1600, and 1585 cm^{-1} (purine nucleus); nmr δ (D_2O)[34] (2 H, singlet, purine H_2 and H_8), 5.34 (1 H, quartet, $J_{AX} + J_{BX} = 7.5$ cps, H_1), 4.50–4.21 (3 H, multiplet, H_4 and $2H_5$), 3.45 (3 H, singlet, CH_3O), and 2.16–1.97 (2 H, multiplet, $2H_2$). The ultraviolet spectra confirmed 9 substitution on the adenine nucleus.[35]

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.69; N, 26.40. Found: C, 49.46; H, 5.77; N, 26.10.

Registry No.—**1,** 16803-00-2; **2,** 16801-99-3; **3,** 16802-00-9; **4,** 16802-01-0; **5,** 16802-02-1; **6a,** 16802-03-2; **9,** 16802-04-3; **11,** 16802-05-4; **12,** 16802-06-5.

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A Kinetic Study of the Acid-Catalyzed Hydrolysis of Some Indolyl-β-D-glucopyranosides[1]

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First-order rate coefficients have been determined along with energies (E_a), enthalpies ($\Delta H^{\ddagger}$), and entropies ($\Delta S^{\ddagger}$) of activation for the acid-catalyzed hydrolyses of 3-indolyl- (**1a**), 5-bromo-3-indolyl- (**1b**), and 5-bromo-4-chloro-3-indolyl-β-D-glucopyranoside (**1c**). It was demonstrated that the rate of oxidation of the intermediate indoxyl (**2**) to indigo (**3**) was not rate determining. No significant difference in E_a is observed over a range of hydronium ion concentration. The relatively good agreement between the observed rate coefficients (k') and the corresponding theoretical values (k) supports the conclusion that the hydrolysis step and not the oxidation of the intermediate indoxyl (**2**) to an indigo (**3**) is rate determining. The solvent isotope effect ($k'_{D_2O}/k'_{H_2O} \geqq 2$) indicates rapid preequilibrium protonation of the glucosides. The dependence of rate on acidity (Hammett–Zucker relationship and the Bunnett w parameter) provides evidence for the unimolecularity of these hydrolyses. On the other hand, the values of $\Delta S^{\ddagger}$, which are narrowly positive, are consistent with several mechanistic possibilities which include the A1 mechanism.

Recent reports[3,4] from this laboratory described the syntheses of a number of indolyl-β-D-glycopyranosides (**1**) which have found application as agents for the histochemical localization of corresponding β-glycosidases in mammalian tissue.[4–6] The chromogenic reaction sequence underlying what has come to be known as "indigogenic staining"[7,8] is initiated by enzymic release of an intermediate indol-3-ol (indoxyl, **2**). The latter (*cf.* Scheme I) is rapidly and irreversibly transformed on air oxidation to an essentially insoluble (and highly colored) indigo (**3**) which is deposited at the sites of the activity.

The *O*-indoxyl derivatives, by virtue of the indigogenic principle, constitute a potentially useful group of substrates for kinetic studies of acid and base catalyzed, as well as enzymatic hydrolyses. The present study was undertaken to ascertain whether indolyl-β-D-glucopyranosides, as a consequence of a unique aglycon moiety, exhibit any unusual features when judged on the basis of the usual criteria (*vide infra*) employed in deciding the mechanism of the acid-catalyzed hydrolysis of relatively simple glycosides.

Experimental Section

Materials.—3-Indolyl-β-D-glucopyranoside {mp 178–180° dec $[\alpha]^{27}_{D}$ −65° (*c* 1.0, 50% aqueous DMF)} was purchased from the J. T. Baker Co. 5-Bromo-3-indolyl-β-D-glucopyranoside [mp 260–261° dec, $[\alpha]^{25}_{D}$ −59° (*c* 1.0, 50% aqueous DMF)] and 5-bromo-4-chloro-3-indolyl-β-D-glucopyranoside {mp 240–243°, $[\alpha]^{23}_{D}$ −89° (*c* 1.0, 50% aqueous DMF)} were prepared according to methods outlined in previous reports.[3,4] The purity of these pyranosides was checked by tlc on silica gel in butanol-water (86:14).

