ionic strength is brought to 0.2 N with tetraethylammonium (TEA^+) bromide, the binding of Na^+ is about twice as large as it is with TMABr at the same ionic strength.[13] Because of their larger size the TEA^+ ions cannot shield the PO_3^--groups as effectively from each other as can the TMA^+ ions.

Effect of Temperature.—If the data obtained at 5 and 25° in Table I are compared, one finds that the values of β_M are somewhat larger at 25 than at 5° at the few lowest concentrations of both Li^+ and Na^+. The effect seems to disappear at higher $(M^+)_0$ and also is not observable with K^+ and Cs^+. The results suggest that the change of enthalpy on binding is slightly positive at low (Li^+) and (Na^+) and very close to zero in the other cases. Since values of equilibrium constants were not obtained at 25°, no quantitative calculation of ΔH and ΔS can be made.

(13) P. D. Ross and U. P. Strauss, unpublished results.

NEW BRUNSWICK, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, RIVERSIDE]

The Lactone–Acid–Salt Equilibria for D-Glucono-δ-lactone and the Hydrolysis Kinetics for this Lactone

BY DONALD T. SAWYER AND JOHN B. BAGGER

RECEIVED APRIL 20, 1959

Polarimetric and coulometric methods have been used for the study of the hydrolysis rate for D-glucono-δ-lactone at various solution conditions. The hydrolysis reaction is first order in lactone concentration and independent of pH from pH 3 to pH 5. The rate constant k at 25° is: by optical rotation, 2.26×10^{-4} sec.$^{-1}$; by coulometry, 1.31×10^{-4} sec.$^{-1}$. The activation energy for the lactone hydrolysis reaction is 15 kcal. per mole for the temperature range from 20 to 25°. To carry out the polarimetric studies it was necessary to redetermine the specific optical rotations for D-glucono-δ-lactone, gluconic acid and sodium gluconate; the values of $[\alpha]^{25}D$ for the three species are, respectively +66.0, +5.40 and +12.0°. The constants for several of the lactone–acid–salt equilibria have been determined at 25° by pH and optical rotation measurements (L, HGH_4 and GH_4^- represent D-glucono-δ-lactone, gluconic acid and gluconate ion, respectively): $K = (H^+)\cdot(GH_4^-)/[(HGH_4) + (L)] = 1.76 \pm 0.05 \times 10^{-4}$; $K_A = (H^+)(GH_4^-)/(HGH_4) = 1.99 \pm 0.07 \times 10^{-4}$; and $K_L = (HGH_4)/(L) = 7.7$.

The existence of strong metal–gluconate complexes, which are formed by the salts of D-glucono-δ-lactone, has brought about renewed interest in the aqueous solution chemistry of this lactone.[1–3] Because the equilibrium constants for the lactone–acid–salt equilibria are frequently necessary for the calculation of the metal–gluconate stability constants, accurate evaluation of the equilibrium constants is desirable. Previous workers[4–6] have reported various values for the dissociation constant of gluconic acid, but they have not taken into account the lactone–acid equilibria and, in some cases, details of temperature and of the purity or preparation of the acid were not reported.

Although empirical data have been reported for the hydrolysis of D-glucono-δ-lactone,[7] quantitative relations were not developed and the effect of the competing equilibria was neglected. Furthermore, the specific rotations which were used for some of the hydrolysis rates do not agree with our values or those reported in the literature[8] and the rotation due to sodium gluconate was not included in the calculations of data reported. The salts of D-glucono-δ-lactone are being used widely as chelating agents and a more fundamental understanding of the hydrolysis kinetics for this lactone is of value. Also, kinetic data may be helpful in establishing the mechanism for chelation and in determining the structure of various metal–gluconate chelates.

The results of a systematic study of the lactone–acid–salt equilibria for D-glucono-δ-lactone are presented as well as a detailed study of the hydrolysis kinetics for the lactone by coulometric and polarimetric techniques. The constants for the equilibria have been evaluated by combining pH measurements with optical rotation data. The specific rotations for gluconic acid, sodium gluconate and the δ-lactone have been determined in order to evaluate the equilibrium constants and the rate constants.

