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THE ACID HYDROLYSIS OF PHENYL β-D-GALACTOPYRANOSIDES

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ABSTRACT

Thirty-two substituted phenyl β-D-galactopyranosides were hydrolyzed in 0.1M aqueous hydrochloric acid at different temperatures. Rate coefficients and kinetic parameters were determined. Influences of the substituents were investigated by linear free-energy relationships and the Leffler–Exner isokinetic relation. Only electronic effects operate. Some ortho-substituents have a rather complex influence on the reaction.

INTRODUCTION

We have for some time been interested in the acid hydrolysis of glycopyranosides. In previous communications, the influence of the acid concentration[1,2] and of the nature of the aglycon group[3,4] have been investigated. We now report on the effect of para, meta, and ortho substituents upon the acid-catalyzed hydrolysis of substituted phenyl β-D-galactopyranosides. The results of analogous[5,6] studies, and further details on the acid-catalyzed hydrolysis of glycosides, may be found in a recent review by BeMiller[7].

RESULTS AND DISCUSSION

Thirty-two substituted phenyl β-D-galactopyranosides were hydrolyzed in 0.1M aqueous hydrochloric acid at different temperatures. The pseudo-first-order rate coefficients at three temperatures. the Arrhenius activation energy, and the activation free-energy, enthalpy, and entropy are presented in Table I.

Influence of the acid concentration

The influence of the concentration of hydrochloric acid on the hydrolysis of several of these phenyl β-D-galactopyranosides was investigated in a previous paper[2]. It was shown that there exists a linear relationship, with slope ~ -1, between the logarithm of the pseudo-first-order rate coefficient and the Hammett acidity function H_0. This finding is in agreement with the generally accepted mechanism for acid-catalysed hydrolysis of glycosides. This mechanism involves a rapid equilibrium-

TABLE I

RATE COEFFICIENTS AND KINETIC PARAMETERS FOR THE HYDROLYSIS OF PHENYL β-D-GALACTOPYRANOSIDES IN 0.1M HYDROCHLORIC ACID

Compound No.	*Substituent*	$10^6 k_1$ (sec^{-1})			E ($kcal.mole^{-1}$)	$\Delta S^{\ddagger}$ (60°) ($cal.deg^{-1}.mole^{-1}$)	$\Delta G^{\ddagger}$ ($kcal.deg^{-1}.mole^{-1}$)	$\Delta H^{\ddagger}$ ($kcal.deg^{-1}.mole^{-1}$)
		60°	70°	80°				
1	None	6.88	24.0	78.1	28.4 ±0.2	+5.2	26.0	27.7
2	*p*-Methyl	7.51	27.4	92.7	29.4 ±0.4	+8.5	25.9	28.7
3	*m*-Methyl	6.51	23.8	78.9	29.4 ±0.3	+3.8	27.5	28.7
4	*o*-Methyl	4.91	19.3	70.5	31.2 ±0.3	+13.0	26.2	30.6
5	*p*-Chloro	5.03	17.6	57.2	28.4 ±0.2	+5.9	26.2	27.8
6	*m*-Chloro	3.24	12.5	44.8	30.7 ±0.4	+10.9	26.4	30.1
7	*o*-Chloro	8.96	29.0	87.0	26.6 ±0.8	+0.5	25.8	25.9
8	*p*-Nitro	1.51	5.66	19.7	30.0 ±0.7	+7.1	26.9	29.3
9	*m*-Nitro	2.32	8.56	29.3	29.6 ±0.3	+7.0	26.6	29.0
10	*o*-Nitro	6.38	21.4	67.0	27.5 ±0.2	+2.5	26.0	26.8
11	*p*-Acetyl	2.31	8.56	29.5	29.9 ±0.4	+7.6	26.7	29.2
12	*m*-Acetyl	3.35	13.2	48.3	31.2 ±0.6	+12.4	26.4	30.5
13	*o*-Acetyl	29.6	94.7	282.	26.4 ±0.6	+2.2	25.0	25.6
14	*p*-Methoxy	8.89	31.1	100.	28.4 ±0.2	+5.8	25.8	27.7
15	*m*-Methoxy	5.57	20.2	68.2	29.3 ±0.3	+7.7	26.1	28.6
16	*o*-Methoxy	20.8	71.7	230.	28.1 ±0.3	+6.6	25.2	27.4

TABLE I (*continued*)