Spectrophotometry.—Spectrophotometric rates were determined using a Cary Model 11 recording spectrophotometer which was equipped with cell jackets thermostated by a Haake Type F constant-temperature bath. Both the jackets and the bath were joined in a series to a Thermo-Cool heat exchanger. This arrangement provided a temperature regulation of ± 0.02° over the desired range (47–65°). Rates were followed by observing the formation of **3a**, **b**, and **c** at 670, 600, and 660 mμ, respectively.

Beer–Lambert plots were utilized to ascertain the quantity of indigo (**3**) formed in the oxidation step. These plots, in turn, afforded a measure of the intermediate indoxyl (**2**) generated in the hydrolysis step. The procedure of Cotson and Holt[9] was adopted for the preparation of the plots which is based on the spectrophotometric measurement of the rate of appearance of the dyes. When such oxidations are carried out in aqueous solutions, the dyes initially form colloidal suspensions, the stabilities of which are not suitable for making reliable optical measurements. The dye sols can be stabilized by inclusion of 0.5% polyvinyl alcohol so that their optical properties do not vary over several hours, and certainly not for the duration of the kinetic measurements. It was found that the Beer–Lambert laws were obeyed by the polyvinyl alcohol stabilized sols of the indigo dyes over the concentration range encountered. Accordingly, it was possible to utilize optical densities directly in calculating velocity constants of the oxidation reactions.

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[1] (a) This investigation was supported in part by Public Health Service Research Grant No. CA-02624 from the National Cancer Institute and in part by an institutional grant to the Detroit Institute of Cancer Research Division of the Michigan Cancer Foundation from the United Foundation of Greater Detroit. (b) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. (c) Taken in part from a dissertation submitted by C. V. Easwaran to the Graduate School of The University of Detroit in partial fulfillment of the degree of Doctor of Philosophy.

[2] To whom all correspondence should be addressed at the Detroit Institute of Cancer Research Division of the Michigan Cancer Foundation.

[3] J. P. Horwitz, J. Chua, R. J. Curby, A. J. Tomson, M. A. DaRooge, B. E. Fisher, J. Mauricio, and I. Klundt, *J. Med. Chem.*, **7**, 574 (1964).

[4] P. L. Wolf, J. P. Horwitz, J. Vazquez, J. Chua, and M. A. DaRooge, *Amer. J. Clin. Pathol.*, **44**, 307 (1965).

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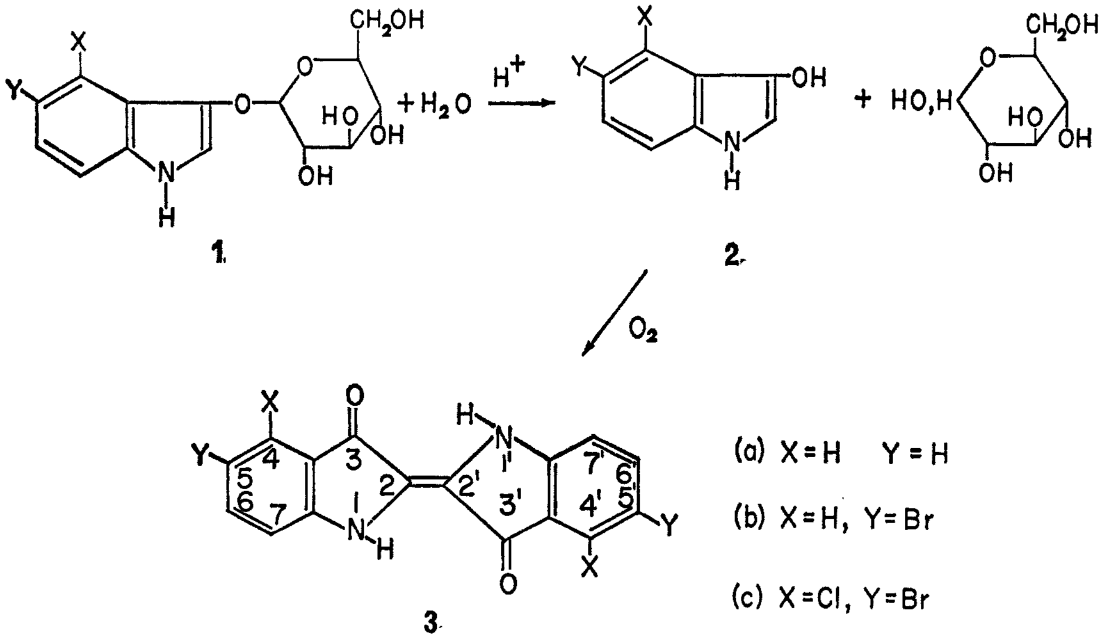
SCHEME I



