# Hydrolysis of D-Glucono-δ-lactone. II. Comparative Studies of General Acid–Base Catalyzed Hydrolysis of Methylated Derivatives[1]

Y. Pocker*[2] and Edmond Green

Contribution from the Department of Chemistry, University of Washington, Seattle, Washington 98195. Received May 26, 1973

Abstract: Polarimetric methods have been used to study the hydrolysis of tetra-*O*-methylglucono-δ-lactone (**2**), tetra-*O*-methylmannono-δ-lactone (**3**), and tri-*O*-methyl-2-deoxyglucono-δ-lactone (**4**) over a wide range of pH values at 25.0°. The reactions of **2–4** are subject to general base catalysis with Brønsted exponents, β, of 0.43, 0.41, and 0.30, respectively. The Brønsted exponents, α, for the hydrolysis of **2** and **4** are 0.43 and *ca.* 0.6, respectively. General acid catalysis in the hydrolysis of lactone **3** was not detectable. With the exception of general acid catalysis, the hydrolytic behavior of δ-lactones is quite similar to that of straight-chain alkyl esters which are activated in the acyl fragment by electron-withdrawing groups. The similarities include large negative entropies of activation for the water-catalyzed reactions, comparable hydroxide ion activation parameters, large deuterium isotope effects, Brønsted exponents near 0.5, and low susceptibility to nucleophilic catalysis. The strained half-chair conformation "activates" δ-lactones. The effects of substitution in the 2 position on the reactivity of δ-lactones are discussed, and an explanation is presented for the absence of oxygen exchange during the hydrolysis of δ- and γ-lactones.

The hydrolysis of D-glucono-δ-lactone (eq 1) has been shown to be subject to both intermolecular general acid and general base catalysis, with Brønsted exponents
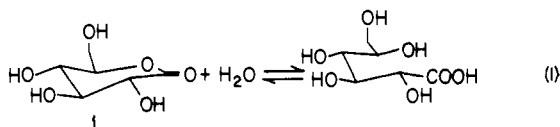

near 0.5.[3] The solvent deuterium isotope effects were similar to those found for many known general acid–general base catalyzed reactions. Also, the hydrolysis reaction was accompanied by negligible amounts of oxygen-18 incorporation into the unreacted lactone. These results were shown to be consistent with a slow general acid–general base catalyzed hydration of the carbonyl double bond followed by rapid ring opening.

Though this investigation helped to establish more firmly the mechanism of hydrolysis of D-glucono-δ-lactone in aqueous solution, it also raised some fundamental questions. For example, what are the peculiar structural features of this lactone that give rise to general acid catalysis—a rare phenomenon in ester hydrolysis?[4–6] Do the hydroxyl groups promote complexation of the general acid with the substrate?[3] Is the reactivity (approaching that of CF₃COOEt)[7] due to intramolecular hydrogen bonding,[8] the strain produced by the exocyclic double bond on a six-membered ring,[9]

the electron-withdrawing character of the α-hydroxyl, or possibly its stereochemistry? Also, does the presence of four hydroxyl groups affect the water structure in such a way as to contribute to the reactivity?

In an attempt to deal with these questions, the following three lactones were synthesized and subjected to a thorough kinetic analysis of their hydrolysis reactions.
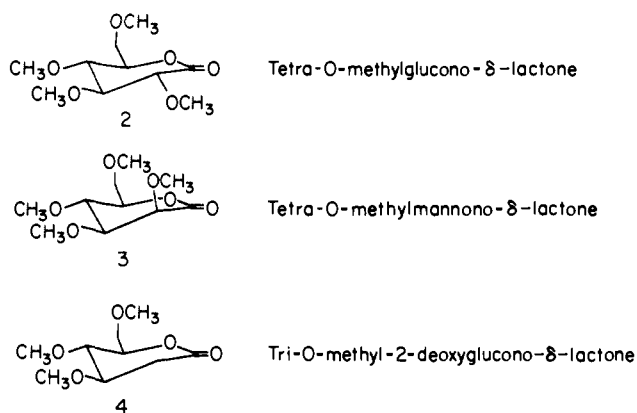
In addition to having the experimental advantages of **1** (high water solubility coupled with the convenience of polarimetry) lactones **2–4** eliminate any possibility of γ-lactone production.[10] Furthermore, **1–4** possess sufficient reactivity to allow the studies to be conducted with low acid and low base concentrations at the thermodynamically convenient temperature of 25°.

The present study demonstrates that the reactivities of **1–4** relative to open chain esters are a combination of the effects of ring strain, electron-withdrawing capacity of the α substituent, and stereochemistry of the α oxygen. Moreover, *experimentally observable* general acid catalysis in these systems is highly dependent on the reactivity.

(1) Support for this work by U. S. 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) Y. Pocker and Edmond Green, *J. Amer. Chem. Soc.,* **95,** 113 (1973).

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

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

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

(7) (a) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.,* 87, 4138 (1965); (b) M. L. Bender and H. d'A. Heck, *ibid.,* 89, 1211 (1967).

(8) T. C. Bruice and T. H. Fife, *J. Amer. Chem. Soc.,* 84, 1973 (1962).

(9) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.,* 76, 467 (1954).

(10) (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).

Table I. Physical and Spectral Properties of Lactones 2–4

Lactone	Bp, °C (mm)	—Specific rotation,[a] deg—— Present work	Lit. value	Purity,[b] %	Nmr (CDCl₃) δ (OCH₃)	Ir (CCl₄) cm⁻¹ (C=O)	Mass spectrum (70 eV) m/e (rel intensity)
2	97–98 (0.02)	$[\alpha]^{25}$D 97.4	98[c]	>99	3.59, 3.55, 3.53, 3.43	1762	234 (9), 145 (73), 101 (100), 88 (80)
3	106–108 (0.05)	$[\alpha]^{25}$D 145		>99	3.63, 3.53, 3.50, 3.47	1754	234 (13), 145 (84), 101 (91), 88 (100)
		$[\alpha]^{18}$D 149	150[c]				
4	136–138 (0.07)	$[\alpha]^{25}$D 107		>99	3.50, 3.44, 3.43	1748	102 (47), 101 (52), 88 (36), 71 (100)
		$[\alpha]^{19}$D 106	106[d]				

[a] In H₂O. [b] Determined by titration. [c] H. D. K. Drew, E. H. Goodyear, and W. N. Haworth, *J. Chem. Soc.*, 1237 (1927). [d] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **88**, 791 (1930).

Experimental Section

Materials. D-Glucose was purchased from Baker Chemical Co.; D-mannose and 2-deoxy-D-glucose were purchased from Sigma Chemical Co. The three lactones were prepared from their corresponding sugars by methylation with dimethyl sulfate and NaOH[11] followed by acid hydrolysis of the methyl glycoside and then Br₂–CaCO₃[12] oxidation to the lactone. Hydrolysis of the glycosides derived from glucose and mannose required refluxing in 2 N HCl for 1 hr, the deoxyglycoside only heating on a steam bath with 0.1 N HCl for 15 min. The three lactones proved to be colorless syrups, and their physical and spectral properties are presented in Table I.

