(15) This interpretation of the respective ρ values suggests that mesomeric dipoles will often be of importance for the magnitude of ρ. As a rule the picture will be more complicated than in the present case due to the presence of mesomeric dipoles in both factor and product (phenols) or the uncertainties of transition state structure. As an example we mention the relatively low ρ values for the solvolysis of ArC(*t*-Bu)$_2$-*p*-nitrobenzoates as observed by H. Tanida and H. Matsumura, *J. Am. Chem. Soc.*, **95**, 1586 (1973) and by J. S. Lomas and J. E. Dubois, *Tetrahedron Lett.*, 407 (1976).

(16) The ρ values corroborate the rule that interposition of a CH_2 group decreases ρ by a factor 2. In 50% ethanol, ρ_m for benzoquinuclidines and $ArCH_2NH_2$, −2.87 and −1.27 (unpublished), already conform reasonably, and ρ_m of $ArCH_2NMe_2$ will be somewhat more negative than that of the primary amine. From this point of view the ρ_m values of $ArNH_2$ and $ArNMe_2$ are "abnormally" highly negative due to the aniline resonance.

(17) Our data in H_2O and 10% and 75% ethanol are less complete but display the same pattern. Again, the groups NH_2 and NHAc in meta position show variations which are much smaller.

(18) J. Hine, *J. Am. Chem. Soc.*, **81**, 1126 (1959); *ibid.*, **82**, 4877 (1960).

(19) Expressions containing $\sigma_R^n(X) - \sigma_R^n(Y)$, as used by Katritzky, Topsom et al. in their infrared work (see footnotes 10 and 21), obviously are not appropriate either. This emphasizes the differences between chemical and infrared criteria.

(20) Due to decomposition during the measurements, our potentiometric pK_a values pertaining to the hydroxy group in the aminophenols are not very accurate. However, they confirm literature values and are sufficiently reliable for the present work.

(21) In ref 4 we gave $\sigma_R^n(O^-) = -0.4$, but we now believe its derivation is wanting for reasons which will be apparent from later papers in this series. All required $\sigma_R^n(\sigma_R^0)$ values have been obtained from ^{19}F NMR [R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963)], and from infrared intensities [A. R. Katritzky and R. D. Topsom, *Angew. Chem., Int. Ed. Engl.*, **9**, 87 (1970), and later papers]. The NMR data give $\sigma_R^0(NH_3^+) - \sigma_R^0(NH_2) = 0.48$ as against $\sigma_R^0(OH) - \sigma_R^0(O^-) = 0.17$; the infrared data give 0.29 and 0.17, respectively. Thus, these differences are indeed smaller for phenols than for anilines. However, there is some doubt as to the applicability of these σ_R^0 values to the present phenomena (cf. footnote 19). In particular it is difficult to accept that donation by NH_3^+ and NMe_3^+ would be larger than by CH_3 and *t*-Bu, as indicated by the infrared data.

(22) R. T. McIver, Jr., and J. H. Silvers, *J. Am. Chem. Soc.*, **95**, 8462 (1973).

(23) C. G. Swain and E. C. Lupton, Jr., *J. Am. Chem. Soc.*, **90**, 4328 (1968).

(24) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969, p 423.

(25) J. P. Schaefer and T. J. Miraglia, *J. Am. Chem. Soc.*, **86**, 64 (1964); cf. F. H. Westheimer and R. P. Metcalf, *ibid.*, **63**, 1339 (1941). Our figures, from thermodynamic values in 50% ethanol,[3] at 25 °C ($\rho_m = 1.52$), give for ΔpK_a^* (4-NO_2): benzoic acid, 1.19; 3-methylbenzoic acid, 1.13; 3,5-dimethylbenzoic acid, 1.05; 3,5-di-*tert*-butylbenzoic acid, 1.05. For ΔpK_a^* (3-NO_2): benzoic acid, 1.07; 4-methylbenzoic acid, 1.07; 4-*tert*-butylbenzoic acid, 1.06.