The following procedure is considered typical. 5-Bromo-4-chloro-3-indolyl-β-D-glucopyranoside (**1c**, 17.5 mg) in 2 ml of ethanol was diluted to 100 ml by the addition of a deoxygenated solution of 0.5% aqueous polyvinyl alcohol. To 3 ml of 1.16 *M* hydrochloric acid, which had previously been swept with (99.9%) nitrogen, was added 3 ml of the stock solution of substrate (**1c**). The reaction mixture was maintained under a positive pressure of highly purified nitrogen[10] until the hydrolysis of **1c** was complete (*ca.* ten half-life periods). Only in this manner was it possible to prepare solutions of **2c** of known strength, *i.e.*, free of the product (**3c**) of oxidation.

Shortly before spectrophotometric measurements were to be made (as described below), 3 ml of the indoxyl solution was withdrawn using a nitrogen-filled pipet and emptied rapidly into 1 ml of oxygenated 0.5% polyvinyl alcohol. The reaction mixture was then quickly transferred to a 3.5-ml cuvette (10-mm path), the mixing and transfer requiring less than 30 sec. The cuvette, after shaking, was inserted in the thermostated block of the spectrophotometer to initiate the recording of the absorbance change. It was found that the Beer-Lambert laws were obeyed by the polyvinyl alcohol stabilized sols of the indigo dyes over the concentration ranges encountered.

Hydrolysis Procedure.—Solutions of **1** in aqueous hydrochloric acid were prepared as described in the previous section. The reactants consisting, for example, of 3 ml of 2.54 *M* hydrochloric acid and 3 ml of the stock solution of substrate (3.43×10^{-4} *M*) were elevated (individually) to the desired temperature by incubation in the constant-temperature bath, then mixed, and immediately transferred to the spectrophotometer. The procedure, in essence, was identical with that described above for the oxidation of **2** to **3** with exception that the hydrolysis was effected under aerobic conditions.

From a knowledge of the concentration of **3** and the initial concentration of **1**, the fraction of unreacted substrate could be calculated. Plots of the natural logarithm of the concentration of unreacted **1** *vs.* time were constructed and first-order rate constants were calculated by least-square straight-line fits. Duplicate rate constant determination agreed within ±2.5%.

Calculation of Activation Parameters.—Energies of activation were obtained from a minimum of five rate constants determined at 47, 50, 55, and 65°. When log *k* was plotted against 1/T, straight lines were obtained throughout. Entropies of activation were calculated from the relationship

$$T\Delta S^{\ddagger} = E - RT - RT \ln (kT/h) + RT \ln (k'/h_0),$$

where T = temperature of the hydrolysis, °K; $k = 1.3805 \times 10^{-16}$ erg deg^{-1} molecule^{-1}; $h = 6.6252 \times 10^{-27}$ erg sec^{-1}; k' = first-order rate coefficient, sec^{-1}; $h_0 = e^{-H_0}$ (at T, °C).

Results

The selection of the particular 3-indolyl-β-D-glucopyranosides was based on the earlier observation that 5-bromo (**1b**) and 5-bromo-4-chloro (**1c**) derivatives afford the most precise histochemical results.[5,6] The unsubstituted derivative (**1a**) was utilized to evaluate, as a first approximation, the effect of the halogen(s).