Experimental

The coulometric generator and cell which were used for the kinetic studies have been described previously.[9] The generator provides a continuously variable constant current for the range from 1 to 150 milliamperes which is regulated to one-quarter of one per cent. Details for the cell system, the electrolyte solution and the procedure for making a rate constant determination are identical to those used in the previous kinetic studies of water-soluble esters.[9] Approximately 28 ml. of electrolyte solution (0.1 F K_2SO_4 and 0.03 F KBr) is introduced into the cell (the cell solution is degassed with purified nitrogen) and the pH is adjusted to the desired value (pH 3.4 to pH 4.6) coulometrically. The weighed sample is introduced as pure solid D-glucono-δ-lactone. The generation of hydroxide is started immediately and the current is adjusted until the desired pH is obtained.

All pH measurements were made with a Beckman Model GS pH meter, which was standardized with N.B.S. buffers. Unless otherwise noted all measurements were made at 25.0 ± 0.1°.

(1) R. L. Pecsok and R. S. Juvet, Jr., THIS JOURNAL, **77**, 202 (1955); R. L. Pecsok and J. Sandera, *ibid.*, **77**, 1489 (1955); R. L. Pecsok and R. S. Juvet, Jr., *ibid.*, **78**, 3907 (1956); R. L. Pecsok and J. Sandera, *ibid.*, **79**, 4069 (1957).

(2) C. L. Mehltretter, B. H. Alexander and C. E. Rist, *Ind. Eng. Chem.*, **45**, 2782 (1953).

(3) Chas. Pfizer and Co., "Gluconic Acid and Derivatives," Technical Bulletin No. 33, Brooklyn, N. Y., 1955.

(4) R. K. Cannan and A. Kibrick, THIS JOURNAL, **60**, 2314 (1938).

(5) J. Boeseken, J. Weisfelt, J. V. D. Spek, C. V. Loon and M. Goeltsch, *Rec. trav. chim.*, **37**, 165 (1918).

(6) E. Heing, *Biochem. Z.*, **321**, 314 (1951).

(7) Chas. Pfizer and Co., "Glucono-Delta-Lactone in Food Products," Technical Bulletin No. 93, Brooklyn, N. Y., 1957.

(8) O. F. Heydenberg, THIS JOURNAL, **37**, 345 (1915).

(9) P. S. Farrington and D. T. Sawyer, *ibid.*, **78**, 5536 (1956).

Optical rotations were measured with a Rudolph Precision Polarimeter, No. 70, to a precision of ± 0.01° of arc. A 200 mm. thermostated polarimeter tube was used for all measurements.

The specific rotation for the δ-lactone was evaluated by adding pure lactone to make a 0.05 or 0.10 *F* solution in a 0.14 *F* formic acid and 0.30 *F* sodium formate buffer. A stopwatch was started and the solution was immediately placed in a thermostated polarimeter tube. Polarimeter readings were taken once a minute, plotted *vs.* time and extrapolated to zero time to obtain the specific rotation for the pure δ-lactone. For gluconic acid, a solution of the δ-lactone was made basic (*p*H 9) and allowed to equilibrate for two days. The gluconate solution then was added quickly to a sulfuric acid solution to give a final gluconic acid concentration of 0.05 to 0.1 *F* with a *p*H of 1. A stopwatch was started simultaneously and polarimetric readings were taken once a minute and treated in a similar manner to those for the δ-lactone with the extrapolated value at zero time taken as the specific rotation for gluconic acid. The value for sodium glyconate was obtained by making a 0.05 to 0.1 *F* solution of the δ-lactone basic to *p*H 9 and allowing the solution to equilibrate for two days before polarimeter readings were taken.

The D-glucono-δ-lactone (Matheson, Coleman and Bell) was recrystallized twice from ethylene glycol monomethyl ether and dried for 1 hr. at 110°. The recrystallized lactone, which had a melting point of 152–153°, was analyzed by adding excess standard sodium hydroxide and back titrating with standard hydrochloric acid. The D-glucono-δ-lactone was found to be 99.6% pure. All other materials were reagent grade.