(26) B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **75**, 1473 (1956). The published pK_a's are apparent values; thermodynamic values are now available and give for ΔpK_a^* (4-NO_2) in 50% ethanol,[3] at 25 °C ($\rho_m = 3.93$): 2-*tert*-butyl-*N,N*-dimethylaniline, 2.69; 2,5-di-*tert*-butyl-*N,N*-dimethylaniline, 2.37. For ΔpK_a^* (5-NO_2): 2-*tert*-butyl-*N,N*-dimethylaniline, 2.79; 2,4-di-*tert*-butyl-*N,N*-dimethylaniline, 2.86.

(27) B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **76**, 357 (1957); cf. also ref 14.

(28) We thank Mr. J. J. M. Potters (Laboratory of Physical Chemistry) for carrying out these calculations (1971). The parameters chosen were: NH_2, $\alpha_N = \alpha + 0.65\beta$; NO_2 and COO^-, $\alpha_N = \alpha + 0.5\beta$; $\alpha_O = \alpha + 1.0\beta$.

Mechanism of Aminolysis of δ-Lactones. Kinetic Behavior of Tri-*O*-methyl-2-deoxyglucono-δ-lactone, Solvent Deuterium Isotope Effects, and Transition-State Characterization[1]

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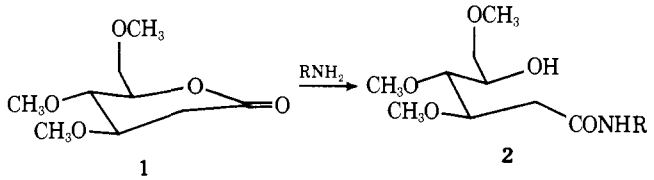
Abstract: Polarimetric and spectrophotometric methods have been used to study the aminolysis of tri-*O*-methyl-2-deoxyglucono-δ-lactone over a wide pH and buffer concentration range at 25.0 °C. Throughout the entire pH and amine nucleophile concentration range, the reaction was found to adhere to the kinetic expression in eq 1. The high reactivity towards aminolysis, the lack of change in the rate-determining step over the entire experimental pH range, and the first-order nucleophilic Brønsted slope of 0.85 place the aminolysis reactions of this δ-lactone within the family of the moderately reactive trifluoroethyl and phenyl acetates. The amines used in the present study (hydroxylamine, glycine ethyl ester, hydrazine, glycinamide, morpholine, 2-methoxyethylamine, ammonia, and glycine) exhibit one or more terms in $[N_f]$. The term for the hydroxide ion catalyzed hydroxylaminolysis is $k_3[N_f]a_{OH^-}$, with a solvent deuterium isotope effect (k_3^H/k_3^D) of 0.6 ± 0.1. The higher-order term $k[N_f]^2a_{OH^-}$ cannot be detected in this reaction. With morpholine the uncatalyzed first-order term in $[N_f]$, k_1, arises from a general-base-catalyzed hydrolysis as shown by product analysis and an isotope effect of 1.9 ± 0.2. The overall results indicate that the ring structure in δ-lactones mimics the effect of the better leaving alkoxy group in open chain esters. These observations are discussed in terms of previously proposed mechanisms for ester aminolysis.

In our continuing effort to characterize the effects of ring structure on the kinetic and mechanistic behavior of lactones in aqueous solution, we have examined the aminolysis of tri-*O*-methyl-2-deoxyglucono-δ-lactone. In previous studies on



1 2

δ-lactone hydrolysis,[2] it was shown that the presence of the ring causes marked departures from the hydrolytic behavior of straight-chain alkyl esters. By analogy, it was felt that the aminolysis reaction of δ-lactones might also produce novel kinetic departures from those encountered with straight-chain alkyl esters.

We report here on a detailed examination of the effect of the ring on the relative contributions to the rate expression of the various aminolysis terms shown in eq 1.[3a-f] In addition this paper also addresses itself to the question of whether or not a change in the rate-determining step is observed with decreasing pH. A break in the pH–rate profile that is caused by a change in the rate-determining step has been used to infer the existence of a tetrahedral intermediate in ester aminolysis.[4-6]

The δ-lactone which we have chosen as the substrate for the present study is the tri-*O*-methyl-2-deoxyglucono-δ-lactone. This lactone combines several important properties which are highly advantageous in the study of its aminolysis reactions.

First, there exists a large difference in optical rotation between the lactone and its corresponding amides, allowing the aminolysis reaction to be monitored polarimetrically with considerable accuracy on an ORD instrument using a fairly low (1×10^{-3} M) substrate concentration. Second, the reactivity of the deoxylactone permits the study of these reactions to be carried out at 25.0 °C using a great variety of amines over a wide range of nucleophile concentrations.