The aerial oxidation of a number of haloindol-3-ols (**2**) to the corresponding indigo (**3**) has been studied kinetically over a pH range of 6–8.5 by Cotson and Holt.[9] The velocity constant for the oxidation of 5-bromo-4-chloroindol-3-ol (**2c**), for example, which was generated from the hydrolysis of the 3-*O*-acetyl derivative was found to be 4×10^{-3} sec^{-1} at pH 8.0. However, the rate of oxidation was observed to decrease sharply below pH 7.4. Accordingly, it was first necessary to demonstrate that the oxidation step in aqueous hydrochloric acid is not rate controlling in the conversion of **1** into **3**. The methods of the English group[9] were applied to the oxidation of **2c** to **3c**, which served as a model. The rate coefficients, compiled in Table I, were determined as a function of temperature at several concentrations of hydrochloric acid. The rate values, as will be shown in a succeeding section, were found to be significantly greater (*cf.* Tables I and

TABLE I
RATE COEFFICIENTS FOR THE
AIR OXIDATION OF 5-BROMO-4-CHLOROINDOL-3-OL
TO 5,5'-DIBROMO-4,4'-DICHLOROINDIGO

Acid molarity	Temp, °C	Rate coefficient $k' \times 10^5$, sec^{-1}
1.16	47.2	10.65
2.95	47.2	8.65
3.70	47.2	7.82
3.70	49.5	9.30
3.70	55	14.70
3.70	60	22.00

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[10] Matheson high purity grade nitrogen (99.9%) was further purified by passing the gas through a train consisting of copper oxide (400°), soda lime, magnesium perchlorate, and manganese oxide (150°), according to the procedure of K. E. Francis and N. Hodge, *At. Energy Research Establ., G. Brit.*, Rept. R-3710, 12 (1961); *Chem. Abstr.*, **56**, 12703 (1962).

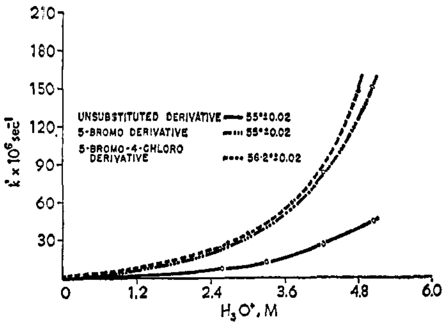

Figure 1.—Effect of hydronium ion concentration on the rate of hydrolysis of some indolyl-β-D-glucopyranosides (Scheme I).

II) than the rate constant for the hydrolysis of **1c** at a corresponding acid molarity. An apparent energy of activation (E_a) of 17.5 kcal for the oxidation step was derived from a plot of ln k *vs.* $1/T$.

Table II

Rate Coefficients for the Hydrolysis of Some 3-Indolyl-β-D-glucopyranosides (1) in Hydrochloric Acid

Glucoside	Temp, °C	$k' \times 10^5$, sec^{-1}				
		2.54 *M*	3.28 *M*	4.26 *M*	5.04 *M*	
1a	55	0.71	1.11	2.57	4.48	
	56.2	0.89	1.26	2.78	6.05	
	60	1.35	2.5	5.5	10.6	
	65	2.51	4.36	10.4	18.2	
1b	47.2	0.75	1.12	3.02	5.5	
	50	1.15	2.04	4.57	8.42	
	55	2.31	3.20	8.42	15.14	
	60	4.57	5.75	15.97	27.80	
		2.67 *M*	2.95 *M*	3.70 *M*	4.80 *M*	5.40 *M*
1c	47.2	0.84	1.13	2.10	5.0	8.45
	50	1.21	1.31	2.81	7.25	14.80
	56.2	2.54	3.02	5.50	14.75	23.65
	60	4.65	5.31	7.95	22.90	35.40

The observed first-order rate coefficients for the hydrolysis of **1**, at several different concentrations of hydrochloric acid and at various temperatures, are shown in Table II. The rate constants for the halogen substituted derivatives (**1b** and **1c**) are only slightly greater than those for the unsubstituted compound (**1a**). Apparently, these substituents are too distant from the site of bond fission to be of any serious consequence in the rate-determining step.

