-36.5	57.2	9.6	57.5	9.6
Benzyl	Ethyl acetate	102-103	-39.5	-81.3	57.7	6.8	57.8	6.7
3-Phenylpropyl	Ethyl acetate	100-102	-12.9	-24.9	60.0	7.4	60.4	7.4
Cyclopentyl	Acetone	104-105	-27.1	-55.3	53.0	8.1	53.2	8.1
Cyclohexyl	Acetone	134-135	-26.7	-54.6	54.9	8.3	55.0	8.4

Our results in this and previous¹ work are in agreement with the results of Timell⁴ and of BeMiller and Doyle⁵, and illustrate the fact that, within series of alkyl β -D-glycopyranosides (equatorial aglycon group), the activation parameters remain approximately constant, whereas this is not the case for alkyl α -D-glucopyranosides⁵ (axial aglycon group).

EXPERIMENTAL

Alkyl β -D-galactopyranosides were prepared by the Koenigs-Knorr^{17,18} synthesis, in the presence of yellow mercuric oxide and mercuric bromide. Benzene (or chloroform) (200 ml), Sikkon (calcium sulfate Fluka) (40 g), yellow mercuric oxide (21.6 g; 0.1 mole), mercuric bromide (1.5 g), the alcohol (0.1 to 1 mole), and tetra-*O*-acetyl- α -D-galactopyranosyl bromide¹⁹ were stirred in a closed vessel for several hours at room temperature (monitoring by t.l.c.). After filtration and thorough washing with water, the solution was evaporated in *vacuo* to a syrup. Since none of the galactoside tetra-acetates crystallised, the crude mixture was deacetylated with sodium methoxide²⁰, and the product was recrystallised from the appropriate solvent. Melting points, optical rotations (in methanol, *c* 1), and purities of products were determined as described previously²¹. Data for the alkyl β -D-galactopyranosides are presented in Table IV. The polarimetric measurements of the reaction velocity, carried out with a Perkin-Elmer Model 141 photoelectric polarimeter, and the calculations of the first-order rate coefficients and of the activation parameters, were performed as described in previous¹⁻³ publications.

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