This paper shows that the aminolysis of δ-lactones resembles more closely that of phenyl acetate and other moderately reactive esters rather than that of straight-chain alkyl esters with poor leaving groups. We suggest that this kinetic and mechanistic resemblance is in part a consequence of facile ring opening, in spite of the fact that the pK_a of the conjugate acid of the leaving group in δ-lactones is significantly higher than that of phenol.

Experimental Section

Materials. Tri-*O*-methyl-2-deoxyglucono-δ-lactone (**1**) was synthesized according to a previously published procedure.[2b] Morpholine was purified by refluxing with $LiAlH_4$ for 20 h and distilling through a 2 ft Vigreux column, bp 128.0–128.5 °C. 2-Methoxyethylamine was freshly distilled, bp 95 °C. Hydrazine monohydrate (98%) and reagent grade NH_4Cl were used without purification. Commercial amine hydrochlorides were recrystallized twice from ethanol–water. Distilled, deionized, and degassed water was used for all buffer solutions. The D_2O (99.8% D) was purchased from Stohler. DCl/D_2O stock solutions were prepared by refluxing dichlorodimethylsilane in D_2O for 4 h followed by separation of the silicone oil.[7] KOD stock solutions were prepared by dissolving anhydrous KOH in D_2O.

Kinetics. The aminolysis of tri-*O*-methyl-2-deoxyglucono-δ-lactone was followed polarimetrically on a Cary Model 60 ORD-CD spectropolarimeter at 293–338 nm employing a jacketed, 5-cm polarimeter cell. The temperature was kept constant at 25.00 ± 0.08 °C using a Forma-Temp Jr. Model 2095 circulating bath. A few hydrazinolysis rates were followed spectrophotometrically at 230 nm (hydrazide absorbance) on a Varian Techtron Model 635, which was thermostated with a Precision Scientific circulating bath (25.0 ± 0.1 °C). The reproducibility between the two methods using identical buffer solutions was ±2%. Pseudo-first-order conditions were maintained throughout by keeping the free amine concentration ($[N_f]$) large relative to substrate concentration. The amine–amine hydrochloride buffers were used within 48 h of preparation and stored at 2 °C. Also, 10^{-4} M EDTA was added to all buffers to reduce possible heavy metal ion catalyzed decomposition.

The pH and pD (pD = pH reading + 0.41[8]) values were determined on a Beckmann 101900 research pH meter. The pH at the end of the reaction in the weakest amine buffer solutions was found to change by a maximum of 0.06 pH units. The serially diluted buffers gave a small pH drift over the amine concentration range. Maximum drift was 0.06 pH unit for all buffers except glycine (0.12 unit). The mean pH was taken as the pH for the set of buffers with constant acid–base ratio. The k_{obsd} values were then adjusted using k_{OH^-} and the change in a_{OH^-}. With the exception of glycine, this correction had little or no effect on the resulting experimental rate constants.

The amine buffer solutions were prepared by serial dilution, keeping the ionic strength (μ) constant at 1.00 M with KCl except for hydroxylamine, where μ was kept constant at 0.5 with NaCl.

The observed pseudo-first-order rate constants (k_{obsd}) may be described in terms of the various catalytic species present in the amine buffer solutions

$$k_{obsd} = k_{OH^-}a_{OH^-} + k_1[N_f] + k_2[N_f]^2 + k_3[N_f]a_{OH^-} + k_4[N_f][NH^+] \quad (1)$$

where $k_{OH^-}a_{OH^-}$ is the hydrolysis rate, $[N_f]$ the free-amine concentration, $[NH^+]$ the concentration of the conjugate acid of the amine, and k_4 the rate constant for general-acid-catalyzed addition of the amine. When the expression $(k_{obsd} - k_{OH^-}a_{OH^-})/[N_f]$ was plotted against $[N_f]$ for a set of serial dilutions at constant pH and acid–base ratio, $r = [NH^+]/[N_f]$, a straight line was obtained whose slope (S) contains second-order terms in $[N_f]$

$$S = k_2 + (k_4[NH^+]/[N_f]) = k_2 + rk_4 \quad (2)$$

The intercept (I) of this plot gives first-order terms in $[N_f]$

$$I = k_1 + k_3a_{OH^-} \quad (3)$$

The values of the slopes (S) were then plotted against r to give k_4 as the slope and k_2 as the intercept. The first-order rate constants k_1 and k_3 were determined by plotting the intercept values I against the corresponding experimentally determined hydroxide ion activities.