All buffer components were reagent grade. Cyanoacetic acid was recrystallized twice from acetone–petroleum ether and pyridine distilled from KOH. The heavy water, containing at least 99.8% D₂O, was purchased from Bio-Rad Laboratories. The kinetics were followed on a Cary Model 60 ORD-CD at 350 nm. The temperature was maintained at 25.00 ± 0.04° using a Forma-Temp Jr. Model 2095-1 circulating bath. A specially designed 5-cm jacketed polarimeter cell was employed for all kinetic runs. Reproducibility of the rate constants was 1–3%. Specific rotations were determined on a Perkin-Elmer Model 141 polarimeter equipped with a Brinkman-Lauda thermostated circulating bath. Nmr spectra were obtained on a Varian A-60, ir on a Perkin-Elmer Model 257, and mass spectra on an A.E.I. Model MS 9 interfaced with a D.E.C. Model PDP-12 computer. 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.

The optical rotations and various equilibria were determined using methods which were described in the first paper of this series.[3] The kinetic technique and activity corrections used in the present investigation were also previously described.[3] Table II summarizes the optical rotation and equilibrium data for the lactones and their hydrolysis products.

Results

The hydrolysis of lactones 2 and 4 is subject to both general acid and general base catalysis while that of lactone 3 exhibits only general base catalysis at the temperature and in the pH range in which the present study was conducted. The kinetic analysis used in the present paper to determine the catalytic rate coefficients associated with the various buffer components was previously described.[3] To summarize briefly: assuming that every activated complex of the rate-determining step of the hydrolysis reaction contains only one molecule each of substrate and catalyst (+ nH₂O), the catalysis may be described by

$$k_{obsd} = k_0 + k_{H_3O^+}(a_{H_3O^+}/f_\pm) + k_{OH^-}(K_w/a_{H_3O^+}f_\pm) + (k_A + k_B/r)[A] \quad (2)$$

where k_{obsd} is the overall pseudo-first-order rate con-

(11) E. S. West and R. F. Holden, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 800.
(12) H. S. Isbell and H. L. Frush, *J. Res. Nat. Bur. Stand.*, **11**, 649 (1933).
(13) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

Table II. Optical Rotation and Equilibrium Values for Lactones 1–4 and Their Hydrolysis Products

Compd	$[\alpha]^{25}$D, deg	Molar rotation, deg, 100-mm po-larimeter tube	$K \times 10^{4\,a}$	pK_a^b	K_H^c
1	66.3	11.8	1.55 ± 0.03[d]		9.0
Anion	15.0	2.68			
Acid	5.80	1.05		3.77 ± 0.02	
2	97.4	22.8	3.15 ± 0.09[e]		54
Anion	65.1	15.2			
Acid	25.7	6.02		3.48 ± 0.02	
3	145	33.7	2.45 ± 0.07[f]		1.0
Anion	12.6	2.93			
Acid	3.30	0.73		3.31 ± 0.03	
4	107	21.9	0.40 ± 0.02[g]		1.8
Anion	22.8	4.66			
Acid	22.9	4.68		4.20 ± 0.02	

[a] $K = a_{H^+}a_{anion}/([acid] + [lactone])$; values determined at 25.0° in distilled, deionized, and carbon dioxide free water; a = activity. [b] $K_a = a_{H^+}a_{anion}/[acid]$. [c] $K_H = [acid]/[lactone]$. [d] Equilibrated 72 hr; lactone concentration 0.050 M at pH 2.57 (two runs). [e] Equilibrated 72 hr; lactone concentrations: 0.0447 and 0.0407 M at pH values 2.45 and 2.46, respectively. [f] Equilibrated 15 days; lactone concentrations: 0.0452, 0.0512, and 0.0549 M at pH values 2.50, 2.46, and 2.45, respectively. [g] Equilibrated 15 days; lactone concentrations: 0.0304 and 0.0684 M at pH values 2.98 and 2.78, respectively.

stant, k_0 the spontaneous rate constant, k_A and k_B the rate coefficients for the acid and base components of the buffer, respectively, $f_\pm^{14}$ the mean ion activity coefficient, and r the ratio of the concentration of acid to that of conjugate base, i.e., $r = [A]/[B]$. Plots of k_{obsd} against [A] generate a series of slopes, S_r (eq 3) and

$$S_r = k_A + k_B/r \quad (3)$$

intercepts, I_r (eq 4). Thus, plots of S_r against the

$$I_r = k_0 + k_{H_3O^+}(a_{H_3O^+}/f_\pm) + k_{OH^-}(K_w/a_{H_3O^+}f_\pm) \quad (4)$$

various corresponding reciprocal buffer ratios give k_A and k_B and I_r vs. the corresponding hydronium or hydroxide ion concentrations (depending on the pH range of the particular buffer) yields $k_{H_3O^+}$ or k_{OH^-} and k_0. The linearity of these plots for lactones 2–4 and for D-glucono-δ-lactone indicates that the activated complexes contain only one molecule of catalyst (+ nH₂O) within the concentration range studied. Some representative values of the above parameters for the hydrolysis of lactones 2–4 are presented in Table III.

(14) $f_\pm = 0.67$ at ionic strength = 0.50 (NaCl), $T = 25.0°$ (see ref 3 for determination of this value).

Table III. Kinetic Parameters for the Buffer-Catalyzed Hydrolysis of Lactones 2-4

Lactone	Buffer	Concn range of acid, M	No. of runs	1/r	$10^4 S_r$, l. mol^{-1} sec^{-1}	$10^4 I_r$, sec^{-1}	pH^a
2	Imidazole^b in H$_2$O	0.080–0.400	5	0.25	32.2	2.7	6.57
		0.100–0.500	8	0.50	58.6	4.3	6.81
		0.020–0.500	10	1.00	104	8.0	7.14
		0.050–0.350	12	2.00	203	15	7.45
	Formate^c in H$_2$O	0.360–0.900	4	0.11	1.68	1.38	2.50
		0.100–0.750	8	0.20	2.30	1.08	2.74
		0.080–0.800	7	0.25	2.55	1.02	2.90
		0.100–0.600	5	0.50	3.84	0.89	3.17
		0.050–0.250	7	2.00	12.6	0.78	3.83
		0.025–0.125	5	4.00	25.8	0.77	4.10
	Formate^c in D$_2$O	0.160–0.800	5	0.25	0.87	0.32	2.89
		0.080–0.600	5	0.50	1.32	0.29	3.22
		0.060–0.500	6	1.00	2.72	0.24	3.60
		0.050–0.250	5	2.00	5.56	0.20	3.88
		0.025–0.125	5	4.00	10.5	0.19	4.22
3	Tris^b in H$_2$O	0.120–0.500	4	0.25	5.38	2.74	7.60
		0.090–0.500	4	0.33	5.48	4.50	7.72
		0.100–0.500	8	0.50	9.72	6.04	7.89
		0.100–0.500	9	1.00	20.0	12.7	8.21
		0.050–0.250	10	2.00	44.1	25.8	8.50
	Pyridine^b in H$_2$O	0.040–0.140	4	5.00	4.2	0.22	6.04
4	Borate^b in H$_2$O	0.040–0.200	6	0.50	7.50	9.92	8.60
	Tris^b in H$_2$O	0.050–0.300	5	2.00	17.6	8.1	8.51