Results and Discussion

D-Glucono-δ-lactone (hereafter the lactone is represented by L, gluconic acid by HGH_4 and the gluconate ion by GH_4^-) hydrolyzes in water to a mixture of the δ-lactone, the γ-lactone and gluconic acid[7]

$$L_\delta \rightleftarrows L_\gamma \qquad (1)$$

$$\searrow\nwarrow \quad \nearrow\swarrow$$

$$HGH_4$$

Because the reported values[8] for the specific rotations of the δ-lactone and γ-lactone are almost identical (+65.5° and +67.5°, respectively), it is not possible to distinguish between the two lactones in aqueous solution. Therefore the subsequent discussion will consider the two lactones as being entirely in the form of the δ-lactone. Gluconic acid dissociates to give a proton and the gluconate ion

$$HGH_4 \rightleftarrows H^+ + GH_4^- \qquad (2)$$

The over-all equilibrium in solution can be represented by the constant

$$K = \frac{(H^+)(GH_4^-)}{(HGH_4) + (L)} \qquad (3)$$

Although several values have been reported for this constant,[4-6] they range from 1.38×10^{-4} to 2.78×10^{-4} and the fact that these values actually represent *K* is only implied. Also, the reported experimental conditions were not specific or complete.

The value for *K* has been determined in our laboratory by *p*H measurements for the pure lactone over the concentration range from 0.006 to 0.2 *F*. The constant also has been evaluated at the half-equivalence point over the same concentration range. The solutions were prepared with carbon dioxide-free water and allowed to equilibrate for 72 hr. before the *p*H was determined. All solutions were run in duplicate. The results of these determinations are summarized in Table I; $K = 1.76 \pm 0.05 \times 10^{-4}$ is taken as the best value.

TABLE I

VALUES FOR LACTONE–ACID–SALT EQUILIBRIUM CONSTANT

Concn., moles/l.	*p*H	*K*
	A. Pure lactone	
0.200	2.22, 2.22	1.88×10^{-4}
.100	2.39, 2.38	1.77×10^{-4}
.050	2.55, 2.54	1.73×10^{-4}
.025	2.71, 2.70	1.70×10^{-4}
.0125	2.87, 2.87	1.64×10^{-4}
.00625	3.04, 3.03	1.60×10^{-4}
	B. Half-neutralized lactone	
0.200	3.70, 3.73	1.93×10^{-4}
.100	3.73, 3.76	1.81×10^{-4}
.050	3.75, 3.78	1.74×10^{-4}
.025	3.78, 3.82	1.63×10^{-4}
.0125	3.81, 3.84	1.56×10^{-4}
.00625	3.85, 3.88	1.49×10^{-4}

The dissociation constant for gluconic acid is also of interest and has been evaluated by measuring

$$K_A = \frac{(H^+)(GH_4^-)}{(HGH_4)} \qquad (4)$$

the optical rotation of an equilibrium solution of the lactone at various concentrations and in the presence of different buffers.

The specific rotation for the δ-lactone has been reported in the literature,[8] but the value was recorded 5 minutes after solution of the lactone in a system which rapidly hydrolyzes. In addition, the work was done at 20°. Values for the specific rotation of gluconic acid were also given, but were evaluated 45 minutes after solution in a system which was equilibrating rapidly, and again at 20°. Subsequently, a value has been reported for sodium gluconate at 20°.[10] Because of the somewhat questionable accuracy of these literature values and because they are at 20° rather than 25°, the specific rotations for D-glucono-δ-lactone, gluconic acid and sodium gluconate have been redetermined at the higher temperature and are summarized in Table II.

