Hydrolysis of D-Glucono-δ-lactone. I. General Acid–Base Catalysis, Solvent Deuterium Isotope Effects, and Transition State Characterization[1]

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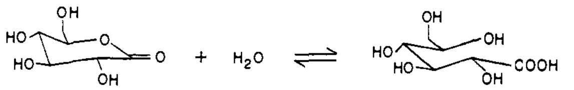
Abstract: Polarimetric and spectrophotometric methods have been used to study the hydrolysis of D-glucono-δ-lactone over a wide range of pH values at 25.0°. The reaction has been found to exhibit both general acid and general base catalysis. Catalytic coefficients for hydronium ion and malonic, formic, and acetic acids conform to the Brønsted relation with an exponent $\alpha = 0.42 \pm 0.02$. General acid catalysis by dihydrogen phosphate monoanion is *ca.* 50-fold larger than that ascribable to it from the pK_a of $H_2PO_4^-$. Catalytic coefficients for water, malonate monoanion, formate, acetate, imidazole, monohydrogen phosphate, and Tris conform to the Brønsted relation with an exponent $\beta = 0.45 \pm 0.02$. Hydroxide ion shows a positive deviation of *ca.* two log units from this line. In the water-catalyzed hydrolysis, the solvent isotope effect k_{H_2O}/k_{D_2O} has a value of 3.9. The solvent deuterium isotope effects associated with a number of general acids and bases are also shown to be quite similar to those observed in the hydration of acetaldehyde and in the mutarotation of glucose. Further transition state characterization follows from the absence of oxygen exchange during the hydrolysis of D-glucono-δ-lactone.

The δ-lactone of D-gluconic acid occupies a central position in biological systems.[3] For example, its 6-phosphate derivative is the immediate oxidation product of glucose 6-phosphate in the hexose monophosphate shunt.[4] Besides its importance in biological systems, the lactone has several diverse functions, including its use as a sequestering agent. Moreover, its hydrolysis to D-gluconic acid (eq 1) is of much chemical as well as biochemical interest. For example, it has long been recognized that δ-lactones[5] are as hydroytically labile as activated esters,[6] yet not nearly as much detailed mechanistic work has been carried out with them.[7] D-Glucono-δ-lactone lends itself to such studies because of its ready water solubility coupled with the convenience with which polarimetric methods may be employed to study its hydrolysis reaction. Furthermore, the enzyme lactonase accelerates the hydrolytic cleavage of D-glucono-δ-lactone to gluconic acid.[3,8] Also, D-glucono-δ-lactone and the lactones derived from *N*-acetylchitotetraose and analogous polysaccharide derivatives proved to be useful probes for the delineation of the binding characteristics of lysozyme[8] and of certain glucosidases.[9]



(1)

Several investigators have studied the various equilibria in eq 2 and a number of kinetic parameters have been determined.

$$\begin{tikzcd} \text{D-glucono-}\delta\text{-lactone} + H_2O \arrow[r, leftrightharpoons] & \text{D-gluconic acid} \arrow[r, leftrightharpoons] \arrow[d, leftrightharpoons] & \text{D-glucono-}\gamma\text{-lactone} \\ & \text{D-gluconate ion} + H^+ & \end{tikzcd} \qquad (2)$$

Sawyer and Bagger[10] studied the rate of hydrolysis of D-glucono-δ-lactone over a limited pH range (3–5) and determined the equilibrium between the δ-lactone and gluconic acid. They also determined the dissociation constant of gluconic acid corrected for concentration of δ-lactone only. Using a colorimetric technique, Jermyn[11a] investigated the spontaneous and enzymatic hydrolysis rates in the pH range 4 to 8 and concluded that hydrolysis proceeded *via* γ-lactone ⇄ δ-lactone ⇄ acid. Direct interconversion between the γ- and δ-lactones was also claimed by Takahashi and Mitsumoto,[11b] but later work by Shimahara and Takahashi[11c] indicated that this interconversion is significant only at high pH. Indeed, Mitchell and Duke[12] have shown that, under conditions similar to those used in the present work, the δ-lactone–gluconic acid equilibrium is established long before sensible amounts of the γ-lactone have been produced.

The present study demonstrates that the hydrolysis of D-glucono-δ-lactone exhibits both general acid and

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[1] Support for this work by Public Health Service Grant AM 09221 from the National Institute of Arthritis and Metabolic Diseases is gratefully acknowledged.

[2] Author to whom correspondence should be addressed.

[3] A. F. Brodie and F. Lipmann, *J. Biol. Chem.*, 212, 677 (1955).

[4] Q. H. Gibson, B. E. P. Swoboda, and V. Massey, *ibid.*, **239**, 3927 (1964).

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[7] For a general discussion of lactone hydrolysis see A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1953, p 316. For a discussion of the mechanism of hydrolysis of β-lactones see A. R. Olson and J. L. Hyde, *J. Amer. Chem. Soc.*, **63**, 2459 (1941); F. A. Long and M. Purchase, *ibid.*, 72, 3267 (1950); P. D. Bartlett and G. Small, *ibid.*, 72, 4867 (1950); A. R. Olson and P. V. Youle, *ibid.*, 73, 2468 (1951); and for γ-lactones see F. A, Long, W. F. McDevitt, and F. B. Dunkle, *J. Phys. Colloid Chem.*, **55**, 829 (1951); F. A. Long and N. Paul, *Chem. Rev.*, **57**, 935 (1957); T. C. Bruice, P. G. Kury, and D. M. McMahon, *J. Amer. Chem. Soc.*, **92**, 6674 (1970); D. R. Storm and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci. U. S.*, **66**, 445 (1970).