In all cases, extrapolation to zero buffer concentration gave intercepts which were in satisfactory agreement with those calculated from the expression for hydroxide-catalyzed hydrolysis; $k_{OH^-}a_{OH^-}$.

Product Analysis. The percentages of amide produced in the morpholinolysis experiments were determined by conversion to the hydroxamate–ferric complex. Pure lactone was used as calibration standard. A 0.01–0.02 M lactone solution in water was quickly prepared and immediately several dilutions were made into 10 ml of water. Aliquots of 0.9 ml were then withdrawn from each dilution and incubated with 0.9 ml of 4 M $H_2NOH{\cdot}HCl$–3.5 M NaOH (4:3, pH 6.17, 10^{-4} M EDTA) solution for 4 h at room temperature in covered test tubes.[9] After cooling, 4.0 ml of a 20% $FeCl_3{\cdot}6H_2O$ in 0.45 M HCl stock solution was added and after vigorous stirring the absorbance was read at 540 nm. Plots of absorbance vs. lactone concentration gave a slope of 9.44×10^2.

The determination of the percentage of amide formed in the morpholine buffers was done as follows. Pure lactone was dissolved in 25 ml of the morpholine buffer and allowed to stand at room temperature for 45 min until the reaction was complete (Table II). After making several dilutions into 10 ml of the morpholine buffer, 0.9 ml was withdrawn and mixed with 0.9 ml of the above stock hydroxylamine solution. The test tubes were sealed and incubated at 40 °C for 20 h. After cooling, 4.0 ml of the stock $FeCl_3$ solution (all stock solutions were freshly prepared every 24 h and stored at 2 °C) was added and the absorbance read at 540 nm. Under these conditions, the carboxylate anion of the hydrolyzed lactone gave no coloration at 540 nm. Also, extrapolation of the absorbance readings to zero dilution gave a similar intercept to that obtained for the calibration line using pure lactone in water. This indicates that the morpholine buffer components did not contribute to the absorbance readings. Incubation times of as long as 40 h gave no change in the experimentally observed percentage of amide formation.

pK_a' Determinations. The method of half neutralization was used to obtain pK_a' values of the conjugate acids of the various amines used in the present work. The pH values for the buffers within the set of serially diluted solutions at $r = 1.00$ were determined. The mean pH value for the set was taken to be pK_a'. Table I presents a compilation of amine–nucleophile concentrations and experimental pH readings employed in the determination of the various rate constants.

Results

The reactions of lactone **1** with the amines used in the present study (Table I) follow the rate law of eq 1 at all pH values around pK_a'. As described in the experimental section, the kinetic analysis provides the rate constants associated with the various terms in free-amine concentration $[N_f]$. These values are summarized in Table II.

An illustration of a plot $(k_{obsd} - k_{OH^-}a_{OH^-})/[N_f]$ vs. $[N_f]$ for the reaction of glycinamide with the lactone at three pH values in H_2O and D_2O is given in Figure 1. The slope provides k_2 and intercept k_1. The graph shows that for this system, the intercept and slope do not vary over the pH range studied, indicating the presence of the k_1 and k_2 terms only. Due to our inability to measure polarimetric reactions with half-lives less than approximately 20 s, it was impossible to measure the aminolysis reactions at sufficiently high pH values where the k_3 term may become evident. Fortunately, however, with the hydroxylamine, hydrazine, and morpholine systems, the k_3 terms were sufficiently large to permit a satisfactory determination of their values within the pH range studied. Figure 2 illustrates the case of the hydrazine reaction, where the intercept values I (eq 3) varied with pH and proved to be a linear function of a_{OH^-}, giving k_3 as the slope and k_1 as the intercept. A general-acid-catalyzed aminolysis term was observed only in the case of the ammonia reaction. In Figure 3, the slopes S of eq 2 are plotted against the acid–base ratio r; the slope of this plot gives k_4 and the intercept k_2.