Compound No.	*Substituent*	$10^6 k_1$ (sec^{-1})			E ($kcal.mole^{-1}$)	$\Delta S^{\ddagger}$ (60°) ($cal \cdot deg^{-1}.mole^{-1}$)	$\Delta G^{\ddagger}$ ($kcal.deg^{-1}.mole^{-1}$)	$\Delta H^{\ddagger}$ ($kcal.deg^{-1}.mole^{-1}$)
		60°	70°	80°				
17	*p*-Bromo	4.30	15.9	54.6	29.7 ±0.4	+8.5	26.2	29.1
18	*m*-Bromo	3.76	14.3	50.5	30.4 ±0.1	+10.1	26.3	29.7
19	*o*-Bromo	8.55	28.1	86.9	27.1 ±0.6	+1.9	25.8	26.4
20	*p*-Ethyl	6.87	25.3	86.7	29.6 ±0.5	+9.2	25.9	29.0
21	*p*-Ethoxy	6.91	26.1	91.5	30.2 ±0.5	+10.9	25.9	29.5
22	*m*-Ethoxy	5.32	20.0	69.4	30.0 ±0.3	+9.8	26.1	29.4
23	*p*-ter-Butyl	8.02	28.1	91.4	28.4 ±0.8	+5.9	25.8	27.8
24	3,4-Dimethyl	6.91	25.9	90.0	30.2 ±1.0	+10.7	25.9	29.5
25	3,4-Dichloro	2.62	9.06	28.3	28.1 ±0.7	+2.5	26.6	27.4
26	2,5-Dichloro	6.34	19.0	53.8	24.9 ±1.3	−5.3	26.0	24.2
27	2,6-Dichloro	106.0	323.	922.	25.2 ±0.3	+1.4	24.1	24.6
28	2,4-Dichloro	5.87	18.1	52.5	25.6± 0.7	−3.2	26.0	25.0
29	2,4-Dibromo	7.75	24.6	73.0	26.2 ±0.5	−0.9	25.6	25.8
30	2,4,6-Trimethyl	29.9	103.8	338.	28.3 ±0.5	+8.2	25.0	27.7
31	2,3,5-Trimethyl	14.4	53.9	186.	29.9 ±0.5	+11.5	25.4	29.3
32	2,4,6-Trichloro	91.5	248.	632.	22.6 ±0.7	−6.9	24.2	21.9

controlled protonation of the exocyclic oxygen atom, followed by the slow, rate-limiting, unimolecular heterolysis of the glycoside conjugate acid to form a cyclic carbonium-oxonium ion, which then reacts with water. It is this A-1 mechanism which serves as the basis for the following discussion.

Influence of meta and para substituents

In studying the effect of the substituents on the reaction rate, it is important to realize that they will have an influence on two consecutive reaction-steps. According to the reaction scheme:

$$S + H^+ \overset{K}{\rightleftharpoons} SH^+ \qquad \text{fast equilibrium}$$

$$SH^+ \overset{K^\ddagger}{\rightleftharpoons} SH^\ddagger \overset{k^\ddagger}{\longrightarrow} \text{Products} \qquad \text{rate-limiting,}$$

the reaction velocity is given by $dP/dt = k^\ddagger (SH^+)$, and, with $K^\ddagger = (SH^\ddagger)/(SH^+)$ and $K_a = (SH^+)/(S)(H^+)$,

$$dP/dt = k^\ddagger \cdot K^\ddagger \cdot K_a \cdot (S)(H^+).$$

Since the concentration of the acid remains constant, the reaction is pseudo-first-order, but the experimental pseudo-first-order rate coefficient is a composite coefficient: $k_1 = k^\ddagger \cdot K^\ddagger \cdot K_a(H^+)$. It includes an equilibrium constant for the protonation, and an overall constant ($K^\ddagger \cdot k^\ddagger$) for the heterolysis of the conjugate acid. Thus, if the reaction constant ρ in a Hammett-type, linear free-energy relationship (LFER) is calculated, the experimental ρ value will be the algebraic sum of ρ_E (equilibrium) and ρ_H (heterolysis). The sign of these ρ values will be different (see below), and thus the experimental, overall reaction constant ρ will probably be small.