Figure 1 shows plots of these same constants *vs.* hydronium ion concentration. The latter were calculated from the ionization of aqueous hydrochloric acid, according to the methods of Young, *et al.*,[11a] and Leininger.[11b] It is apparent that the rate constants are nearly proportional to the hydronium ion concentration at low concentrations but increase rapidly above approximately 1.5 *M*.

The activation energies and their estimated standard deviations (Table III) were calculated from least-squares straight-line fits of Arrhenius plots. No significant difference in activation energies was detected over a range of hydronium ion concentrations. The relatively good agreement (*cf.* Table IV) between the observed rate coefficients (k') and the corresponding theoretical values (k), calculated from the relationship

$$k = AT^n e^{-E/RT}$$

supports the conclusion that the hydrolysis, and not the oxidation step, is rate determining.

Table III

Kinetic and Thermodynamic Parameters for the Hydrolysis of Some 3-Indolyl-β-D-glucopyranosides in Hydrochloric Acid[a,b]

Glucoside	E_a kcal mol^{-1}	$\Delta S^{\ddagger}$ cal deg^{-1} mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta F^{\ddagger}$ kcal mol^{-1}
1a	28.4 ± 0.5	2.2 ± 0.2	27.7 ± 1.0	27.0 ± 1.0
1b	27.8 ± 0.15	0.6 ± 0.01	26.75 ± 0.75	26.5 ± 0.5
1c	26.4 ± 0.4	0.4 ± 0.01	27.1 ± 1.0	26.9 ± 1.0

[a] Concentration of HCl ranged from 2.54 to 5.04 *M*. [b] Reaction examined over the temperature range of 47–60°.

Table IV

Theoretical and Experimental Rate Coefficients for the Hydrolysis of Some 3-Indolyl-β-D-glucopyranosides in Hydrochloric Acid

Glucoside	HCl, *M*	Temp, °C	Rate constant, × 10^{-5}, sec^{-1} Theoretical k	Observed k'
1a	2.54	55	0.74	0.71
		56.2	0.87	0.89
		60	1.41	1.35
		65	2.57	2.51
1b	2.54	47.2	0.93	0.75
		50	1.29	1.15
		55	2.37	2.31
		60	4.93	4.57
1c	3.70	47.2	2.65	2.10
		50	2.95	2.81
		55	5.58	5.50
		60	8.15	7.95

A solvent isotope effect was observed (*cf.* Table V) in the hydrolysis of **1** by measuring the reaction rates in normal and heavy water. The ratios of these constants (k'_{D_2O}/k'_{H_2O}) are in a range (1.9–2.7) indicative of rapid pre-equilibrium protonation of the glucosides and of specific acid catalysis.[12,13] Evidence for the molecularity of the slow step was derived from examination of the dependence of rate on acidity. Plots of log k'_{obsd} *vs.* H_0 are straight lines (Figure 2) of virtually unit negative slopes (Table VI). This implies, according to the Hammett–Zucker hypothesis,[14] that the rate-determining step in-

Table V

Rate Coefficients for the Hydrolysis of Some 3-Indolyl-β-D-glucopyranosides in D_2O and H_2O

Glucoside	Temp, °C	Rate constants × 10^5, sec^{-1} k'_{H_2O}	k'_{D_2O}	k'_{D_2O}/k'_{H_2O}
1a	55	0.704	1.35	1.92
	60	1.30	2.44	1.88
1b	50	1.10	2.84	2.58
	60	4.36	11.10	2.54
1c	50	1.13	3.04	2.70
	60	4.45	11.75	2.63