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[11] (a) M. Jermyn, *Biochim. Biophys. Acta*, **37**, 78 (1960); (b) T. Takahashi and M. Mitsumoto, *Nature (London)*, **199**, 765 (1963); (c) K. Shimahara and T. Takahashi, *Biochim. Biophys. Acta*, **201**, 410 (1970).

[12] R. E. Mitchell and F. R. Duke, *Ann. N. Y. Acad. Sci.*, **172**, 129 (1970).

general base catalysis, an observation which has important implications regarding the reaction mechanism under conditions where little or no γ-lactone is formed. The conclusion that a proton is being transferred in the rate controlling step is drawn from the relation between acid–base strength and catalytic power, coupled with the large solvent deuterium isotope effects noted in this lactone hydrolysis. Additional characterization of the activated complex is achieved through a parallel examination of oxygen-18 exchange data.

Experimental Section

Materials. D-Glucono-δ-lactone (Aldrich) was recrystallized twice from ethylene glycol monomethyl ether (mp 153°). Titration of the recrystallized lactone showed it to be 99.8% pure. All buffer components were reagent grade. Malonic acid was recrystallized twice from Et_2O–benzene. Tris (tris(hydroxymethylamino)methane) was recrystallized twice from 95% ethanol. The heavy water, containing at least 99.8% D_2O, was purhcased from Bio-Rad Laboratories. The oxygen-18 enriched water contained 1.7% excess oxygen-18.

The oxygen-18 exchange experiments were carried out at pH 5.3 and an ionic strength of 0.50 using 0.100 g of δ-lactone dissolved in 4 ml of a 0.600 *M* acetate buffer. The series of flasks containing buffer and dissolved lactone was immediately thermostated in a water bath at 25.0° and at appropriate time intervals a flask was removed and the reaction quenched by freezing in liquid nitrogen. After lyophilization and extraction with dry dioxane, the unhydrolyzed δ-lactone was dried, recrystallized, and then pyrolyzed in an evacuated ampoule with 1 μl of concentrated H_2SO_4 at 150° for 48 hr. The resulting CO_2 gas was analyzed for the mass 46 to mass 44 ratio using a General Dynamics Corporation Model 103 mass spectrometer equipped with an isotope ratio chassis. The reproducibility of the method determined by pyrolyzing a series of identical samples of δ-lactone showed a precision of ±1%. The kinetics were followed on either a Cary Model 60 ORD-CD at 300 or 340 nm or on a Bendix Automatic digital polarimeter at 5461 Å. In a few cases, confirmatory runs were also carried out on a Beckman DU spectrophotometer at 222 nm. The temperature was maintained at 25.00 ± 0.04° using a Forma-Temp. Jr. Model 2095-1 circulating bath or a Precision-Scientific circulating system. Rates run on all three instruments were reproducible to within 2–4%. Specific rotations were determined on a Perkin–Elmer Model 141 polarimeter.

All buffers were made up to an ionic strength of 0.50 using sodium perchlorate or sodium chloride. Measurements of pH and pD (pD = pH reading + 0.41)[13] were made on a Beckman 101900 research pH meter. A specially designed 5-cm jacketed polarimeter cell was employed for most kinetic runs.

Equilibria. All equilibrium and optical rotation data were determined at 25.0°. The specific rotation for the δ-lactone was determined by dissolving pure lactone to give a 0.050 *M* solution in a 0.60 *M* acetate buffer (pH 4.63). The solution was placed in a 10 cm, thermostated, polarimeter tube and several optical rotation readings were taken during 2 hr. Extrapolation of the initial rotation to zero time gave the specific rotation for the δ-lactone. For gluconate anion, the δ-lactone was dissolved in 0.20 *M* NaOH and the optical rotation measured after allowing the solution to equilibrate for 48 hr. The specific rotation for gluconic acid was determined by adding δ-lactone to a NaOH solution and equilibrating for 1 day. A hydrochloric acid solution was then added to give a final gluconic acid concentration of 0.050 *M* (pH 0.8). Polarimetric readings were taken periodically. The optical rotation values were again plotted *vs.* time and extrapolation gave the specific rotation for gluconic acid.

The overall equilibrium in solution can be represented by the constant *K*, eq 3, where a_{G^-} is the activity of the gluconate anion,

$$K = \frac{a_{H^+}a_{G^-}}{a_{HG} + a_L} \simeq \frac{a_{H^+}a_{G^-}}{[HG] + [L]} \qquad (3)$$

and [HG] and [L] are the concentrations of gluconic acid and lactone, respectively.

The value of *K* was determined by measuring the equilibrium pH of a solution of pure lactone in water and in 0.50 *M* NaCl. The solutions were prepared with carbon dioxide free distilled, deionized water and allowed to equilibrate for 72 hr. All solutions were run in duplicate. The above constant was also determined in 99.85% D_2O keeping the ionic strength constant at 0.50 with NaCl. The results of these determinations are summarized in Table I.

Table I. Values for Lactone–Salt–Acid Equilibrium Constant at 25.0° [a]

Solvent	pH or pD	$K \times 10^4$, *M*
H_2O–0.5 *M* NaCl	2.43, 2.44	3.04
D_2O–0.5 *M* NaCl	2.67, 2.66[b]	1.00
H_2O	2.57, 2.57	1.55
D_2O	2.81, 2.80[b]	0.51

[a] $[\text{Lactone}]_{\text{total}} = 0.050$ *M*. [b] pD values obtained using glass electrode correction (pD = pH reading + 0.41).

The acid dissociation constant of gluconic acid, K_a, in H_2O and D_2O was evaluated using eq 4 from values of *K* in H_2O and D_2O,

$$K_a = \frac{a_{H^+}a_{G^-}}{a_{HG}} \simeq \frac{a_{H^+}a_{G^-}}{[HG]} \qquad (4)$$

and the equilibrium concentration of the lactone.

Values for the specific and molar rotations of D-glucono-δ-lactone, gluconate anion, and gluconic acid were redetermined in the present work and are summarized in Table II.