^{a} Refers to experimental meter reading; in D$_2$O: pD = pH (meter reading) + 0.41. ^{b} Ionic strength adjusted to 0.50 using sodium chloride. ^{c} Ionic strength adjusted to 0.50 using sodium perchlorate.

concentration. The slope of a plot of k_{obsd} vs. the concentration of conjugate base gives the specific rate coefficient for the particular general base. In the pH range 6–9 the catalysis by general acids is negligible and the intercept of this plot is $k_0 + k_{OH^-}[OH^-]$. The second-order rate constant for hydroxide ion catalysis, k_{OH^-}, was determined at pH 8–9. The spontaneous rate constant, k_0, was deduced at pH 6 by subtracting $k_{OH^-}[OH^-]$ from the value of the intercept. The specific rate coefficients for the various catalytic species in the hydrolysis of lactones 2–4 are presented in Table IV.

The data for general acid catalysis for lactone 2 are shown in Figure 1 as a plot of the Brønsted[15] relationship (eq 5) where k_A is the acid catalytic coefficient and

$$\log k_A/p = \alpha \log (qK_a/p) + G_A \qquad (5)$$

K_a is the acid dissociation constant. Similarly, the data for general base catalysis for lactones 2–4 are shown in Figure 2 as a plot of the Brønsted relationship (eq 6)

$$\log k_B/q = \beta \log (p/qK_a) + G_B \qquad (6)$$

where k_B is the general base catalytic coefficient. The statistical corrections for the various acids and bases are given in Table IV. A summary of the observed α and β values for the hydrolysis of lactones 1–4 is given in Table V.

Experiments to obtain the temperature dependence of k_0 for 2 were conducted in 0.020 M acetate buffer (pH

Table IV. Catalytic Rate Coefficients for Acids and Bases in the Hydrolysis of Lactones 2–4^a

Catalyst	k_o,^{b} l. mol^{-1} sec^{-1} — 2	3	4	p^c	q^c	$pK_a{}^d$	k_{H_2O}/k_{D_2O} (2)
H$_3$N$^+$CH$_2$COOH	2.8 × 10^{-4}		1.5 × 10^{-5}	1	2	2.3	
H$_3$N$^+$CH$_2$COO$^-$	1.4 × 10^{-4}						
CNCH$_2$COOH	1.2 × 10^{-4}			1	2	2.5	
CNCH$_2$COO$^-$	1.5 × 10^{-4}						
H$_2$C(COOH)$_2$	2.4 × 10^{-4}			2	2	2.9	
H$_2$C(COO$^-$)(COOH)	3.4 × 10^{-4}						
HCOOH	1.0 × 10^{-4}			1	2	3.7	2.5
HCOO$^-$	6.1 × 10^{-4}						2.4
CH$_3$COOH	4 × 10^{-5}			1	2	4.8	
CH$_3$COO$^-$	8.2 × 10^{-4}						
C$_5$H$_5$NH$^+$	e			1	1	5.2	
C$_5$H$_5$N	2.3 × 10^{-3}	8.3 × 10^{-5}					
IMH$^+$	e			1	1	6.9	
IM	9.9 × 10^{-3}	6.8 × 10^{-4}	3.0 × 10^{-4}				2.9
H$_2$PO$_4^-$	e			2	3	7.2	
HPO$_4^{2-}$	9.4 × 10^{-3}	1.3 × 10^{-3}	5.1 × 10^{-4}				
Tris-H$^+$				3	1	8.1	
Tris		2.1 × 10^{-3}	8.8 × 10^{-4}				
B(OH)$_3$				3	4	9.2	
B(OH)$_4^-$ ^{f}		4.6 × 10^{-3}	1.5 × 10^{-3}				
H$_2$O	8.5 × 10^{-6}/55.5	1.1 × 10^{-5}/55.5	0.5 × 10^{-6}/55.5	2	1	15.74	4.0
H$_3$O$^+$ ^{g}	2.4 × 10^{-2}	1.4 × 10^{-3}	4.7 × 10^{-3}	3	1	−1.74	0.9
OH$^-$	3.4 × 10^3	5.7 × 10^2	1.8 × 10^2				0.8

^{a} At 25.0° and ionic strength I = 0.50. ^{b} k_c refers to the catalytic rate coefficients for the forward reaction in H$_2$O ($k_{obsd} = k_t$ at pH values above 5). ^{c} Taken from R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, **291**, 297 (1966). ^{d} Values of pK_a in H$_2$O taken from G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids and Bases in Aqueous Solution," Butterworths, London, 1961. At 25.0° pK_w taken as 14.00 and pK_{D_2O} as 14.82: A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966). ^{e} Too small to obtain an accurate rate coefficient. ^{f} The reaction used to define the dissociation constant and statistical corrections of boric acid is B(OH)$_3$ + 2H$_2$O ⇌ B(OH)$_4^-$ + H$_3$O$^+$, mentioned in Bell and Evans, footnote c above. For a further discussion of borate equilibria see N. Ingri, *Acta Chem. Scand.*, **17**, 573 (1963). ^{g} The values for H$_3$O$^+$ were determined in HCl solutions, I = 0.50 (NaCl), and represent the catalytic rate coefficient for the forward reaction, k_t. For δ-lactone hydrolysis, $k_{obsd} = k_t + k_r$ and the equilibrium constant, $K_H = k_t/k_r$, is 54 for **2**, 1.0 for **3**, and 1.8 for **4**.