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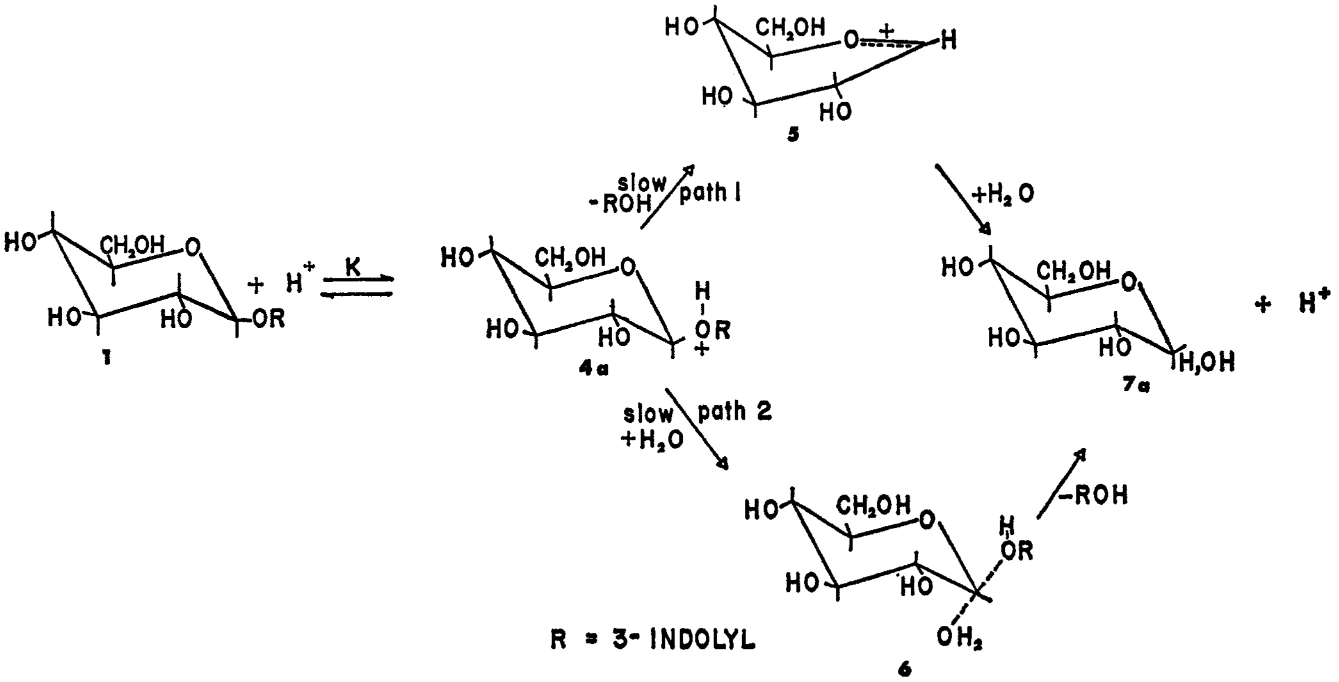
[11] (a) T. F. Young, L. F. Maranville, and H. M. Smith, "The Structure of Electrolytic Solutions," W. J. Hamer, Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p 48; (b) P. M. Leininger and M. Kilpatrick, *J. Amer. Chem. Soc.*, **60**, 2892 (1938).

[12] (a) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 6008 (1956); **80**, 4162 (1958); (b) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 3207 (1961).

[13] (a) D. McIntyre and F. A. Long, *ibid.*, **76**, 3240 (1954); (b) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 938 (1957).

[14] (a) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1939); (b) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 273.

SCHEME II



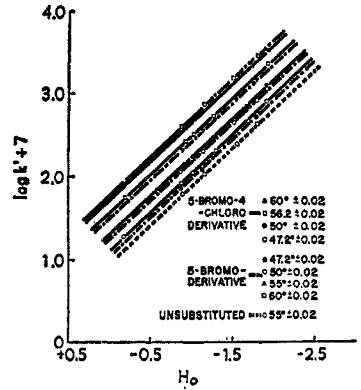


Figure 2.—Hammett–Zucker plot (log *k vs.* H_0) for the hydrolysis of **1** in hydrochloric acid.