Table II

	$[\alpha]^{25}\text{D}$	Molar rotation 100-mm tube
D-Glucono-δ-lactone	66.3°	+11.8°
Gluconate anion	15.0°	+2.68°
Gluconic acid	5.80°	+1.05°

The rotation of a lactone–salt–acid solution can be related to the concentration of the three gluconate species by eq 5, where *R* is the

$$R = 11.8[L] + 2.68[G^-] + 1.05[HG] \qquad (5)$$

optical rotation of the solution in a 100-mm polarimeter tube. The sum of the concentrations of the three gluconate species is equal to the total concentration of lactone C_T originally placed in the solution, eq 6. By assuming that $[G^-] = [H^+]$ eq 5 and 6 may be

$$C_T = [L] + [G^-] + [HG] \qquad (6)$$

combined to obtain [L]. This value was then combined with eq 3 to obtain K_a. All solutions were equilibrated for 72 hr before readings were taken. The pK_a of gluconic acid was found to be 3.77 ± 0.02 in H_2O and 4.26 ± 0.02 in D_2O.

An expression for the hydrolysis equilibrium constant K_H was obtained by dividing eq 3 by eq 4 and rearranging terms.

$$K_H = \frac{[HG]}{[L]} = \frac{K}{K_a - K}$$

The value of K_H was found to be 9.0 in H_2O and 12 in D_2O.

Kinetics. A buffer solution containing 0.005 *M* lactone was injected into a thermostated cell and the optical rotation, α_t, read as a function of time. A plot of log ($\alpha_t - \alpha_\infty$) *vs. t* gave straight lines for at least 5 half-lives (Figure 1). The absolute value of the slope of such a plot multiplied by 2.303 yields k_{obsd}. Below pH ~5 lactone, gluconic acid, gluconate anion, and hydronium ion exist in equilibrium, and $k_{obsd} = k_f + k_r$, where k_f is the rate constant for hydrolysis and k_r the rate constant for lactonization. Above pH ~5 the reaction proceeds to completion, and $k_{obsd} = k_f$. The total buffer concentrations ranged from 0.02 to 1.00 *M*. A matrix of at least 16 buffers per buffer system was employed. All kinetic parameters were determined in the pH region 1.97 to 8.60. The pH readings were corrected for activity effects using eq 7 and 8, where *I*

$$pH = -\log([H_3O^+]f_\pm) \qquad (7)$$

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(13) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

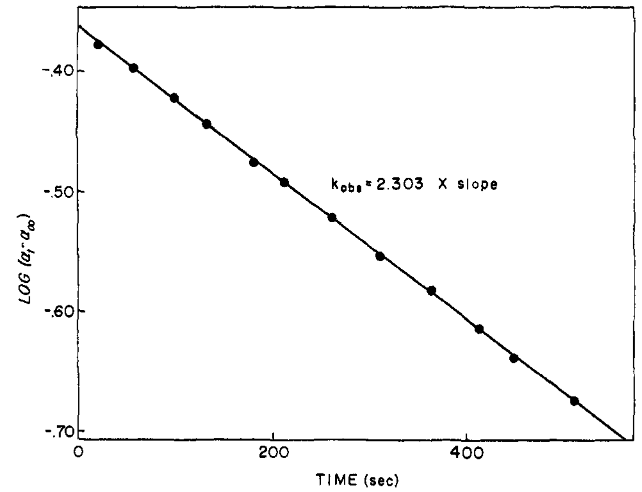

Figure 1. Semilog plot of kinetic data from typical run; [lactone] = 0.005 *M*. Kinetics followed polarimetrically at 300 and 340 nm, 25.0°.

$$\log f_{\pm} = \frac{-0.51 z^2 I^{1/2}}{1 + 1.5 I^{1/2}} \tag{8}$$

and z stand for the ionic strength and charge, respectively. Equation 8 has been successfully used to calculate the mean activity coefficients of hydronium and hydroxide ions up to an ionic strength I of 0.2. However at $I = 0.5$ some improvement in the value of $f_{\pm}$ is effected by subtracting a term bI from the right side of eq 8 where b is an adjustable parameter. Inasmuch as at $I = 0.5$, eq 8 gives $f_{\pm} = 0.67$, a value which is in good agreement with those experimentally determined for many uniunivalent electrolytes,[14a] we have chosen to neglect the $-bI$ term.

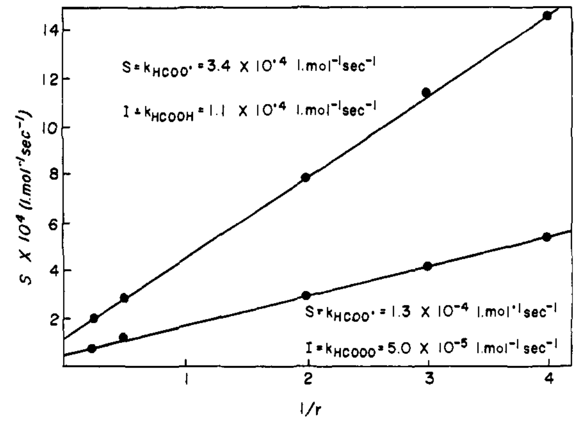

Figure 2. Determination of specific rate coefficients of the components of formate buffer in H_2O and D_2O at 25.0°: upper curve, formate-catalyzed hydrolysis of D-glucono-δ-lactone in H_2O; lower curve, formate-catalyzed hydrolysis of D-glucono-δ-lactone in D_2O.