Several general base rate coefficients in the pH range 6–9 were determined in a series of buffers with equal acid–base ratio and pH, but with increasing total buffer

4.44) (Figure 3). At this pH the catalytic contribution from either H$_3$O$^+$ or OH$^-$ is negligible compared to

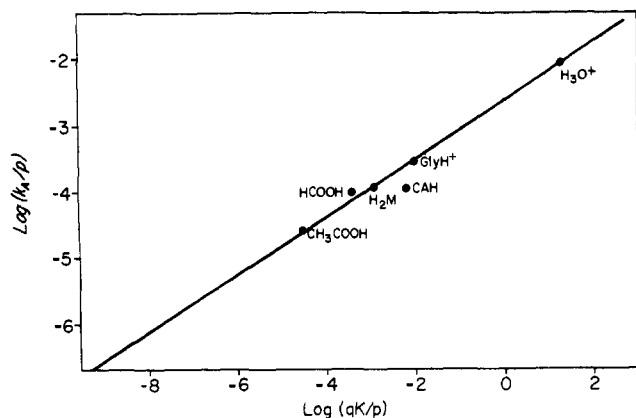(15) J. N. Brønsted, *Chem. Rev.*, **5**, 322 (1929).

Figure 1. Brønsted plot of log (k_A/p) vs. log (qK/p) for acid catalysts in the hydrolysis of lactone **2**; H_2M = malonic acid, CAH = cyanoacetic acid, GlyH$^+$ = H_3N^+-CH_2COOH. Statistical corrections have been made according to Bell and Evans (footnote c, Table IV).
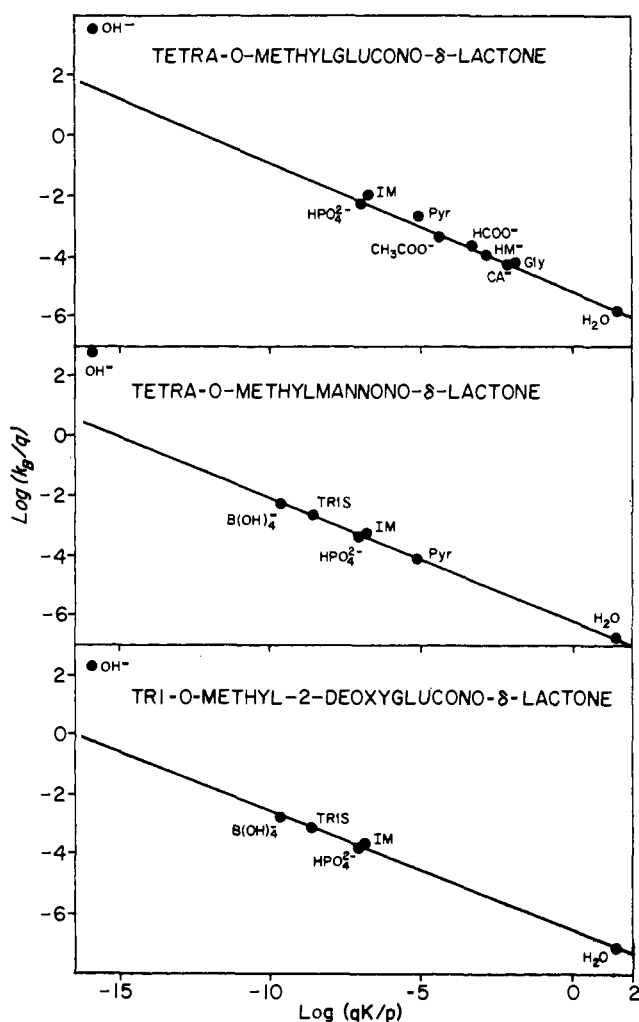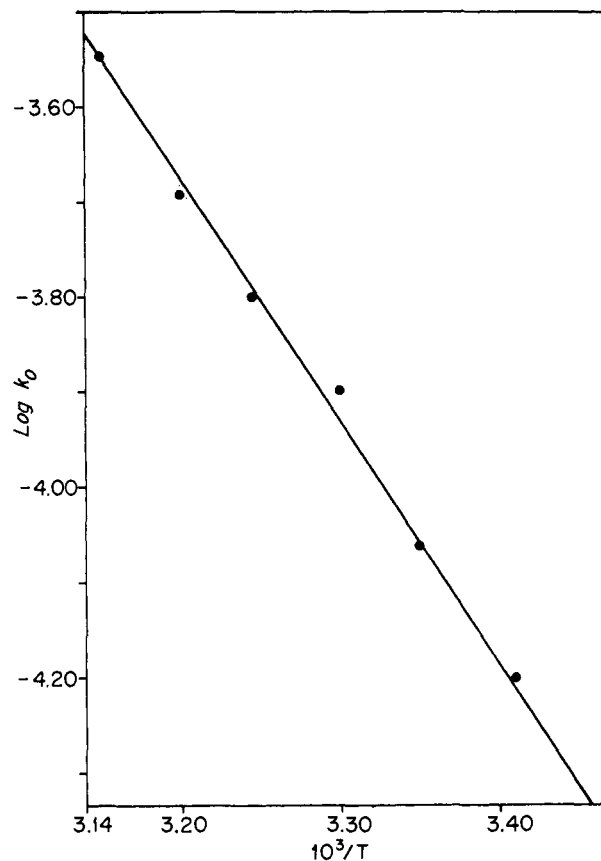

Figure 3. A plot of the logarithm of the rate constant, k_0, for the spontaneous hydrolysis of tetra-O-methylglucono-δ-lactone vs. $1/T$,°K^{-1}. Values of k_0 were deduced from data obtained in 0.020 M acetate buffer (pH 4.44) and an ionic strength of 0.5 using the equation: $k_0 = k_{obsd} - (k_{HOAc}[HOAc] + k_{OAc^-}[OAc^-])$.

Figure 2. Brønsted plot of log (k_B/q) vs. log (qK/p) for base catalysts in the hydrolysis of tetra-O-methylglucono-δ-lactone, tetra-O-methylmannono-δ-lactone, and tri-O-methyl-2-deoxy-glucono-δ-lactone; IM = imidazole, Pyr = pyridine, HM$^-$ = monohydrogen malonate, CA$^-$ = cyanoacetate, Gly = H_3N^+-CH_2COO^-, B(OH)$_4^-$ = borate, Tris = tris(hydroxymethylamino)-methane.

water. The temperature dependence of k_{OH^-} for **1** was determined in 0.020 M Tris, **2** in 0.040 M imidazole, **3** in 0.060 M borate, and **4** in 0.100 M borate (Figure 4).