Using the σ constant of McDaniel and Brown[8] and the k_1 values of Table I, we first calculated the LFER for the meta-substituted derivatives **1**, **3**, **6**, **9**, **12**, **15**, **18**, and **22**. This was done because possible complications, due to direct mesomeric interaction of the substituent with the reaction centre, are less probable for meta substituents. Regression analysis yielded the following equations:

at 60°: $\log 10^6 k_1 = 0.797 - 0.639\sigma$, with the standard error of the estimate $s_{y/x} = 0.035$, the reaction constant $\rho = -0.639 \pm 0.051$, the correlation coefficient $r = -0.981$, and the number of points $n = 8$.

at 70°: $\log 10^6 k_1 = 1.36 - 0.605\sigma$, with $s_{y/x} = 0.025$, $\rho = -0.605 \pm 0.037$, $r = -0.989$, and $n = 8$.

at 80°: $\log 10^6 k_1 = 1.882 - 0.557\sigma$, with $s_{y/x} = 0.024$, $\rho = -0.557 \pm 0.036$, $r = -0.987$, and $n = 8$.

Thus, for the meta derivatives, there exists a highly significant, linear correlation between the $\log k_1$ values and the electronic effect of the substituent. The experimental, overall, Hammett reaction-constant ρ has a small but real negative value, which means that electron-donating substituents increase the reaction velocity. Such substituents decrease the rate of glycosyl-oxygen bond heterolysis (ρ_H is positive), but stabilize the conjugate acid (ρ_E is negative), because the ability of the aglycon group to share the positive charge on the oxygen atom increases. The negative overall ρ-value then indicates that the effect on the protonation is dominant.

The calculation of the LFER for the para derivatives posed some problems. For those substituents which are mesomeric electron-acceptors, there exists the possibility of a direct mesomeric interaction of the substituent with the electron-donating reaction centre. Hence, the normal Hammett σ-values will not represent the actual electronic effect of such substituents. Indeed, it was found that all but two para derivatives did fit the meta-line, and that the two exceptions were the mesomeric, electron-accepting nitro and acetyl groups. This difficulty could not be overcome by using the enhanced (σ^-) values for phenols because the points then deviated to the other side of the line. These two derivations were thus omitted from the calculations. If all meta and para derivatives, with the exception of the p-nitro and p-acetyl galactosides, are considered as one single reaction series, regression analysis yields for the derivatives **1, 2, 3, 5, 6, 9, 12, 14, 15, 17, 18, 20, 21, 22, 23, 24,** and **25**:

$$\log 10^6 k_1(60°) = 0.783 - 0.519\sigma, \quad \text{with} \quad s_{y/x} = 0.034, \quad \rho = -0.591 \pm 0.034, \quad r = -0.982, \quad n = 15.$$

$$\log 10^6 k_1(70°) = 1.345 - 0.564\sigma, \quad \text{with} \quad s_{y/x} = 0.024, \quad \rho = -0.564 \pm 0.024, \quad r = -0.990, \quad n = 15.$$

$$\log 10^6 k_1(80°) = 1.867 - 0.517\sigma, \quad \text{with} \quad s_{y/x} = 0.021, \quad \rho = -0.517 \pm 0.020, \quad r = -0.991, \quad n = 15.$$

The highly significant correlations and the ρ-values clearly indicate that meta and "normal" para derivatives belong to the same reaction series, and that the electronic effects of the para substituents are qualitatively analogous to those of the meta substituents. For a series of phenyl β-D-glucopyranosides, Nath and Rydon[5] calculated $\rho = -0.66$, and Semke *et al.*[6] $\rho = -0.48$. For phenyl β-D-glucopyranosiduronic acids, Semke[6] found $\rho = -0.09$. For phenyl β-D-xylopyranosides[4], we found $\rho = -0.146$.

The reason for the deviation of the p-nitro and p-acetyl derivatives is that the actual σ-values for such para substituents depend on the variation[9] of the mesomeric para-interaction. This variation gives rise to a multiplicity of σ-values, each depending on the type of reaction from which they are derived. As pointed out by Lupton and Swain[10], and by Charton[11], a solution to this problem can be found by representing the electronic substituent effect as a linear combination of two effects (inductive and mesomeric) in an extended Hammett equation. In our calculations, we used the inductive substituent constants (σ_I) from Charton[11]. The mesomeric constants (σ_R)

are the differences ($\sigma_P - \sigma_I$) between the normal para-substituent constant (σ_P) from the compilation of McDaniel and Brown[8], and σ_I.