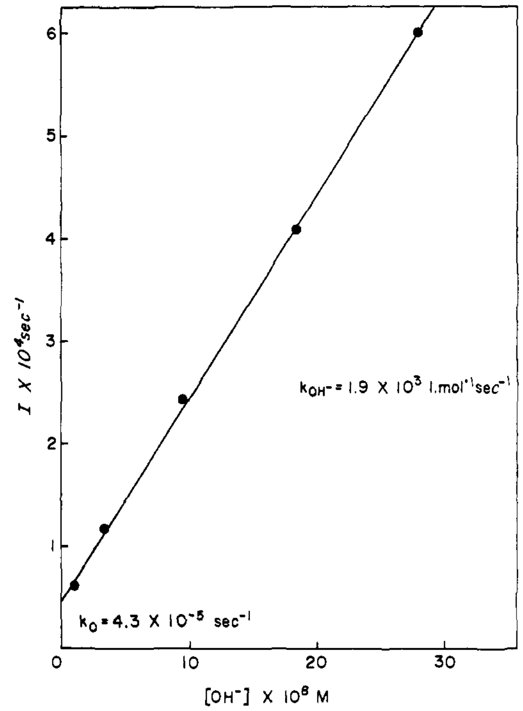

Figure 3. Catalysis of hydrolysis of D-glucono-δ-lactone by OH^- and H_2O. Kinetic data determined in phosphate buffer.

Results

When D-glucono-δ-lactone was hydrolyzed in a series of buffers of equal acid–base ratio and ionic strength, but with increasing total buffer concentration, the rate increased proportionately. The overall pseudo-first-order rate constant, k_{obsd}, can be described by eq 9 where k_0 is the spontaneous rate coefficient,

$$k_{obsd} = k_0 + k_{H_3O^+}(a_{H_3O^+}/f_{\pm}) + k_{OH^-}\left(\frac{K_w}{a_{H_3O^+} f_{\pm}}\right) + k_A[A] + k_B[B] \tag{9}$$

$a_{H_3O^+}$ is the experimentally determined hydronium ion activity, and k_A and k_B are the rate coefficients for the acidic and basic components of the buffer respectively. The mean ion activity coefficient, $f_{\pm}$, was calculated from eq 8. Rearranging eq 9 gives eq 10, where r is the ratio of the concentration of acid

$$k_{obsd} = k_0 + k_{H_3O^+}\left(\frac{a_{H_3O^+}}{f_{\pm}}\right) + k_{OH^-}\left(\frac{K_w}{a_{H_3O^+} f_{\pm}}\right) + (k_A + k_B/r)[A] \tag{10}$$

to that of conjugate base, *i.e.*, $r = [A]/[B]$. Plots of k_{obsd} against [A] were found to be linear with slope $S_r = k_A + k_B/r$ with intercept $I_r = k_0 + k_{H_3O^+}(a_{H_3O^+}/f_{\pm}) + k_{OH^-}(K_w/a_{H_3O^+} f_{\pm})$. Thus k_A and k_B can be evaluated by plotting S_r *vs.* several different reciprocal buffer ratios. Such a plot for the formate buffer is shown in Figure 2. The fact that this plot for formate and all other buffer systems studied is linear indicates the absence of catalytic components arising from the concerted action of both A and B within the concentration range studied.

The coefficients k_{OH^-} and k_0 were evaluated from data obtained from rates carried out in imidazole, phosphate, and Tris buffers. Because I_r is a linear function of hydroxide ion concentration, k_{OH^-} may be deduced by plotting values of I_r *vs.* the corresponding hydroxide ion concentration (Figure 3). Similarly, k_0 and $k_{H_3O^+}$ were deduced in formate and malonate buffers. The above analysis was also used to determine the various catalytic coefficients of acetate, imidazole, phosphate, and Tris.

The specific rate coefficients in H_2O and D_2O for the various catalytic species present in the above mentioned buffers are given in Table III. The data for

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(14) (a) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1964; (b) G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids and Bases in Aqueous Solution," Butterworths, London, 1961.

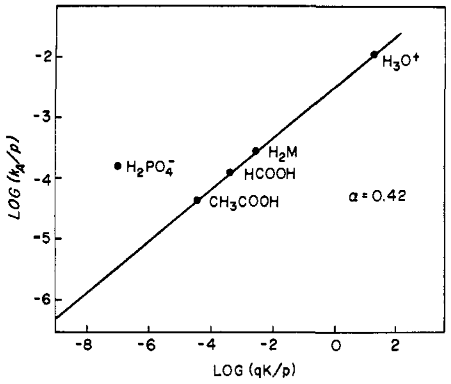

Figure 4. Brønsted plot of log (k_A/p) *vs.* log (qK/p) for acid catalysts in the hydrolysis of D-glucono-δ-lactone, H_2M = malonic acid. Statistical corrections have been made according to R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, **291**, 297 (1966).

Table III. Catalytic Rate Coefficients for Acids and Bases in the Hydrolysis of D-Glucono-δ-lactone[a]

Catalyst	k_c,[b] l. mol^{-1} sec^{-1}	pK_a[c]	k_{H_2O}/k_{D_2O}
CH_3COOH	5.0×10^{-5}	4.8	
CH_3COO^-	4.4×10^{-4}		
$HCOOH$	1.1×10^{-4}	3.7	2.2
$HCOO^-$	3.4×10^{-4}		2.6
$H_2C(COOH)_2$	5.7×10^{-4}	2.9	
$H_2C(COO^-)(COOH)$	1.8×10^{-4}		
IMH^+	*d*	6.9	
IM	2.0×10^{-3}		
$H_2PO_4^-$	1.2×10^{-3}	7.2	2.4
HPO_4^{2-}	2.7×10^{-3}		1.5
$HTris^+$	*d*	8.1	
Tris	9.1×10^{-3}		1.4
H_3O^+	2.9×10^{-2}	−1.74	1.1
H_2O	$4.3 \times 10^{-5}/55.5$	15.74	3.9
OH^-	$1.9 \times 10^{+3}$		0.8

[a] At 25.0° and ionic strength I = 0.50. [b] Catalytic coefficients in H_2O. [c] Values of pK_a at 25.0° taken from ref 14b for H_2O and ref 13 and A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966), for D_2O. [d] Too small to obtain an accurate rate coefficient.

general acid catalysis are shown in Figure 4 as a plot of the Brønsted[15,16] relationship (eq 11) where k_A is

$$\log k_A/p = \alpha \log (qK_a/p) + G_A \qquad (11)$$

the acid catalytic coefficient and K_a is the acid dissociation constant. The statistical factors for the carboxylic acids were taken as $p = 1, q = 2$ and for $H_2PO_4^-$ as $p = 2, q = 3$.