Figure 4. A plot of the logarithm of the rate coefficient, k_{OH^-}, for the hydroxide ion catalyzed hydrolysis of lactones 1–4 vs. $1/T$, °K^{-1}. Ionic strength held constant at 0.50 with NaCl.
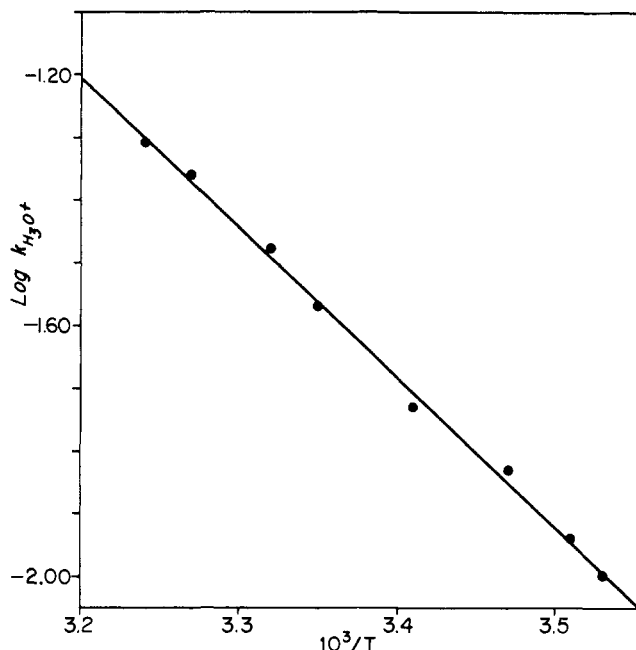
Figure 5. A plot of the logarithm of the rate coefficient, $k_{H_3O^+}$, for the hydronium ion catalyzed hydrolysis of tetra-O-methyl-glucono-δ-lactone vs. $1/T$,$°K^{-1}$. Rate constants determined in 0.100 M HCl, ionic strength = 0.50 (NaCl).

Table V. Values of the Parameters α and β of the Brønsted Relationships[a]

Lactone	α	β
1	0.42[b]	0.45[b]
2	0.43[c]	0.43[d]
3		0.41[d]
4	(0.6)[e]	0.30[d]

[a] pK_a values at 25.0°. [b] Reference 3. [c] Deduced from Figure 1. [d] Deduced from Figure 2. [e] Approximate value.

The following corrections were applied in the calculation of k_{OH^-} at each temperature: (1) the contribution due to general base catalysis (never more than 19%) was subtracted from the observed rate constant; (2) a pH measurement was carried out at every temperature for all four buffers; and (3) use was made of the appropriate ionization constant of water, K_w, at the particular temperature and ionic strength.[16] The activation parameters for the hydrolysis of 2 in HCl were also determined (Figure 5). Table VI presents a summary of all the activation data for lactones 1–4.

Discussion

The generalization that arises from the present investigation is that the hydrolytic behavior of δ-lactones parallels that of acyl-activated esters with poor leaving groups. The two classes of compounds exhibit general base catalysis, significant spontaneous hydrolysis with large negative entropies of activation, similar hydroxide ion activation parameters, and similar solvent deuterium isotope effects, and neither is subject to nucleophilic catalysis by imidazole.[17] Table VII compares kinetic

(16) H. S. Harned and G. E. Mannweiler, J. Amer. Chem. Soc., 57, 1873 (1935).

(17) For excellent summaries of ester hydrolysis, see (a) S. L. Johnson, Advan. Phys. Org. Chem., 5, 237 (1967); (b) E. K. Euranto in "The Chemistry of Carboxylic Acids and Esters," S. Patai, Ed., Interscience, New York, N. Y., 1969, Chapter 11; (c) A. J. Kirby in "Comprehensive Chemical Kinetics," Vol. 10, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1972, Chapter 2.

Table VI. Activation Parameters at 25.0° [a]

Catalytic species	Lactone	E_A, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta H^{\ddagger}$, kcal/mol
H_2O	1	13.5 ± 0.5[b]	−36[b]	12.9[b]
	2	11.6 ± 0.4	−40	11.0
OH^- [c]	1	7.0 ± 0.2	−20	6.4
	2	6.5 ± 0.2	−21	5.9
	3	7.0 ± 0.2	−22	6.4
	4	7.2 ± 0.2	−24	6.6
H_3O^+ [d]	2	10.7 ± 0.1	−31	10.1

[a] Ionic strength, $I = 0.50$. [b] Reference 3. [c] $\Delta S^{\ddagger}$ values based on k_{OH^-} (25.0°) calculated using $K_w = 5.17 \times 10^{-15}$ at $I = 0.50$ (NaCl) and $T = 25.0°$; see ref 16 for calculation of K_w. [d] Determined in 0.100 M HCl. Ionic strength adjusted to 0.50 with NaCl.

data for several acyl-activated esters. p-Nitrophenyl acetate is included to show the behavior of esters whose hydrolysis is largely nucleophilic.

δ-Lactones of common sugars, however, exhibit general acid catalysis. In an effort to explain the differences and similarities between the two classes of compounds, lactones with different acyl substitution were examined. The study of the hydrolysis reactions of lactones 2–4 provides an insight into the reasons why general acid catalysis is observed in these systems and not in acyl-activated esters, and clarifies some interesting mechanistic problems associated with the hydrolysis of D-glucono-δ-lactone. The following discussion assumes that the mechanisms of hydrolysis of lactones 1–4 (and acyl activated esters with poor leaving groups) are nearly identical in that the first step involves a rate-determining hydration of the carbonyl to produce a tetrahedral intermediate. (See ref 3 for a discussion of the mechanism of this reaction.)

1 vs. 2. The hydrolysis of D-glucono-δ-lactone (1) is very similar to its fully methylated derivative (2). The rate coefficients for acids and bases, Brønsted exponents, and the isotope effects differ only slightly. The great similarity in the kinetic parameters associated with the hydrolysis of these two lactones indicates (a) that intramolecular hydrogen bonding of the 2-hydroxyl to the carbonyl oxygen in lactone 1 is not important, and (b) that with most general acids the critical water structure is little affected by replacing OH by OMe. Further, the lack of radical departure in the kinetic and equilibrium data (Table II) of 1 vs. 2 (lactone 2 is incapable of forming a γ-lactone) lends added support to our earlier finding[3] that the δ-lactone (1)–gluconic acid equilibrium is established long before sensible amounts of γ-lactone have been produced.

The only important difference in the hydrolytic behavior of 1 and 2 is the catalytic efficiency of $H_2PO_4^-$. The value of the rate coefficient fell ca. 1.7 log units above the Brønsted line for general acid catalysis of 1,[3] whereas in the hydrolysis of 2 it was too small to be measured accurately. Thus, a clear distinction in catalytic efficiency of $H_2PO_4^-$ between 1 and 2 is apparent. The difference may reflect the ability of $H_2PO_4^-$ to hydrogen bond with the hydroxylactone more efficiently than with its methylated derivative. This conclusion is supported by the finding that phosphate ions associate with glucose in aqueous solution.[18]

2 vs. 3. Interestingly, tetra-O-methylmannono-δ-

(18) A. W. Fonds and J. M. Los, J. Electroanal. Chem., 36, 479 (1972).