Multiple regression analysis then yields the following equations. For para derivatives (**2, 5, 8, 11, 14, 17, 20, 21, 23**): $\log 10^6 k_1(70°) = 1.305 - 0.663\sigma_I - 0.700\sigma_R$, with $s_{y/x} = 0.048$, $n = 9$, multiple correlation coefficient $R = 0.985$, partial correlation product of σ_I, $PCP(\sigma_I) = 0.547$, and $PCP(\sigma_R) = 0.424$.

For meta derivatives (**3, 5, 9, 12, 15, 18, 22**): $\log 10^6 k_1(70°) = 1.321 - 0.517\sigma_I - 0.212\sigma_R$, with $s_{y/x} = 0.021$, $n = 7$, $R = 0.993$, $PCP(\sigma_I) = 0.829$, and $PCP(\sigma_R) = 0.158$.

Thus, for both series, there exists a highly significant correlation between $\log k_1$ and the electronic effects of the substituents. Parallel to the Hammett ρ value, the coefficients of σ_I and σ_R are negative, indicating that electron-donating groups increase the reaction velocity by their inductive as well as by their mesomeric effect. As might be expected, the mesomeric contribution is greater in the para than in the meta position (*cf.* PCP), whereas both effects are approximately equal in the para position.

Analogous results are obtained when the field (F) and resonance (R) parameters of Swain and Lupton[10] are used in the calculations.

For para derivatives: $\log 10^6 k_1(70°) = 1.304 - 0.367F - 0.702R$, with $s_{y/x} = 0.047$, $n = 9$, $R = 0.986$, $PCP(F) = 0.464$, and $PCP(R) = 0.507$.

For meta derivatives: $\log 10^6 k_1(70°) = 1.299 - 0.289F - 0.228R$, with $s_{y/x} = 0.035$, $n = 7$, $R = 0.979$, $PCP(F) = 0.742$, and $PCP(R) = 0.216$.

From these analyses, it can be concluded that, at least for para and meta derivatives, the influence of the substituent may be completely accounted for in terms of electrical effect parameters. The fact that relative steric effects are unimportant is in accordance with the unimolecular rate-limiting step and the equatorial position of the aglycon group.

Enthalpy–entropy relationship

From the data in Table I, it can be seen that neither the activation enthalpy nor the entropy is constant for this galactoside series. According to Exner[12,13], a linear relation between these activation parameters (a Leffler isokinetic relationship[14]) can be proved by plotting two values of $\log k_1$, obtained at two different temperatures, against each other. Using the k_1 values from Table I, a plot of $\log 10^6 k_1$ at 80°(T_1) *versus* $\log 10^6 k_1$ at 60°(T_2) indeed shows a linear relation. Regression analysis yields the equation: $\log 10^6 k_1(80°) = 1.157 + 0.884 \log 10^6 k_1(60°)$, with $s_{y/x} = 0.057$, slope $b = 0.884 \pm 0.025$, $r = 0.988$, and $n = 32$.

From the slope b, the isokinetic temperature (β) can then be calculated by the Exner formula: $\beta = T_1 \cdot T_2(b-1)/(T_1 b - T_2)$. With $b = 0.884$, β takes the value 651 °K. However, because the standard error on b amounts to 0.025, the absolute value of β is too uncertain[15,16] to have a real meaning. The only possible conclusion seems to be that the isokinetic temperature is higher than the mean temperature of the experiment (343 °K), and thus that the Hammett reaction constant ρ has a real mechanistic meaning.

Notwithstanding the high correlation coefficient ($r = 0.988$), the question may arise whether the ortho-substituted derivatives do in fact belong to the same reaction series, and thus whether inclusion of the $\log k_1$ values of these derivatives in the regression is correct. To answer this question, the isokinetic relation was recalculated, firstly for the ortho derivatives, and secondly for all the others.

For ortho derivatives: $\log 10^6 k_1(80°) = 1.093 + 0.920 \log 10^6 k_1(60°)$, with $s_{y/x} = 0.07$, slope $b = 0.920 \pm 0.05$, $r = 0.985$, and $n = 13$.

For non-ortho derivatives: $\log 10^6 k_1(80°) = 1.125 + 0.955 \log 10^6 k_1(60°)$, with $s_{y/x} = 0.03$, slope $b = 0.955 \pm 0.03$, $r = 0.990$, and $n = 19$.

From the above results, it is clear that there is no statistically significant difference between the slopes, and thus there is no proof that the two series have different isokinetic temperatures. Hence, there is good evidence that the ortho derivatives hydrolyse *via* the same A-1 mechanism.