The data for general base catalysis are shown in Figure 5 as a plot of the Brønsted relationship, eq 12,

$$\log k_B/q = \beta \log (p/qK_a) + G_B \qquad (12)$$

where k_B is the base catalytic coefficient and K_a the dissociation constant of the conjugate acid of the base B. The statistical factors for carboxylate anions were taken as $p = 1, q = 2$, for HPO_4^{2-} as $p = 1, q = 3$. For the acid pairs H_3O^+–H_2O and H_2O–OH^- values $p = 3, q = 2$ and $p = 2, q = 1$ were used, respectively.

Hydrolysis of D-glucono-δ-lactone in 1.7% oxygen-18 enriched water showed no incorporation of oxygen-18 into the lactone up to 75% reaction. Table IV depicts the accuracy of the oxygen-18 analysis.

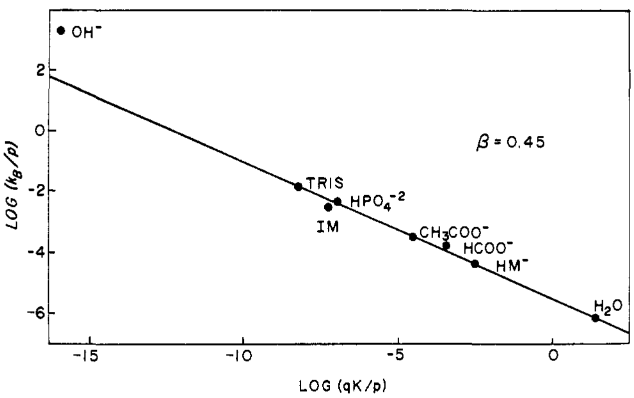

Figure 5. Brønsted plot of log (k_B/q) *vs.* log (qK/p) for base catalysts in the hydrolysis of D-glucono-δ-lactone: HM^- = monohydrogen malonate; IM = imidazole.

Table IV. Oxygen-18 Exchange Data for the Hydrolysis of D-Glucono-δ-lactone[a]

Reaction, %	No. of runs	Mass 46/ mass 44_{av}
0	3	0.00406
15	2	0.00404
50	2	0.00404
75	2	0.00403

[a] In 0.600 *M* acetate buffer, pH 5.31, ionic strength 0.50 and 1.7% excess oxygen-18 water.

The variation of reaction rate with temperature was determined at pH 4.44 in 0.02 *M* acetate buffer. In this region catalysis by both hydronium and hydroxyl ions is negligible so that the rate constant for the water ("spontaneous") reaction can be easily determined by subtracting the contribution of the buffer component. This correction never amounted to more than 11% of the observed rate. Furthermore at this pH the reverse reaction is insignificant, *i.e.*, $k_{obsd} = k_f$, and k_0 refers to the forward rate constant of the spontaneous hydrolysis. A plot of k_0 *vs.* $1/T$ at temperatures ranging from 20 to 45° (Figure 6) yielded the following activation parameters: E_A = 14.0 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 13.4 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = −36 eu.

Discussion

Buffer Catalysis in H_2O and D_2O. An interesting outcome of the present investigation is that the hydrolysis of D-glucono-δ-lactone is subject to both intermolecular general acid and general base catalysis, a phenomenon occurring in a very limited number of known hydrolysis reactions.[17–19] However, in the reversible hydration of aliphatic aldehydes[20–22] and of pyridinecarboxaldehydes[23] such findings are quite common. In fact, the rate-limiting step of the hydrolysis may be viewed

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(15) J. N. Brønsted, *Chem. Rev.*, **5**, 322 (1929).

(16) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(17) G. Di Sabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4400 (1961).

(18) E. R. Garrett, *J. Amer. Chem. Soc.*, **80**, 4049 (1958).

(19) (a) S. Milstein and L. A. Cohen, *ibid.*, **91**, 4585 (1969); (b) S. Milstein and L. A. Cohen, *ibid.*, **92**, 4377 (1970); (c) S. Milstein and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970).