Table VII. Comparison of Activated Esters[a]

Compound	α	β	k_0, sec^{-1}	k_{H_2O}/k_{D_2O}	$\Delta S^{\ddagger}(H_2O)$, eu	k_{IM}, l. mol^{-1} sec^{-1}	k_H/k_D (IM)	k_{OH^-}, l. mol^{-1} sec^{-1}	$\Delta H^{\ddagger}$ (OH$^-$), kcal/mol	$\Delta S^{\ddagger}$ (OH$^-$), eu
2	0.43	0.43	8.5 × 10^{-5}	4.0	−40 (ΔH‡ = 11.0)	9.9 × 10^{-3}	2.9	3.4 × 10^3	5.9	−21
4	0.6[b]	0.30	0.5 × 10^{-5}			3.0 × 10^{-4}		180	6.6	−24
Cl₂CHCOOEt		0.47[c]	0.5 × 10$^{-5\,c}$	5[c]		1.4 × 10$^{-3\,c}$	3.0[c]	677[d]	5.86[d]	−25.9[d]
F₂CHCOOEt			5.7 × 10$^{-5\,c}$	2.1[c]		1.0 × 10$^{-2\,c}$	2.8[c]	4.5 × 10$^{3\,c}$		
Cl₂CHCOOMe			1.56 × 10$^{-5\,e}$		−42[e] (ΔH‡ = 11.4)			1.5 × 10$^{3\,d}$	6.15[d]	−23.4[d]
p-Nitrophenyl acetate		0.8[f]	8.46 × 10$^{-7\,g}$			0.58[h]	1[i]	9.5[h]		

[a] In water at 25.0°. [b] Approximate value. [c] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **83**, 1743 (1961). [d] E. K. Euranto and A.-L. Moisio, *Suom. Kemistilehti B*, **37**, 92 (1964). [e] N. J. Cleve and E. K. Euranto, *ibid.*, **37**, 126 (1964). [f] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960); an arbitrary line drawn through several amines and represents largely nucleophilic catalysis. [g] V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. B*, 515 (1968). [h] J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 837 (1964). [i] B. M. Anderson, E. H. Cordes, and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961).

lactone (3), with the 2-methoxyl in the axial position, proved to be less reactive than **2** by a factor of *ca.* 10; the actual rate ratios for five bases varied from 6.0 to 28 (Table IV). General acid catalysis was not detectable and the Brønsted exponent, β, for general base catalysis is 0.41 ± 0.02. This result means that the reactivity of δ-lactones and the ability to detect general acid catalysis in these systems is a function of the configuration of a substituent in the 2 position. A tenfold decrease in substrate reactivity is sufficient to render the catalysis by general acids (except hydronium ion) undetectable under the conditions of the present study. The magnitude of the catalysis by general bases is much larger than by general acids in δ-lactone hydrolysis, and a tenfold decrease in substrate reactivity of **3** *vs.* **2** means that general base catalysis is still measurable. Indeed, the rate of hydrolysis of lactone **3** in the acid region (pH 1.5–5.5) was prohibitively slow.

The *ca.* tenfold difference in reactivity of **2** (equatorial methoxyl) over **3** (axial methoxyl) (actually $\Delta F^{\ddagger}_3 - \Delta F^{\ddagger}_2$ varies from 1.21 kcal/mol for water catalysis to 1.96 kcal/mol for pyridine catalysis) is in all probability a consequence of the unfavorable dipole repulsion of the equatorial methoxyl and the nearly parallel dipole of the carbonyl.[19] The situation is analogous to the well-known case of α-halocyclohexanones. In these systems the infrared carbonyl stretching frequency of the equatorial halogen is increased over both the axial and unsubstituted cyclohexanone[20a] and the ring is largely (but not exclusively) in the form in which the halogen is axial.[20b,c] A similar difference in carbonyl stretching frequency was found in the present work for lactones **2** and **3** (see Table I). Direct evidence for the conformational preference of an axial 2-methoxyl in δ-lactones comes from a study of the epimerization of **2** ⇌ **3**.[21] It was shown that equilibration of either **2** or **3** in aqueous pyridine gives a mixture consisting of 95% **3** (axial 2-methoxyl) and 5% **2** (equatorial 2-methoxyl). This represents a free energy difference between the two lactones, in this medium, of 1.75 kcal/mol at 25°. The

(19) It is also possible, though less probable, that the lower reactivity of lactone 3 is in part associated with a steric or electrostatic barrier afforded by its axial methoxyl to the approach of a nucleophile or general catalyst.

(20) (a) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952); (b) E. J. Corey, *ibid.*, **75**, 2301 (1953); (c) N. L. Allinger, J. Allinger, L. A. Freiberg, R. F. Czaja, and N. A. LeBel, *ibid.*, **82**, 5876 (1960).

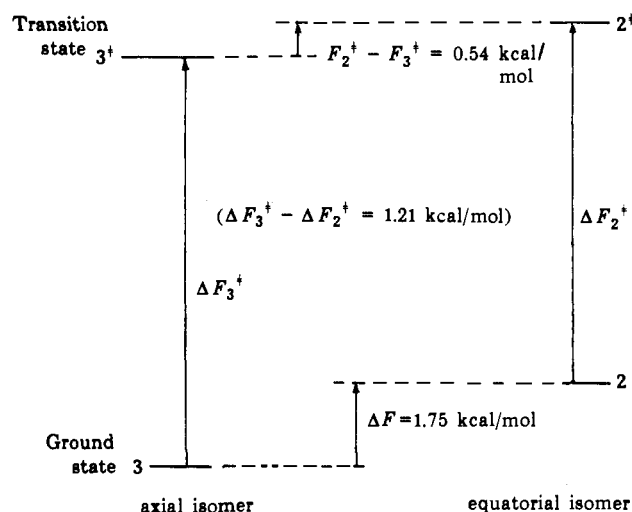(21) W. N. Haworth and C. W. Long, *J. Chem. Soc.*, 345 (1929).

Figure 6. Energy level diagram for the water-catalyzed hydrolysis of lactones **2** and **3**. The activation free energy differences, $\Delta F^{\ddagger}_3 - \Delta F^{\ddagger}_2$, and the transition state free energy differences, $F^{\ddagger}_2 - F^{\ddagger}_3$, for H₂O catalysis are: 1.21 and 0.54 kcal/mol, respectively; for HPO₄²⁻, 1.17 and 0.58 kcal/mol; for OH⁻, 1.06 and 0.69 kcal/mol; for imidazole, 1.58 and 0.17 kcal/mol; for pyridine, 1.96 and −0.21 kcal/mol. Note: since $F^{\ddagger}_2 - F^{\ddagger}_3$ for pyridine catalysis is actually negative, the diagram will show the level of **3**‡ higher than that of **2**‡.

effect of the unfavorable dipole repulsion between the equatorial 2-methoxyl and carbonyl must outweigh the steric crowding of the 2-methoxyl in the axial position. In Figure 6 the reactivity of **2** relative to **3** may be seen to result from the combination of ground state free energy difference between the two lactones ($\Delta F = 1.75$ kcal/mol) and a smaller free energy difference between the two transition states, $F^{\ddagger}_2 - F^{\ddagger}_3$, ranging from 0.54 kcal/mol for water catalysis to −0.21 kcal/mol for pyridine catalysis (see legend to Figure 6).