TABLE VI

SLOPES DERIVED FROM PLOTS OF HAMMETT–ZUCKER AND BUNNETT PARAMETERS

Glucoside	Temp Range, °C	Hammett–Zucker slope values	Bunnett (w) slope values
1a	55–65	-0.970 ± 0.03	$+0.2 \pm 0.02$
1b	47.2–60	-0.970 ± 0.005	$+0.25 \pm 0.03$
1c	47.2–60	-0.950 ± 0.003	$+0.33 \pm 0.01$

volves unimolecular decomposition of the conjugate acid without participation of water (A1). However, Timell[15] has recently shown that, in the hydrolysis of methyl α-D-glucopyranoside, the requirement of unit slope is only approximately fulfilled in three of four mineral acids examined. For this reason, acidity dependence was investigated by the method of Bunnett.[16] Plots of log $k'_{\text{obsd}} + H_0$ *vs.* a_{H_2O} for the three glucosides were straight lines (Figure 3) with slopes ("w" parameter) in the range of +0.2 to +0.4 (*cf.* Table VI). These slopes are narrowly within the range of w values (+0.4 to −5.0) for the acid-catalyzed hydrolysis of glycopyranosides which are classified by Bunnett as proceeding by the unimolecular mechanism. It is pertinent to note, however, that a distinction in mechanism in the case of certain glycosides, made on the basis of this criterion, is not in accord with conclusions reached from interpretation of entropy data.[17]

In view of the doubts associated with rate–acidity correlations as a basis for predicting molecularity, additional evidence was deemed necessary to decide the mechanism of hydrolysis of **1**. Accordingly, the thermodynamic activation parameters of the three glucosides were calculated on the basis of the theory of absolute reaction rates.[18] The method of determination of specific rates utilized in the calculation of the free energies of activation was described above. The activation energies used, in turn, to calculate the enthalpies of activation were average values taken over the range of hydronium ion concentration examined. The results are listed in Table III. It is apparent that the enthalpies of activation for the three glucosides are essentially the same and the small differences in the rate constant are, accordingly, a consequence of the entropy function.

Discussion

The mechanism generally accepted for the acid-catalyzed hydrolysis of simple alkyl glycopyranosides is that first suggested by Edward.[19] It involves a rapid, equilibrium-controlled protonation of the glycosidic oxygen to give the corresponding conjugate acid (Scheme II, **4a**). In the rate-determining step, **4a** decomposes in a unimolecular heterolysis (A1 mechanism) to form an alcohol and a carbonium–oxonium ion (**5**), which reacts with water to form glucose (**7a**). However, the suggestion has been made that some glycopyranosides hydrolyze by the A2 mechanism[16] which is characterized by the presence of a molecule of water in the transition state (**6**). If the reaction were bimolecular, then the

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[15] T. E. Timell, *Can. J. Chem.*, **42**, 1456 (1964).

[16] J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

[17] L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

[18] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1963, p 77.

[19] J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

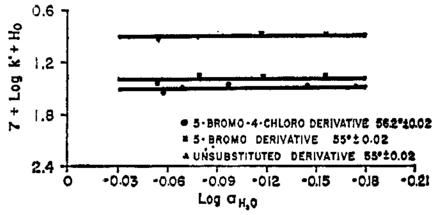


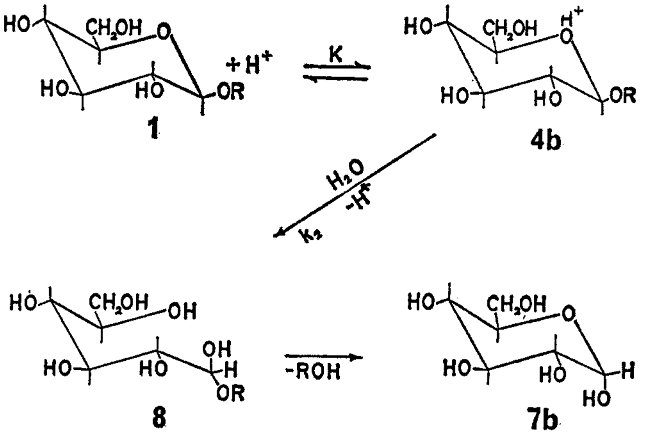
Figure 3.—Bunnett plot (log k + H_0 *vs.* log a_{H_2O}) for the hydrolysis of **1** in hydrochloric acid.

transition step would constitute a more highly ordered structure than the ground state (**4a**). This would result in a decrease in entropy and $\Delta S^{\ddagger}$ would tend to be negative. The unimolecular reaction, on the other hand, presents a less ordered transition state relative to **4a** and, $\Delta S^{\ddagger}$ should be positive.