Table I. Experimental Conditions for the Determination of Rate Constants for the Aminolysis of Tri-*O*-methyl-2-deoxyglucono-δ-lactone at 25.0 °C

Amine	pK_a'	$[N_f]$,[b] M	r[b]	No. points	pH or pD[c]
H_2NOH[a]	6.01	0.025–0.25	1.00	5	6.01
		0.068–0.34	0.47	5	6.43
		0.08–0.40	0.25	5	6.74
		0.09–0.45	0.111	5	7.11
in D_2O[a]	6.57	0.05–0.25	1.00	5	6.57
		0.068–0.34	0.47	5	6.85
		0.080–0.40	0.25	4	7.15
		0.084–0.336	0.191	4	7.35
H_2NCH_2COOEt[d]	7.81	0.120–0.60	0.50	5	8.05
H_2NNH_2[d]	8.26	0.02–0.10	4.0	4	7.61
		0.02–0.10	2.0	4	7.98
		0.02–0.10	1.0	4	8.26
		0.02–0.10	0.5	4	8.55
		0.02–0.10	0.25	4	8.85
		0.02–0.10	0.20	4	9.11
$H_2NCH_2CONH_2$[d]	8.39	0.08–0.20	5.00	5	7.58
		0.06–0.30	1.00	5	8.39
		0.04–0.40	0.25	2	9.09
in D_2O[d]	8.94	0.03–0.30	1.00	6	8.94
Morpholine[d]	8.94	0.10–0.50	2.00	5	8.55
		0.09–0.90	1.00	6	8.94
		0.01–1.00	0.50	6	9.31
		0.10–1.00	0.40	6	9.39
		0.08–1.60	0.25	6	9.58
in D_2O[d]	9.54	0.05–0.50	2.00	5	9.18
		0.06–0.60	1.00	4	9.54
		0.10–1.00	0.50	4	9.84
		0.20–2.00	0.30	6	10.10
		0.16–1.60	0.25	6	10.14
NH_3[d]	9.60	0.080–0.20	4.0	4	9.09
		0.12–0.30	2.0	4	9.35
		0.10–0.50	1.0	5	9.60
		0.10–0.60	0.5	4	10.00
$CH_3OCH_2CH_2NH_2$[d]	9.79	0.08–0.80	1.00	6	9.79
Glycine[d]	9.86	0.080–0.40	4.0	5	9.30
		0.060–0.30	2.0	5	9.65

[a] Ionic strength maintained at 0.50 with NaCl. [b] Total amine buffer concentration = ($[N_f] + [NH^+]$); where $[N_f]$ is the concentration of free amine and $[NH^+]$ is the concentration of its conjugate acid (amine hydrochloride); $r = [NH^+]/[N_f]$. [c] pD = pH meter reading + 0.41. [d] Ionic strength maintained at 1.00 with KCl.

Table II. Rate Constants for the Aminolysis of Tri-*O*-methyl-2-deoxyglucono-δ-lactone at 25 °C[a,b]

Amine	pK_a' [c]	k_1, $M^{-1}\,s^{-1}$	k_2, $M^{-2}\,s^{-1}$	k_3, $M^{-2}\,s^{-1}$	k_4, $M^{-2}\,s^{-1}$
Hydroxylamine	6.01		2.3×10^{-2}	4.4×10^{4}	*d*
Glycine ethyl ester	7.81	6×10^{-4}	1.23×10^{-2}		*d*
Hydrazine	8.26	8.8×10^{-2} [e]	1.7	5.2×10^{3}	*d*
Glycinamide	8.39	3.0×10^{-3}	2.3×10^{-2}		*d*
Morpholine	8.94	4.5×10^{-3}		1.3×10^{2}	
Ammonia	9.60	1.4×10^{-2}	1.6×10^{-2}	(4.7)[f]	2.0×10^{-3}
2-Methoxyethylamine	9.79	6.2×10^{-2}	8.9×10^{-3}		*d*
Glycine	9.86	3.3×10^{-2}	0.15		*d*