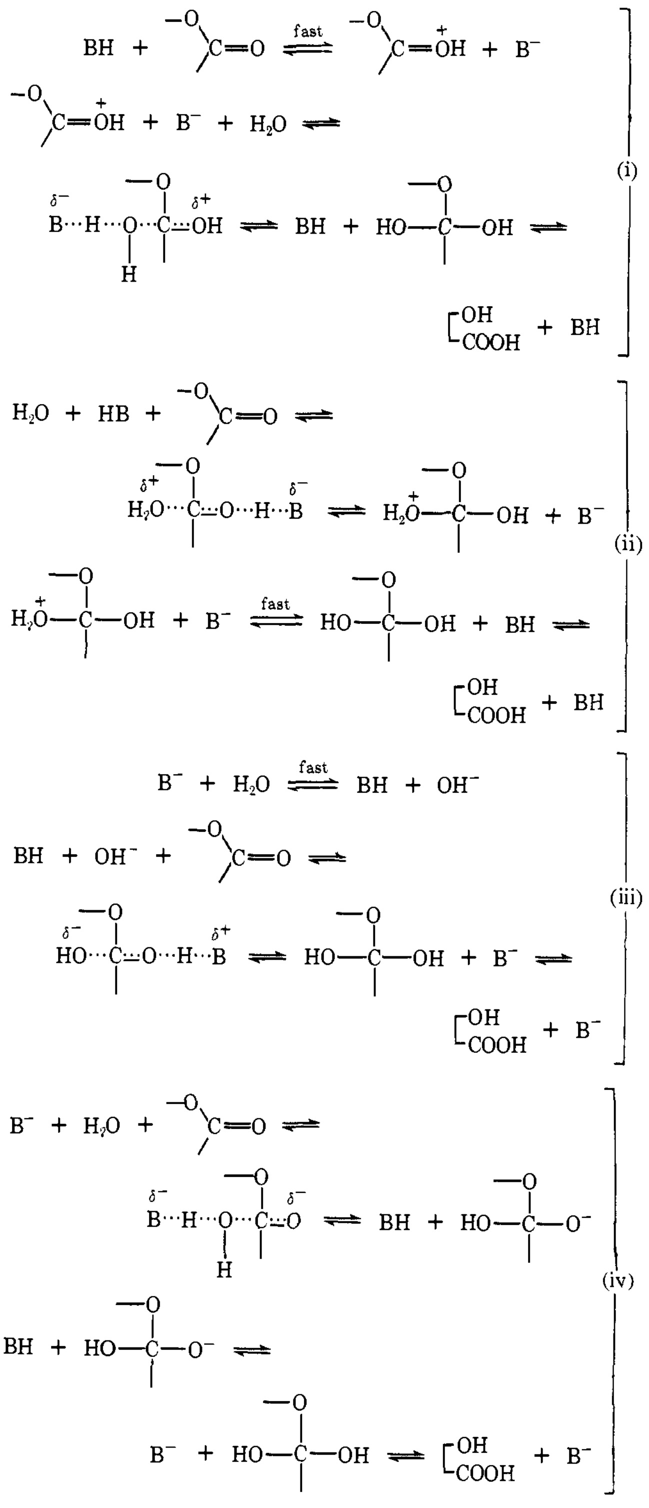
(20) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, **291**, 297 (1966).

(21) Y. Pocker and J. E. Meany, *J. Phys. Chem.*, **71**, 3113 (1967); also unpublished observations.

(22) Y. Pocker and D. G. Dickerson, *J. Phys. Chem.*, **73**, 4005 (1969).

(23) Y. Pocker and J. E, Meany, *ibid.*, **72**, 655 (1968); **73**, 1857 (1969).

Scheme I



as a concurrent general acid and general base catalyzed hydration of the carbon–oxygen double bond of the lactone followed by rapid ring opening.

General acid catalysis may proceed through one of the two kinetically indistinguishable transition states, (i) and (ii) (Scheme I), which may be preceded by one or more preequilibrium steps. Mechanism i requires that

$$k^*[B^-][LH^+][H_2O] = k_{HB}[L][HB]$$

where k^* is the actual rate coefficient for the formation of the tetrahedral intermediate; $[LH^+]$ is the concentration of protonated lactone and k_{HB} is the observed catalytic rate coefficient for the general acid HB. Estimating the pK_a of LH^+ to be -7[24a] and using known dissociation constants for the various HB acids, one obtains values of k^* ranging between 10^{11} and 10^{13} M^{-1} sec^{-1}. This means that with certain general acids the rate constant for the second step in mechanism i is slightly larger than the theoretical maximum for a diffusion-controlled reaction.[24b] A similar calculation for general base catalysis based on mechanism iii also yields a k^* which exceeds the diffusional limit. Consequently, both (i) and (iii) can be ruled out, leaving (ii) as the preferred mechanism for general acid, and (iv) the preferred mechanism for general base catalysis. However, similar calculations can be carried out to show that the respective rate-determining steps for the reverse processes in schemes ii and iv cannot be correct either in their simplest form. Thus the reverse of scheme ii includes B^- and the conjugate acid of the hydrate of D-glucono-δ-lactone (*i.e.*, the conjugate acid of the tetrahedral intermediate) while the reverse of scheme iv includes HB and the conjugate base of the hydrate of D-glucono-δ-lactone as an intermediate. Reasonable estimates of the equilibrium constants associated with the formation of these intermediates from D-gluconic acid indicate that such unstable species will be present in extremely low concentrations and the bimolecular rate constants of dehydration to lactone would, in certain cases, be larger than the diffusion controlled limit. Eigen[24b] has suggested that the catalytic efficiency of general acids and bases in such reactions may be due

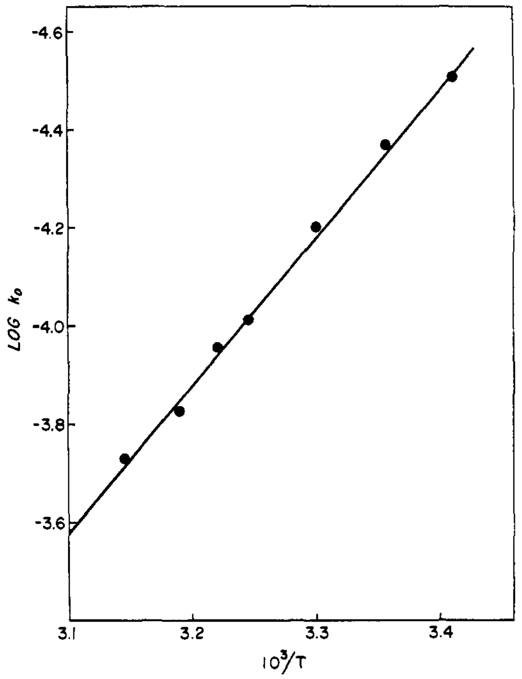


Figure 6. A plot of the logarithm of the rate coefficient, k_0, for the spontaneous hydrolysis of D-glucono-δ-lactone *vs.* $1/T$, °K^{-1}. Values of k_0 were deduced from data obtained in acetate buffer, pH 4.44, and an ionic strength of 0.5 using the eq: $k_0 = k_{obsd} - (k_{HOAc}[HOAc] + k_{OAc^-}[OAc^-])$.