3 *vs.* **4.** General acid catalysis now reappears in the hydrolysis of tri-*O*-methyl-2-deoxyglucono-δ-lactone with α ∼ 0.6 (based on two points). Inspection of Table IV shows that the catalysis by hydronium ion is three times greater than with **3**. This rate enhancement is just sufficient to make catalysis by general acids of low pK$_a$ observable (*i.e.*, the rates are conveniently measurable only up to pH ∼2.3). However, the larger α value of *ca.* 0.6 means that the catalysis by general acids of pK$_a$ > 2.5 rapidly becomes negligible compared to that of hydronium ion. Thus, detectable general acid

catalysis in 3 and 4 not only depends on the magnitude of the acid catalysis, but on the sensitivity (α) to the pK_a of the general acid catalyst. A similar behavior has been observed in general acid catalyzed ketal and acetal hydrolyses.[22]

The 2-methoxyl also has the effect of raising β relative to the 2-unsubstituted lactone (4). This result indicates that an increase in acyl activation of esters by adding electron-withdrawing groups raises β where a cooperative (operating through water molecules) general catalyzed mechanism is involved.[23] Comparison of this result with data in the literature is difficult. Some data do exist, however, that show a parallel trend in β with increasing acyl activation.[17b,24] The variation of β with changes in acyl activation is associated with changes in the shape and position of the potential energy surfaces for proton transfer. Any structural change in the substrate which affects the activation energy of the acid or base catalyzed reaction also affects that of the proton transfer. Different shapes and positions of the potential energy diagrams for proton transfer generate a change in the slopes of the linear branches around the region of overlap. These slopes are related to the Brønsted exponents, α and β.[24,25]

Reactivity of δ-Lactones. We have seen that the ability to detect general catalysis in the hydrolysis of lactones 1–4 is attributable to their high reactivity relative to straight chain esters. A possible explanation for the difference in reactivity was offered by Huisgen and Ott who investigated the rates of alkaline hydrolysis of ω-lactones.[26] The higher rates of lactones with five- to nine-atom rings were attributable to the cis configuration of these lactones whose free energy in the ground state is higher than the free energy in the trans conformation of the open-chain esters and lactones that have ten or more atoms in the ring.
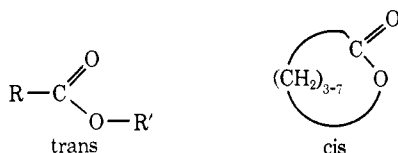
The "cis" effect, however, cannot fully account for the enhanced reactivity of δ-lactones (six atoms in the ring). The data of Huisgen and Ott show the rate of alkaline hydrolysis of the δ-lactone is by far the highest in the series and 40-fold greater than that of the γ-lactone. Brown[9] has suggested that the lower ground state free energy of γ- vs. δ-lactone is a consequence of bond oppositions produced by the sp^2 carbon. The hydrogen atoms are more eclipsed in the half-chair[27] conformation of the δ-lactone than in the γ-lactone. Furthermore, the 40-fold higher rate of alkaline hydrolysis of δ- vs. γ-lactone must also be due to the free energy

difference of the transition states leading to the tetrahedral intermediates (T_δ and T_γ) since saturated six-membered rings are known to be more stable than five.

Thus, the enhanced reactivity of δ-lactones is a combination of (i) the cis effect, (ii) the strain produced by the exocyclic double bond, and (iii) the relative heights of the transition states leading to the tetrahedral intermediates, T_δ and T_γ. Our data taken in conjunction with that of Huisgen and Ott indicate that at 25° the unusual reactivity of the δ-lactone relative to that of an open-chain ester or a trans lactone is associated with a change in free energy, $\Delta\Delta F^{\pm} = -RT \ln (k_\delta/k_{trans})$, of ca. 5.8 kcal/mol. Similar calculations show that at 25° the cis effect contributes around 3.7 kcal/mol (i.e., ca. 64%) and the exocyclic strain taken together with the transition state free energy differences contribute around 2.1 kcal/mol (i.e., ca. 36%).[26]

General Acid Catalysis. The abnormally higher reactivity of δ-lactones requires that these compounds be placed in the category of acyl activated esters with poor leaving groups (see Table VII). The electron-withdrawing groups attached to the α carbon of straight-chain esters cause a significant base-catalyzed reaction to occur by stabilizing a developing negative charge in the transition state, and by raising the free energy of the ground state. They also, however, decrease the magnitude of the hydronium ion catalyzed reaction by destabilizing the partial positive charge in the transition state. The decrease in the acid-catalyzed rate is sufficient to prevent any detectable catalysis by general acids. δ-Lactones are "activated" without electron-withdrawing groups in the acyl fragment. Consequently, they exhibit comparable base catalysis, the hydronium ion rate is higher, and significant general acid catalysis is detectable.

Nature of the Tetrahedral Intermediate. Oxygen-18 experiments show that the hydrolysis of lactone 1 does not exchange oxygen with solvent[3] (though oxygen-18 experiments were not carried out on lactones 2–4, it is reasonable to assume that they also do not incorporate oxygen-18). This result indicates that hydration of the carbonyl to give the tetrahedral intermediate is rate determining followed by a relatively rapid ring opening (eq 7). This is a curious observation in view of the fact
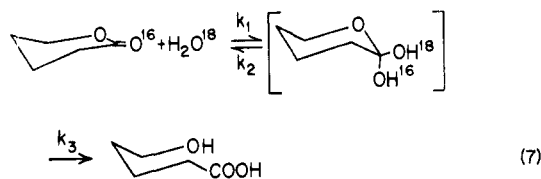
that hydrolysis of highly activated ethyl trifluoroacetate (eq 8) proceeds with significant partitioning of the

(22) T. H. Fife and E. Anderson, *J. Org. Chem.*, **36**, 2357 (1971).

(23) This interpretation is subject to the usual uncertainties associated with the magnitude of steric interactions of the α substituent.
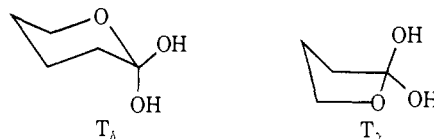
(24) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter 10; W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

(25) M. Eigen, *Angew. Chem.*, **75**, 489 (1963).

(26) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959); using the data in this paper, the free energy differences were calculated from the rate constants for alkaline hydrolysis of a typical trans lactone or open-chain ester, k_{trans}, of γ-butyrolactone, k_{cis}, and of δ-valerolactone, k_δ: $k_\delta/k_{trans} = 18,300$; $k_\delta/k_{cis} = 37$; $k_{cis}/k_{trans} = 493$.