[a] At ionic strength 1.00 (maintained with KCl) except hydroxylamine, where the ionic strength was maintained at 0.50 using NaCl. [b] The second-order rate constant for the hydroxide ion catalyzed hydrolysis of the lactone was redetermined in the present work using triethylamine and carbonate buffers in H_2O and D_2O, ionic strength 1.00 (KCl), and found to be 1.25×10^2 and 1.67×10^2 $M^{-1}\,s^{-1}$, respectively, based on activity. These values were determined by extrapolation to zero buffer concentration. For the hydroxylamine studies at ionic strength 0.50 (NaCl), previously determined values of k_{OH^-} and k_{OD^-} were used based on concentration.[2] The pK_w values were taken to be 14.00 in H_2O and 14.82 in D_2O.[10] [c] At 25.0 °C; a mean value of pH determinations of $r = 1.0$ (half-neutralized) buffers which were employed in the kinetic experiments. [d] A reasonable upper limit for these values would be around 5% of the corresponding k_2 values. [e] The k_1 value for the "α-effect" nucleophile, hydrazine, would place it 1.7 log units above the Bronsted line shown in Figure 4. [f] This value is inaccurate and may be due to a nonspecific salt effect. The presence of this term is therefore suspect.

The morpholinolysis experiments showed that there is no second-order dependence of k_{obsd} on $[N_f]$, i.e., plots of k_{obsd} vs. $[N_f]$ were linear up to 2.0 M free morpholine. The intercepts were in satisfactory agreement with calculations based on the assumption that the intercepts represent only the hydroxide ion catalyzed hydrolysis reaction. The slopes increased linearly

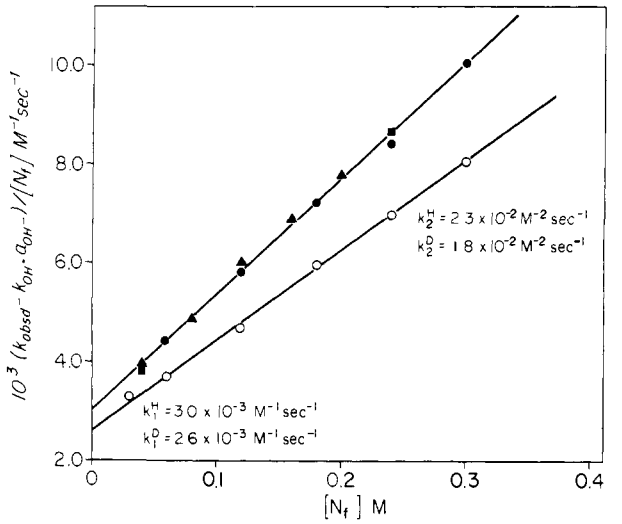


Figure 1. Plots of $(k_{obsd} - k_{OH^-}a_{OH^-})/[N_f]$ vs. $[N_f]$ for the reaction of glycinamide with tri-*O*-methyl-2-deoxyglucono-δ-lactone in H_2O (●, pH 7.58; ▲, pH 8.39; ■, pH 9.09) and D_2O (○, pD 8.94) at 25.0 °C, μ = 1.00 (KCl): $[N_f]$ = free-amine concentration.

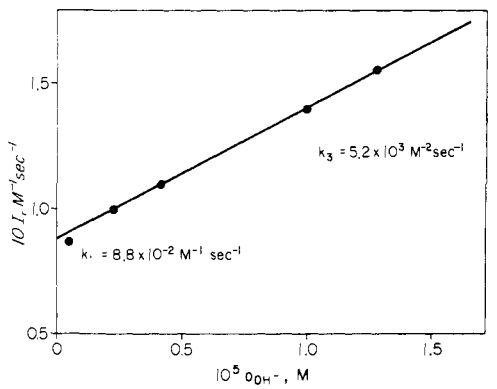


Figure 2. A plot of I ($I = k_1 + k_3a_{OH^-}$) vs. the activity of hydroxide ion (a_{OH^-}) for the hydrazinolysis of the lactone at 25.0 °C, μ = 1.00 (KCl).

with hydroxide-ion activity, indicating the presence of a hydroxide ion catalyzed aminolysis reaction (k_3). The rate expression is then given by

$$k_{obsd} = k_{OH^-}a_{OH^-} + k_1[N_f] + k_3[N_f]a_{OH^-} \quad (4)$$

In view of this unusual rate expression for the reaction in morpholine buffers a product study was undertaken (see Experimental Section) to determine the relative proportions of aminolysis and general-base-catalyzed hydrolysis associated with k_1. The results of three determinations of the percentage of amide formed in morpholine buffers all agreed to within 3% of the calculated value, requiring k_1 to be mostly (95 ± 5%) hydrolysis on the assumption that k_3 gives only aminolysis. This observation was largely substantiated by the finding that in morpholine buffers the solvent deuterium isotope effect for k_1 gave $k_1^H/k_1^D = 1.9 \pm 0.2$. Table III summarizes the isotope effects obtained in the present study.