Since $b < T_2/T_1$ and $\beta > T_1$, the reaction belongs to class 3/a of the Hinshelwood–Exner classification. In this class, both the activation enthalpy and entropy are variable, but between these parameters, there exists a linear relation in the sense that their effects partially compensate each other. The Exner criterion thus indicates that the Leffler isokinetic relationship, $\Delta H^{\ddagger} = \text{constant} + \beta \Delta S^{\ddagger}$, is real.

However, the exact calculation of β from the Leffler equation is impossible, because of the high scattering of the points representing the ortho derivatives. Thus, although there was no proof of a statistically different slope b in the Exner plots, it remains possible that special ortho effects[15] operate at least for some ortho derivatives, but without changing the basic A-1 mechanism.

Influence of ortho substituents

As could be expected, the ortho-substituted derivatives do not belong to the LFER of the para/meta series. This is normal because special (proximity) effects may occur when substituent and reaction site are bonded to adjacent atoms in an aromatic ring. According to Charton[17], this ortho effect, in the general case, is an electrical rather than a steric effect. However, there seems to be no way to define a single, generally useful set of ortho-substituent constants characteristic of the electrical effect of the substituent. Among the many sets of "ortho-substituent constants", we chose the $\Delta\delta$ values (the relative chemical shifts of hydroxyl in substituted phenols) of Tribble and Traynham[18]. They afford an excellent, relative measure of the electric effects, and are free of steric effects, except in those cases where direct interaction with the hydroxyl group is possible (*o*-nitro, *o*-acetyl, and 2,6-disubstituted phenols).

To test these $\Delta\delta$ parameters, and to make further comparisons possible, we first calculated a LFER with $\Delta\delta$, using the para and meta derivatives (**1, 2, 3, 5, 6, 8, 9, 11, 14, 17, 20–24**):

$\log 10^6 k_1(70°) = 1.322 - 0.347 \Delta\delta$, with $s_{y/x} = 0.04$, $r = -0.987$, reaction constant $\rho' = -0.347 \pm 0.016$, and $n = 15$.

The high correlation indicates that the $\Delta\delta$ parameter is indeed a good measure of the electronic effect of a substituent. For the ortho-substituted derivatives **7, 16, 19,**

26, **28**, **29**, and **31**, regression analysis yields:

$\log 10^6 k_1(60°) = 1.143 - 0.258\,\Delta\delta$, with $s_{y/x} = 0.058$, $\rho' = -0.258 \pm 0.032$, $r = -0.963$, and $n = 7$.

$\log 10^6 k_1(70°) = 1.683 - 0.297\,\Delta\delta$, with $s_{y/x} = 0.056$, $\rho' = -0.297 \pm 0.031$, $r = -0.974$, and $n = 7$.

$\log 10^6 k_1(80°) = 2.189 - 0.330\,\Delta\delta$, with $s_{y/x} = 0.058$, $\rho' = -0.330 \pm 0.03$, $r = -0.977$, and $n = 7$.

The above equations strongly suggest that the relative differences between ortho-substituted derivatives are due only to electronic effects of the substituent. The reaction constant ρ' seems smaller for the ortho than for the para/meta series. However, a t-test based on the pooled variance[19] yields $t = 0.743$ (for $DF = 18$) for the ρ'-values at 70°, and thus the difference between $\rho' = -0.347$ and $\rho' = -0.297$ is not statistically significant. As the same is true at the other temperatures, there is no proof that the sensitivity of the reaction to electronic influences of the substituent is different in the ortho series. This strongly favours the theory of Charton.

If the effect of an ortho substituent is entirely an electrical effect, it should be possible to correlate $\log k_1$ with σ_I (or F) and σ_R (or R) in an extended Hammett equation. Since polysubstituted derivatives cannot be used in these calculations, only the galactosides **4**, **7**, **10**, **13**, **16**, and **19** were available. However, neither the *o*-nitro nor the *o*-acetyl derivative fitted the equations, and thus only four points remained available. This diminishes the mechanistic value of the equations.