TABLE II

SPECIFIC AND MOLAR ROTATIONS

	$[\alpha]^{25}D$	Molar rotation, 200 mm. tube
D-Glucono-δ-lactone	+66.0°	+23.5°
Gluconic acid	+ 5.40°	+ 2.12°
Sodium gluconate	+12.0°	+ 5.25°

The molar rotations for the three gluconate molecules using a 200 mm. polarimeter tube at 25° are also given in Table II.

By assuming that the molar rotations are additive and by using the values given in Table II, the rotation of a lactone–acid–salt solution can be

(10) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **26**, 355 (1916).

related to the concentration of the three gluconate species

$$R = 23.5(L) + 2.12(HGH_4) + 5.25(GH_4^-) \quad (5)$$

where R is the optical rotation for the solution in a 200 mm. polarimeter tube. The sum of the concentrations for the three gluconate species is equal to the total concentration of lactone C_T originally placed in the solution

$$C_T = (L) + (HGH_4) + (GH_4^-) \quad (6)$$

By combining equations 3, 5 and 6 the dissociation constant for gluconic acid (K_A in equation 4) can be evaluated. To do this, the pH and the optical rotation of a gluconate solution must be measured, and the amount of lactone originally placed in the solution and K (equation 3 and Table I) must be known. All solutions were allowed to equilibrate for at least 72 hr. before readings were taken. The values for K_A at various concentrations in different buffer solutions which have been calculated by this method are summarized in Table III; $K_A = 1.99 \pm 0.07 \times 10^{-4}$ is taken as the best value.

TABLE III

VALUES FOR GLUCONIC ACID DISSOCIATION CONSTANT

Lactone concn., moles/l.	Buffer system	Optical rotation R	pH	$K_A \times 10^4$
0.100	0.05 F potassium acid phthalate	+0.360°	3.08	1.86
.100	0.30 F sodium formate, 0.14 F formic acid	+ .504°	3.72	2.02
.100		+ .468°	2.36	1.99
.050	0.60 F sodium formate, 0.29 F formic acid	+ .240°	3.96	1.94
.050	0.42 F sodium formate, 0.47 F formic acid	+ .280°	3.64	2.14

By dividing equation 3 by equation 4 and rearranging terms an equilibrium expression is obtained for the hydrolysis of the lactone

$$L + H_2O \rightleftharpoons HGH_4 \quad (7)$$

$$K_L = \frac{(HGH_4)}{(L)} = \frac{K}{K_A - K} = 7.7 \quad (8)$$

Equations 3, 5 and 6 also can be used to determine the concentrations of lactone, gluconic acid and gluconate ion at any instant for a hydrolyzing lactone solution. This can be accomplished by placing a known amount of lactone into a buffered solution of known pH and measuring the optical rotation of the solution in a thermostated tube. Using a formate buffer of pH 4 and an initial lactone concentration of 0.05 F, a plot of the logarithm of the lactone concentration (corrected for the equilibrium lactone concentration) *vs.* time gives a linear curve, as shown in Fig. 1; several other studies at different conditions also are shown in Fig. 1. These data support the conclusion that the hydrolysis is first order with respect to lactone concentrations. Graphing the data in terms of three-halves order and second-order kinetics gave non-linear curves. Table IV summarizes the kinetic studies by the optical rotation method at 25° using various buffers and initial lactone concentrations.

TABLE IV

RATE OF LACTONE HYDROLYSIS BY OPTICAL ROTATION METHOD

Initial lactone concn., moles/l.	Buffer system	pH	k, sec.$^{-1}$
0.05	0.60 F sodium formate .29 F formic acid	3.98	2.98×10^{-4}
.05	.42 F sodium formate .47 F formic acid	3.67	3.06×10^{-4}
.10	.30 F sodium formate .14 F formic acid	4.00 → 3.72	1.86×10^{-4}
.10	.05 F potassium acid phthalate	4.01 → 3.08	1.16×10^{-4}

For those systems where the pH has changed during the course of the hydrolysis, corrections based on the approximate pH at a given time have been made in the calculations. From the data in this table the hydrolysis appears to be independent of pH in the region covered by the data.