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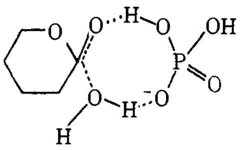
[24] (a) M. L. Ahrens and H. Strehlow, *Discuss. Faraday Soc.*, 39, 112 (1965); E. M. Arnett, R. P. Quirk, and J. W. Larsen, *J. Amer. Chem. Soc.*, 92, 3977 (1970); (b) M. Eigen, *Discuss. Faraday Soc.*, 39, 7 (1965).

to a concerted process involving two or more water molecules. Such a scheme allows multistep mechanisms i–iv to be replaced by a concerted process where the water molecules and catalyst function as bridges across the carbon–oxygen double bond. Thus, the transition state is cyclic[21] and produces the tetrahedral intermediate in one step. A different mechanism may also be envisioned in which water molecules and catalyst bridge the ethereal oxygen and the carbonyl carbon, thus allowing the direct interconversion of lactone and hydroxy acid in the rate-determining step. The latter mechanism, however, assumes that a discrete tetrahedral intermediate is not formed on the reaction pathway.

A particularly attractive concerted mechanism involves simultaneous proton donation and acceptance by a bifunctional catalyst containing both acidic and basic groups. Again one or more water molecules may be interposed between the catalyst and the lactone. Dihydrogen phosphate monoanion not only fulfills these requirements but has the added advantage that its acidic and basic groups are of moderate strength and are situated on different atoms. Apparently a significant amount of additional stabilization is gained by its bifunctional catalysis as depicted in **1**. Similarly it has also been suggested that positive deviations from the Brønsted line result when such bifunctional catalysts are hydrogen bonded to water,[22,25] and the complex attacks the substrate. It has not escaped our attention that in this particular case, $H_2PO_4^-$ may have the additional advantage of forming stable hydrogen-bonded complexes both with D-glucono-δ-lactone and with water. In this respect it is interesting to note that one of the few reactions in which $H_2PO_4^-$ is especially effective is the hydrolysis of phenyliminolactones, studied by Cunningham and Schmir.[26]



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Results of parallel studies in D_2O are highly instructive (Table V). They not only support a general acid–general base mechanism but point to the great similarity between δ-lactone hydrolysis and aldehyde hydration.[21,27] The magnitude of the solvent isotope effect coupled with the Brønsted exponents α and β with values near 0.5 strongly suggest that a proton transfer is an integral part of the transition state of the rate-determining step in this hydrolysis reaction.[21,28,29]

Table V. Solvent Deuterium Isotope Effects, k_{H_2O}/k_{D_2O}, Involved in the Hydration of Acetaldehyde, Mutarotation of Glucose, Hydrolysis of Ethyl Dichloroacetate, and the Hydrolysis of D-Glucono-δ-lactone

Catalyst	Hydration of acetaldehyde	Mutarotation of glucose	Hydrolysis of ethyl dichloroacetate	Hydrolysis of D-glucono-δ-lactone
H_2O	3.9[a]	3.8[c]	5[e]	3.9
OH^-	~1[b]	~1[c]		0.8
$H_2PO_4^-$	1.8[b]	1.9[c]		2.4
HPO_4^{2-}	2.2[b]	2.5[c]	3.0[e]	1.5
HCOOH		2.2[c]		2.2
$HCOO^-$		2.4[c]		2.6
H_3O^+	1.3[a]	1.4[c,d]		1.1

[a] Reference 27. [b] Reference 21. [c] Reference 31. [d] Reference 28. [e] Reference 6.

Though the above considerations suggest a general catalyzed mechanism, there are two pieces of evidence to indicate that the catalysis by which hydroxide ions operate may, at least in part, be nucleophilic. Firstly, a positive deviation of *ca.* two orders of magnitude from the Brønsted line for general base catalysis has been attributed to a direct nucleophilic attack of hydroxide ion on the carbonyl carbon rather than an attack of water, catalyzed by hydroxide ion.[30] Here one should note that recent studies on aldehyde hydration[22] and glucose mutarotation[31] place OH^- on the Brønsted line whereas deviations of this kind are not uncommon for a nucleophilic attack by OH^-. Secondly, the observed value of 0.8 for the ratio k_{OH^-}/k_{OD^-} is in good agreement with that noted in the hydroxide ion catalyzed hydrolysis of esters.[32a,b] The observed value for the ratio k_{OH^-}/k_{OD^-} is somewhat lower than the corresponding ratio in acetaldehyde hydration (~1)[21] and in glucose mutarotation (~1)[31] and somewhat higher than the one noted in the racemization of mandelate ion (~0.7),[33a] the decomposition of diacetone alcohol (0.7),[33b] the aldol condensation of acetaldehyde (0.7),[33c] and the bromination and deuterium exchange in acetone and acetone-d_6 (0.7).[33d] A value of 0.72 for k_{OH^-}/k_{OD^-} was also noted recently by Walters and Long in the detritiation of 1,4-dicyano-2-butene-*1-t*.[33e]

Hydrogen bonding to the nucleophile in the uncatalyzed water reaction is evidently quite important. The large negative entropy of activation obtained for the spontaneous hydrolysis (−36 eu) is very similar to that obtained in acetaldehyde hydration (−38 eu)[21] and can be explained by assuming that either a number of reactant water molecules are tightly constrained in the transition state, or that the transition state is highly polar, resulting in electrostriction of the bulk solvent. At least two water molecules must be tightly bound in the transition state to give rise to the observed isotope effect of *ca.* 4 which is probably due to primary as well as secondary contributions.[21,28] Furthermore, since water falls on the Brønsted line for general base catalysis, it must act as a general base toward water, thus

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(25) A. R. Olson and R. J. Miller, *J. Amer. Chem. Soc.*, **60**, 2687 (1938).