If the $\log k_1$ values of the derivatives **4**, **7**, **16**, and **19** are correlated with the equation $\log k_1 = a + b\sigma_I + c\sigma_R$ or $\log k_1 = a + b\mathrm{F} + c\mathrm{R}$, calculation shows that only R or σ_R makes a significant contribution. Regression analysis with σ_R or R yields:

$\log 10^6 k_1(60°) = 0.563 - 1.494\,\sigma_R$, with $r = 0.986$;
$\log 10^6 k_1(70°) = 1.124 - 1.417\,\sigma_R$, with $r = 0.999$;
$\log 10^6 k_1(80°) = 1.654 - 1.338\,\sigma_R$, with $r = 0.991$;
$\log 10^6 k_1(60°) = 0.633 - 1.392\,\mathrm{R}$, with $r = 0.919$;
$\log 10^6 k_1(70°) = 1.178 - 1.366\,\mathrm{R}$, with $r = 0.964$;
$\log 10^6 k_1(80°) = 1.694 - 1.339\,\mathrm{R}$, with $r = 0.993$.

If the equations are meaningful, they suggest that the effect of the ortho substituent on the acid hydrolysis of these galactosides is entirely a resonance effect. Charton[20] came to the same conclusion in the case of the acid-catalyzed hydrolysis of ortho-substituted benzoates and the acid-catalyzed esterification of ortho-substituted benzoic acids. Analogous to the glycoside hydrolysis, these reactions consist of two steps: an equilibrium protonation, and the reaction of the protonated ester or acid. This analogy and the high correlation coefficients seem to indicate that the above equations are not merely fortuitous.

Since no reliable $\Delta\delta$ values, free of steric effects, are available for the *o*-nitro and *o*-acetyl substituents, it is difficult to determine if they deviate from the $\Delta\delta$

equation which was calculated for the other ortho derivatives. If the above equations (with σ_R or R) are not fortuitous, then the deviations of the *o*-nitro and *o*-acetyl derivatives should indicate that special effects operate. But even then, these special influences cannot be large, as can be judged from the kinetic parameters in Table I.

The much larger enhancement of rate of the 2,6-dichloro and 2,4,6-trichloro derivatives cannot be explained by the normal electrical effect. Nor is it a steric effect, as indicated by the practically normal behaviour of the 2,4,6-trimethylphenyl galactoside, whose rate can easily be explained by the influence of the three electron-donating groups. As can be judged from Table I, all the galactosides with negative ortho groups have lower activation enthalpies and less positive entropies, whereas this is not the case for positive ortho groups (*cf.* **4, 30, 31**). Thus, the nature of the group seems more important than its position.

The reason for the less positive entropy of activation could be the attraction between the lone-pair electrons of negative ortho substituents and the positive charge on the oxygen atom of the conjugate acid. This should result in a more rigid structure of the transition state, and a decrease of the rate. However, in accordance with the LFER and the isokinetic relation, the ortho substituents also have an influence on the enthalpy, which is lowered so that the overall effect is an increase of the rate. For some ortho derivatives (2,6-dichloro and 2,4,6-trichloro), the linear correlation between the effect on $\Delta H^{\ddagger}$ and the effect on $\Delta S^{\ddagger}$ seems to be disturbed by rather special influences of these groups on the reaction centre.

The fundamental nature of these special effects is not clear. Too many factors possibly operate: the large concentration of negative charge in the vicinity of the reaction centre, the possibility of hydrogen bridges, direct field effects, steric hindrance of mesomeric effects, etc. We therefore feel that further explanation of this "ortho effect" in the present state of knowledge is too speculative and must await further experimental facts on the hydrolysis of a larger group of ortho-substituted phenyl β-D-galactopyranosides.

EXPERIMENTAL

The substituted phenyl β-D-galactopyranosides were synthesized as described previously[21]. When the solubility of the galactosides permitted, the hydrolysis was followed at 436 nm with a Perkin–Elmer model 141 photoelectric polarimeter, with jacketed polarimeter tubes connected to an ultrathermostat bath. The pseudo-first-order rate coefficients (ln *e*; sec^{-1}) were calculated from least-squares, straight-line fits of plots: log ($\alpha \pm \alpha_\infty$) *versus* time. The values of α_∞ were determined experimentally for corresponding solutions of D-galactose. As a check, some rate coefficients were also determined by the Guggenheim[22] method. These duplicate runs agreed within the estimated error.

If the solubility of the galactosides was too low, the release of phenol was followed by the method of Folin and Ciocalteu[23]. For each phenol, a calibration curve had to be constructed with the aid of known concentrations of the phenol in

similar conditions. The pseudo-first-order coefficients were then calculated from the usual log plots: log S_t *versus* time. The calculations of the thermodynamic activation functions were based on absolute-reaction rate theory[24], and performed as described previously[3].

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