Because the coulometric method has been shown to be a convenient method for studying the kinetics of fast hydrolysis reactions,[9] the technique has been applied to the hydrolysis of D-glucono-δ-lactone. The general equations and theory of the coulometric method are the same as previously described[9] but are summarized briefly here. Equation 7 represents the hydrolysis reaction for the lactone. At pH's greater than 3 significant portions of the gluconic acid react with base to form the gluconate ion as shown by equation 4. The rate of coulometric generation of hydroxide ion to maintain a constant pH is exactly equal to the rate of production of gluconate ion

$$\frac{d(GH_4^-)}{dt} = \frac{d(OH^-)}{dt} = \frac{i}{VF} \quad (9)$$

where

i is the current in amperes
V is the volume in liters
F is the faraday

The rate of disappearance of lactone can be related to the rate of production of gluconate ion by using equation 4

$$\frac{-d(L)}{dt} = \frac{d(HGH_4)}{dt} + \frac{d(GH_4^-)}{dt} = \left[1 + \frac{(H^+)}{K_A}\right] \frac{d(GH_4^-)}{dt} \quad (10)$$

which, when combined with equation 10, gives

$$\frac{-d(L)}{dt} = \left[1 + \frac{(H^+)}{K_A}\right] \frac{i}{VF} \quad (11)$$

The data in Table V summarize the results of a series of coulometric studies at various lactone concentrations and pH's at 25, 22.5 and 20°. At least three separate runs have been made for each value in Table V. The lactone concentrations have been corrected for depletion during the course of the run (less than 500 sec.) and from these corrected values the final equilibrium lactone con-

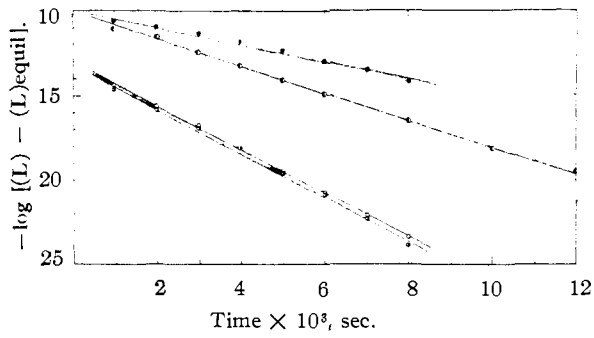

Fig. 1.—Rate of hydrolysis of D-glucono-δ-lactone at 25° using various buffers and initial lactone concentrations: (○) 0.05 *F* lactone, 0.60 *F* sodium formate–0.29 *F* formic acid, *p*H 3.98; (◑) 0.05 *F* lactone, 0.42 *F* sodium formate–0.47 *F* formic acid, *p*H 3.67; (◐) 0.10 *F* lactone, 0.30 *F* sodium formate–0.14 *F* formic acid, *p*H 4.00→3.72; (●) 0.10 *F* lactone, 0.05 *F* potassium acid phthalate, *p*H 4.01 → 3.08.

centrations as determined by equations 3 and 4 have been subtracted (the constants have been assumed to hold for the 20 and 22.5° runs). The data in Table V support the conclusion that the rate of hydrolysis for the lactone is independent of *p*H from *p*H 3 to *p*H 5.