The rate constants for the uncatalyzed (or water-catalyzed) addition of the amine nucleophile (k_1) are plotted logarithmically as a function of the basicity of the amine in Figure 4. The slope is 0.85 ± 0.1.

Discussion

A striking result of the present investigation is the lack of any observable change in the rate-determining step in a pH range around the pK_a' of the amine nucleophile. This interpretation follows from the close adherence of the kinetics to eq 1 throughout the experimental pH range. Satterthwait and Jencks[6] have found that for a series of straight-chain alkyl esters, breakdown of the kinetic adherence to eq 1 occurred at pH values within the buffer region of the particular amine. This evidence, taken together with the observation that the various forms of tetrahedral addition intermediates are not in protonic equilibrium,[5,11-14] suggested the existence of a change in rate-determining step with changing pH and the existence of a chemically significant intermediate.[4] On the other hand, the aminolysis reactions of phenyl acetates and other esters with

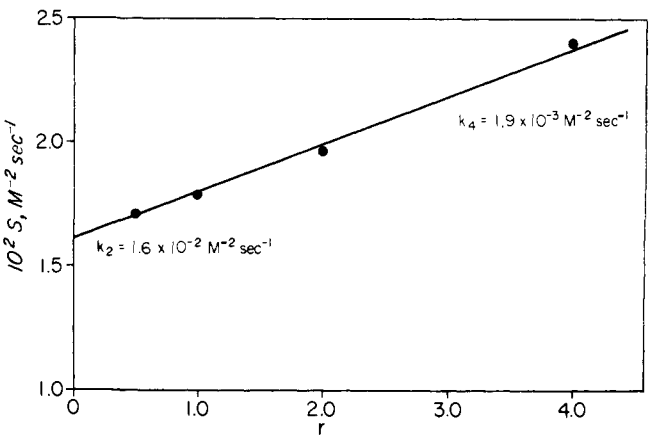


Figure 3. A plot of S ($S = k_2 + rk_4$) vs. r ($r = [NH^+]/[N_f]$): $[NH^+]$ = concentration of the conjugate acid of the amine.

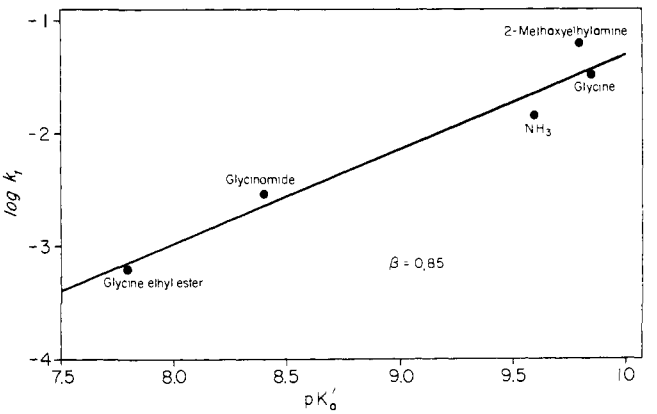


Figure 4. Bronsted plot of log k_1 vs. pK_a' for the aminolysis of the lactone at 25.0 °C, μ = 1.00 (KCl): k_1 = second-order rate constant for the nucleophilic addition of the amine; pK_a' = experimentally determined dissociation constant of the conjugate acid of the amine.