(26) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

(27) Y. Pocker, *Proc. Chem. Soc., London*, 17 (1960).

(28) B. C. Challis, F. A. Long, and Y. Pocker, *J. Chem. Soc.*, 4679 (1957).

(29) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 675 (1960).

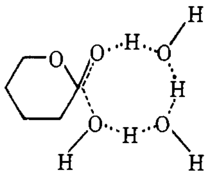
(30) The long arm of coincidence prevents us from taking a more positive stand here since a number of reactions involving proton abstraction from C–H by OH^- also show positive deviations from Brønsted plots: R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940); R. P. Bell, R. D. Smith, and L. A. Woodward, *ibid.*, **192**, 479 (1948); E. A. Walters and F. A. Long, *J. Amer. Chem. Soc.*, **91**, 3733 (1969).

(31) Y. Pocker, J. W. Long, and D. B. Dahlberg, unpublished results from this laboratory.

(32) (a) K. Wiberg, *Chem. Rev.*, **55**, 713 (1955). (b) Differences between k_{OH^-} and k_{OD^-} can be attributed mainly to changes in O–H frequencies of water molecules which are hydrogen-bonded to hydroxide ion and do not at present have the characteristics of a mechanistic criterion.

(33) (a) Y. Pocker, *Chem. Ind. (London)*, 1117 (1958); (b) *ibid.*, 17 (1959); (c) *ibid.*, 599 (1959); (d) *ibid.*, 1383 (1959); (e) E. A. Walters and F. A. Long, *J. Phys. Chem.*, **76**, 362 (1972).

requiring a minimum of two water molecules in the activated complex. Possible transition states illustrating only the principle reactant water molecules are shown in structures **2** and **3**. Structures similar to **4**



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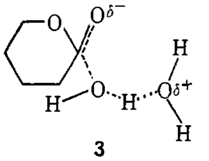

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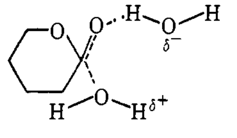

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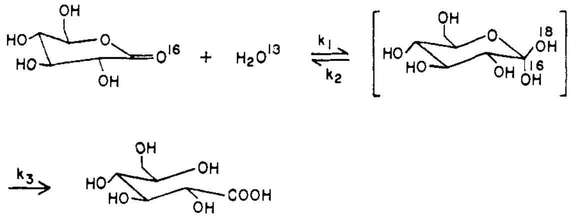
can be ruled out by noting that the value for water is well removed from the Brønsted line for general-acid catalysis.

Oxygen-18 Experiments. The lack of oxygen-18 incorporation into the lactone does not necessarily require the reaction to be SN2 in character. If k_3 is greater than k_2 by a factor of 100, the method of isotopic analysis would not detect exchange (eq 13). Further-



(13)

more, the absence of oxygen-18 incorporation into the remaining lactone means that addition to the carbonyl carbon atom is rate determining and all subsequent steps are relatively fast. The observed rapid rate of breakdown of the tetrahedral intermediate to the hydroxy acid relative to return to the lactone is, in all likelihood, associated with the difference in the number of rotational degrees of freedom between the two species. Indeed, this effect may also be implicated in the lack of oxygen-18 exchange in the five-membered lactones γ-butyrolactone and phthalide.[34]

The question arises: where does bond scission occur in D-glucono-δ-lactone during hydrolysis? Ample evidence exists in the literature which strongly suggests that the acyl–oxygen, rather than the alkyl–oxygen, bond is broken in the hydrolysis reaction.[35]

It is interesting to note that D-glucono-δ-lactone is almost as labile to hydrolysis as *p*-nitrophenyl acetate.[36] Brown[5] has pointed out that relief of conformational strain in going from the half-chair conformation of the lactone[37] to the fully staggered tetrahedral intermediate can account for the reactivity of this substrate (and of other δ-lactones). Also, intramolecular catalysis by one or more hydroxyls cannot account for the lability since the tetra-*O*-methyl derivative hydrolyzed nearly as rapidly as the hydroxylactone.[38]

The unusual observation of general acid catalysis is quite likely a consequence of this reactivity. In those cases where general catalysis has been observed, the ester was activated with electron-withdrawing groups in the acyl or alkyl fragments. The carbonyl oxygen was thus rendered too weakly basic to sufficiently coordinate with a general acid to be catalyzed, and only general base catalysis is observed. However, in the case of D-glucono-δ-lactone, the reactivity exists without a decrease in the basicity of the carbonyl oxygen except that possibly due to the α-hydroxyl, and thus both general base and general acid catalysis is observed. If this hypothesis is correct, then other (appropriately substituted) δ-lactones may exhibit general acid catalysis.

[34] (a) F. A. Long and L. Friedman, *J. Amer. Chem. Soc.*, 72, 3692 (1950); (b) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *ibid.*, **83**, 4193 (1961).

[35] (a) J. W. E. Glattfeld and D. MacMillan, *ibid.*, **56**, 2481 (1934); (b) W. H. G. Lake and S. Peat, *J. Chem. Soc.*, 1417 (1938).

[36] T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, 80, 2265 (1958).

[37] M. L. Hackert and R. A. Jacobsen, *Acta Crystallogr., Sect. B*, 27, 203 (1971).

[38] H. D. K. Drew, E. H. Goodyear, and W. N. Haworth, *J. Chem. Soc.*, 1237 (1927); Y. Pocker and E. Green, unpublished observations.