The $\Delta S^{\ddagger}$ values for **1** are all narrowly positive (*cf.* Table III) and, as such, are in accord with the fact that unimolecular acid-catalyzed hydrolyses usually exhibit entropies of activation near zero, though exceptions are known.[17,20] Moreover, the entropy data, when viewed in context with other criteria of molecularity that have been examined in this study, constitute convincing evidence for the A1 mechanism. On the other hand, the observed entropies of activation are considerably lower than the mean of +13.7 eu reported by Overend and coworkers[21] for 24 glycosides for which the A1 mechanism has also been suggested. It might be argued that this difference indicates a change of mechanism, possibly some participation by water in the transition state, *i.e.*, partial A2 character. However, the incursion of the A2 mechanism in the case of pyranosides encounters the objection that nucleophilic attack on a six-membered ring is a slow process.[22]

An alternative explanation of the low entropy values can be derived by assuming that the 3-indolyl-β-D-glucopyranosides, unlike the simple alkyl derivatives, react with ring opening; that is, the reactive conjugate acid (**4b**) is the ring-protonated species, shown in Scheme III. Obviously, the requirement of rapid proton transfer, indicated by the solvent isotope effect, is satisfied by either conjugate acid (**4a** or **b**). Attack by water concerted with ring opening would lead to an acyclic hemiacetal (**8**) and ultimately to glucose (**7b**) in a manner analogous to that suggested by Capon[23] for furanosides. The observed rate constant would be given by $k'_{\text{obsd}} = k_2K$ where

Scheme III



K is the equilibrium constant for the initial proton transfer reaction. The observed entropy of activation would then be $\Delta S^{\ddagger} = \Delta S^0 + \Delta S_2^{\ddagger}$ where ΔS^0 is the standard entropy of proton-transfer. The latter is normally positive and, in addition, usually large.[24] While $\Delta S_2^{\ddagger}$ is negative, since it is the entropy of activation of the bimolecular reaction (k_2) between the ring-protonated conjugate acid and water, the observed entropy of activation ($\Delta S^{\ddagger}$) might still be positive if ΔS^0 is dominant.[25]

The possibility of an acyclic ion was considered along with a carbonium–oxonium ion by Vernon and coworkers[26] in connection with the unimolecular mechanism. There remains the problem of distinguishing experimentally between these possibilities and consequently the argument still rages. One objection to the "open-chain" mechanism is that it would lead to extensive anomerization unless recyclization of the carbonium ion is much faster than rotation about the C_1–C_2 bond. No effort was made to resolve this question in the present study, but it should be noted that attack by water concerted with ring opening overcomes this objection. However, this interpretation, while it perhaps provides a more satisfactory explanation of the observed entropy data, stands in contradiction to the molecularity of the slow step as established on the basis of rate *vs.* acidity studies.

It is apparent that the present data precludes a firm choice between the several mechanistic possibilities. However, the bulk of the evidence favors an A1 mechanism for the acid-catalyzed hydrolysis of **1**.

Registry No.—**1a**, 16934-10-4; **1b**, 16934-09-1; **1c**, 15548-60-4.

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[20] R. K. Chaturvedi and E. H. Cordes, *J. Amer. Chem. Soc.*, **89**, 4631 (1967).

[21] W. G. Overend, C. W. Rees, and J. S. Sequeiva, *J. Chem. Soc.*, 3429 (1962).

[22] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, p 265.

[23] B. Capon and D. Thacker, *J. Chem. Soc.*, 185 (1967).

[24] E. Whalley, *Trans. Faraday Soc.*, **55**, 799 (1959).

[25] Because of the high values of ΔS^0 that can occur, an observed entropy of activation of +10 eu, according to Whalley (see ref 24), cannot be considered to prove or even to suggest strongly an A1 mechanism.

[26] C. A. Bunton, T. A. Lewis, R. Llewellyn, and C. A. Vernon, *J. Chem. Soc.*, 4419 (1955).