TABLE V

RATE OF LACTONE HYDROLYSIS BY COULOMETRIC METHOD

Initial lactone concn. × 10² moles/l.	Effective lactone concn. × 10² (L)cor. − (L)equil.	*p*H	$-\frac{d(L)}{dt}$ × 10⁶	$k \times 10^4$, sec.$^{-1}$ $\frac{-\frac{d(L)}{dt}}{[(L)_{cor} - (L)_{equil}]}$	*T*, °C.
10.00	9.05	4.00	14.09	1.56	24.93
7.50	7.08	4.00	8.95	1.26	24.93
5.00	4.73	4.00	4.76	1.01	24.93
2.50	2.29	4.00	1.97	0.86	24.93
10.00	9.46	4.60	15.87	1.68	24.93
10.00	9.48	4.48	15.78	1.66	24.93
10.00	9.42	4.30	15.25	1.62	24.93
10.00	9.39	4.18	14.80	1.58	24.93
10.00	8.88	3.70	9.24	1.04	24.93
10.00	8.24	3.40	6.87	0.84	24.93
10.00	9.40	4.00	11.03	1.17	22.44
10.00	9.37	4.00	8.75	0.93	19.95
7.50	7.05	4.00	5.60	.79	19.95
5.00	4.70	4.00	3.04	.65	19.95
2.50	2.26	4.00	1.23	.55	19.95
10.00	9.68	4.60	14.47	1.50	19.95
10.00	9.55	4.48	11.55	1.21	19.95
10.00	9.42	4.30	9.66	1.03	19.95
10.00	9.11	3.70	5.84	0.64	19.95
10.00	8.63	3.40	4.37	0.51	19.95

Although the rate constant *k* has been calculated in Table V on the basis that the kinetics are first order with respect to lactone concentration, the order of the reaction can be confirmed by a logarithmic plot of the rate of disappearance for the lactone *vs.* the adjusted concentration. The slope of the

$$\frac{-d(L)}{dt} = k\,[(L)_{cor} - (L)_{equil}]^x \qquad (12)$$

$$\log\left(-\frac{d(L)}{dt}\right) = \log k + x \log\,[(L)_{cor} - (L)_{equil}] \qquad (13)$$

curve equals the order of the reaction, *x*. The

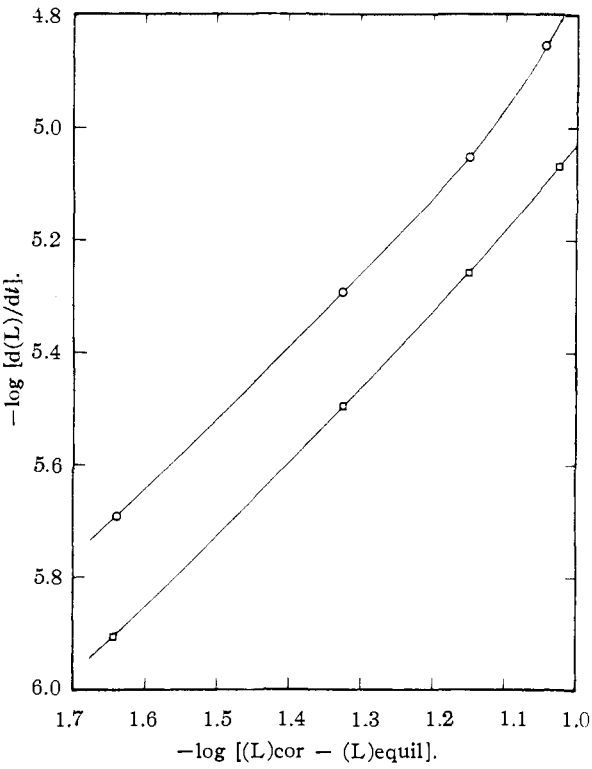

Fig. 2.—Effect of lactone concentration on the reaction rate for the hydrolysis of D-glucono-δ-lactone at *p*H 4.00. The slope of the curve represents the order of the reaction: (○) 24.93°; slope, 1.2 to 2.0; (□) 19.95°; slope, 1.2 to 1.6.

results of such a plot for the data in Table V at *p*H 4.0 are shown in Fig. 2 and indicate that the order of the reaction apparently is changing with lactone concentration. An alternative and more probable conclusion is that the activity coefficients for the reacting species change significantly with concentration and that the reaction is first order. The latter conclusion is supported by the data for the hydrolysis of γ-butyrolactone in various salt solutions.[11] The coulometric method is particularly attractive for studying reaction kinetics at constant concentrations of reactants. By this technique changes in the rate constant at different concentrations of reactants can be detected while classical methods can only give the over-all rate constant, *e.g.*, the optical rotation method discussed earlier in the paper.