(27) M. L. Hackert and R. A. Jacobsen, *Acta Crystallogr., Sect. B*, **27**, 203 (1971).
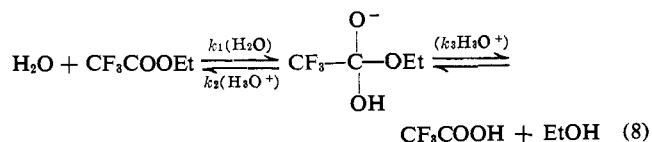
$$H_2O + CF_3COOEt \underset{k_2(H_3O^+)}{\overset{k_1(H_2O)}{\rightleftharpoons}} CF_3-\overset{O^-}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-OEt \overset{(k_3H_3O^+)}{\rightleftharpoons}$$

$$CF_3COOH + EtOH \quad (8)$$

tetrahedral intermediate ($k_{hyd}/k_{ex} = 0.6$),[7b] i.e., k_3 must be partially rate determining. It could be argued that since the alcohol product derived from lactones **1–4** is probably a stronger acid than ethanol (i.e., the poly-hydroxy alcohol is a better leaving group than ethanol) ring opening is much faster than return to the lactone, and no partitioning of the tetrahedral inter-mediates of lactones **1–4** should be observed. Another reasonable explanation is that the free energy barrier between δ-lactone and its relatively stable tetrahedral intermediate (see above) is sufficiently high relative to the ring-opening step to prevent return whereas a much lower barrier exists between ethyl trifluoroacetate and its tetrahedral intermediate. Another explanation must be found, however, in view of the observation that the basic hydrolysis of γ-butyrolactone (**5**) is also not accompanied by oxygen-18 exchange.[28] Clearly the

5

arguments presented for the above δ lactones are not applicable in this system, since the leaving group of **5** is no better than ethanol, and according to the principle of microscopic reversibility, return (dehydration) of the tetrahedral intermediate ($T_γ$) to γ-lactone is favored relative to dehydration of $T_δ$ to the δ-lactone, yet both the γ- and δ-lactones showed no [18]O exchange. The low free energy of activation for the k_3 step (eq 7) may be a consequence of a positive $T\Delta S^{\ddagger}$ term arising from an increase in the number of vibrational and rotational degrees of freedom in the transition state of the ring-opening step (Figure 7).

Imidazole and Tris Catalysis. The following observa-tions strongly suggest that imidazole operates as a general base in the hydrolysis of lactones **1–4**: the deuterium isotope effect is ca. 3, the k_{OH^-}/k_{IM} ratio is near 10^7, and the value of the rate coefficient for imidazole falls on the Brønsted plot defined by authentic general bases with β values near 0.5.[17] Also, $k_{IM}/k_{HPO_4^{2-}}$ is around 1 as would accord with the fact that the basicities of IM and HPO_4^{2-} are nearly iden-tical.[17a] In contrast, the imidazole-catalyzed hydrolysis of esters with good leaving groups, e.g., p-nitrophenyl acetate, is known to be largely nucleophilic. This re-action exhibits a k_{OH^-}/k_{IM} ratio of $10–10^3$, a deuterium isotope effect of around 1, and a $k_{IM}/k_{HPO_4^{2-}}$ value of ca. 10^3 (see Table VII and references therein). Nucleo-philic catalysis becomes important when the leaving group is of comparable basicity to the attacking nucleo-phile. Since imidazole acts as a general base in the hydrolysis of δ-lactones, expulsion of imidazole from the tetrahedral intermediate must be fast relative to ring opening ($k_5 \gg k_6$, eq 9). Clearly, this intermediate does not lie on the pathway of δ-lactone hydrolysis and is probably a blind alley equilibrium. This behavior is due to the large difference in basicity between imidazole and the leaving alkoxide group of the lactone.

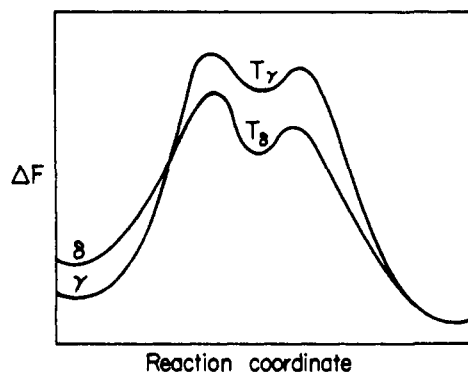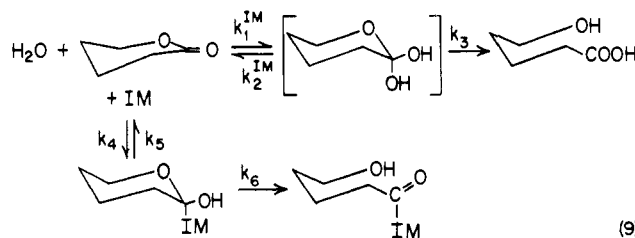(28) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, J. Amer. Chem. Soc., 83, 4193 (1961).

Figure 7. Transition-state diagram for the hydrolysis of five- and six-membered lactones.

(9)

The catalytic rate coefficients for Tris fell on the Brønsted line for general base catalysis of lactones **1**, **3**, and **4**. Jencks and Carriuolo[29] found that Tris was acting as a nucleophile in the hydrolysis of the acyl-activated ester, ethyl dichloroacetate. This result suggests that though the hydrolyses of δ-lactones and acyl-activated esters with poor leaving groups have several common mechanistic features, the factors which cause a change from general to nucleophilic catalysis may not be equally important for the two systems.

Importance to Intramolecular Rate Accelerations. General acid and general base catalyses are strongly indicative of reactions in which the proton transfer itself is an important process occurring in the transition state. Furthermore, in δ-lactone hydrolysis, the proton is being transferred between oxygen atoms, and the involvement of water bridges is of paramount im-portance in the transition state. Clearly, by the principle of microscopic reversibility, these considera-tions also apply to the reverse process, i.e., to lactoniza-tion, and thus have a direct bearing on recent discus-sions concerning the efficiency of intramolecular vs. intermolecular reactions in aqueous solution.[6,30] In this regard, we suggest that a more complete description of intramolecular rate accelerations associated with lactonization should also include a detailed considera-tion of water bridges acting in a cooperative fashion in the transition state.

(29) W. P. Jencks and J. Carriuolo, J. Amer. Chem. Soc., 83, 1743 (1961).

(30) (a) D. R. Storm and D. E. Koshland, Jr., Proc. Nat. Acad. Sci. U. S., 66, 445 (1970); (b) T. C. Bruice, A. Brown, and D. O. Harris, ibid., 68, 658 (1971); (c) M. I. Page and W. P. Jencks, ibid., 68, 1678 (1971); (d) A. Dafforn and D. E. Koshland, Jr., ibid., 68, 2463 (1971).