The close comparison for the values of the rate constants determined by the optical rotation and coulometric methods strongly supports the conclusion that the reaction is first order with respect to lactone concentration. The linearity of the curves in Fig. 1 also strongly supports this conclusion.

The activation energy for the hydrolysis reaction can be determined on the basis of the data shown in Fig. 3, which is a plot of the logarithm of the rate constant *vs.* the reciprocal of the absolute temperature over the temperature range from 20 to 25°. From this plot, the activation energy for 0.1

$$\ln k = -E_a/RT + \text{constant} \qquad (14)$$

(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 140.

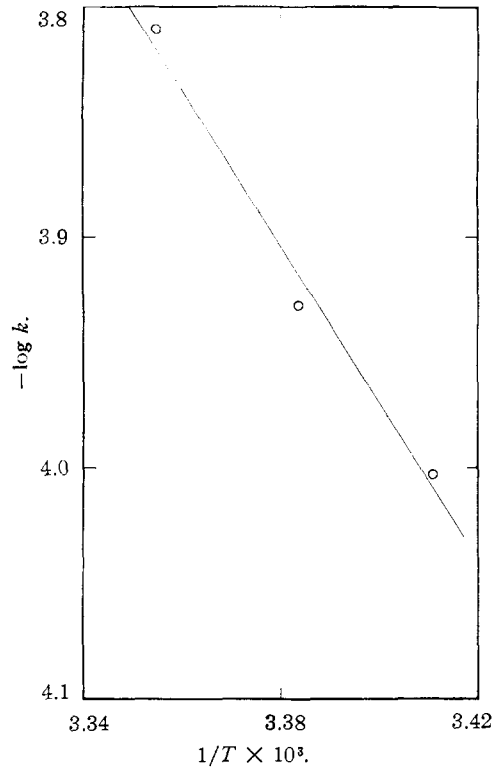

Fig. 3.—Effect of temperature on the rate constant for the hydrolysis of D-glucono-δ-lactone: $E_a/R = -2.303 \times$ slope; slope $= -3.34 \times 10^3$.

F lactone at pH 4.0 is calculated to be 15 kcal. per mole.

On the basis of the observed kinetics, the rate-determining step is postulated to be

$$L + H_2O \rightleftharpoons HGH_4 \text{ slow} \qquad (15)$$

followed by a fast, pH dependent dissociation reaction

$$HGH_4 + H_2O \rightleftharpoons H_3O^+ + GH_4^- \text{ fast} \qquad (16)$$

The rate equation for the hydrolysis reaction is

$$-\frac{d(L)}{dt} = k(L) - k_1(HGH_4) \qquad (17)$$

where k_1 is the rate constant for the lactonization reaction. Because the hydrolysis reaction does not go to completion but comes to equilibrium (equation 8), the reverse reaction takes place. At equilibrium

$$k(L)_{equil} = k_1(HGH_4)_{equil} \qquad (18)$$

and the rate equation reduces to

$$\frac{-d(L)}{dt} = k[(L) - (L)_{equil}] \qquad (19)$$

which represents the expression used in the kinetic studies. Combination of equation 18 with equation 8 gives

$$k_1 = \frac{k}{K_L} = \frac{1.78 \times 10^{-4}}{7.7} = 2.3 \times 10^{-5} \text{ sec.}^{-1} \qquad (20)$$

by using the average of the rotational and coulometric values for k, 2.26×10^{-4} sec.$^{-1}$ and 1.31×10^{-4} sec.$^{-1}$, respectively.

The independence of the rate of hydrolysis from hydrogen ion or hydroxide ion concentration is surprising. This is particularly true in view of the mechanisms for ester hydrolysis listed by Frost and Pearson[12] and the implication that lactones with unstrained rings tend to have reaction mechanisms similar to those of simple esters. The polyhydroxy character of glucono-lactone undoubtedly complicates the mechanism interpretations, but the data clearly indicate that the reaction rate is pH independent from pH 3 to pH 5. Apparently the reaction with water is more important in this pH range.

RIVERSIDE, CALIFORNIA

(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 265–269, 276–278.