Table III. Solvent Deuterium Isotope Effects for the Aminolysis of the Lactone at 25.0 °C[a]

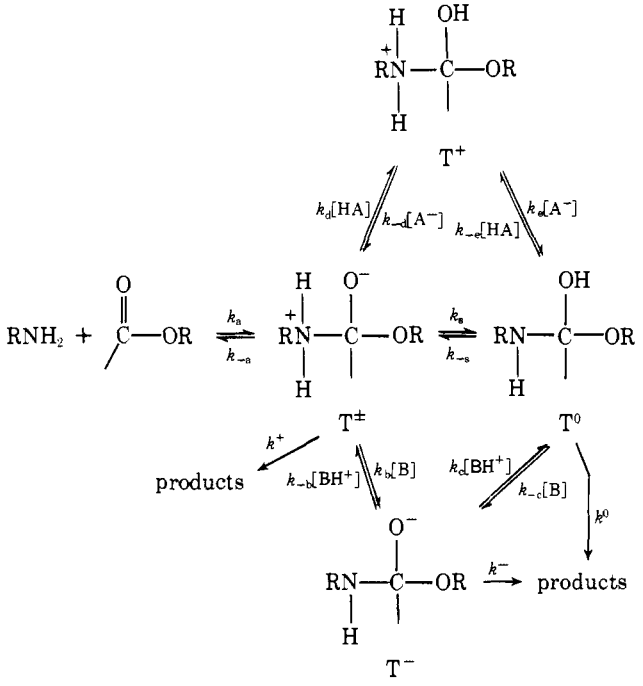
Amine	pK_a'	k_1^H/k_1^D [b]	k_2^H/k_2^D	k_3^H/k_3^D
Hydroxylamine[c]	6.01		2.0	0.6
Glycinamide[d]	8.38	1.1[e]	1.3	
Morpholine[d]	8.94	1.9		1.4

[a] At 25.0 °C, pK_w was taken as 14.00 in H_2O and as 14.82 in D_2O.[10] [b] k^H and k^D refer to rate constants determined in water and deuterium oxide, respectively. [c] At ionic strength 0.50 using NaCl. [d] At ionic strength 1.00 using KCl. [e] The solvent deuterium isotope effect for the aminolysis of the δ-lactone by ethanolamine (pK_a 9.89) was essentially identical, $k_1^H/k_1^D = 1.1$ (unpublished observations at an ionic strength of 0.50 using NaCl).

moderately good leaving groups,[15] i.e., with pK_a' values of leaving alcohol ranging from ca. 7 (*p*-nitrophenol) to about 12.5 (trifluoroethanol), were shown to proceed without a change in rate-determining step over the entire pH range studied.[16]

In the proposed mechanism[6] the formation of the zwitterionic aminolysis intermediate $T^{\pm}$ is rapid and reversible for both the alkyl and moderately reactive phenyl acetates and by inference for the aminolysis of the present lactone (Scheme I).

Scheme I

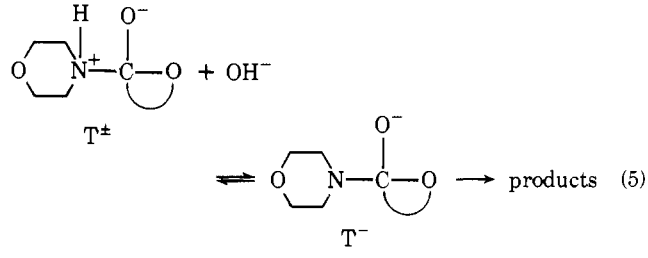


According to this mechanism, the uncatalyzed reaction (k_1) represents a rate-determining expulsion of phenolate or lactone alkoxide ($k_{\pm}$), while k_2 and k_3 involve rate-determining proton removals by a second molecule of amine (k_b[amine]) or hydroxide ion (k_b[OH^-]), respectively, which convert $T^{\pm}$ into T^-. For phenyl acetates and δ-lactones the formation of T^- is followed by a rapid expulsion of the leaving group. For alkyl acetates with poor leaving groups (i.e., ethyl acetate, methoxyethyl acetate, chloroethyl acetate, etc.; pK_a alcohol $\gtrsim$12.5) a proton switch through water that converts $T^{\pm}$ to the neutral intermediate T^0 becomes the rate-determining step. Decreasing the pH of the kinetic experiments to values around the pK_a' of the amine and below changes the rate-determining step to breakdown of T^-.[17] Therefore, in the aminolysis of δ-lactones the effect of the six-membered ring is to enhance the leaving ability of the internal alkoxide to the extent that it mimics the leaving ability of phenolate and trifluoroethoxide ions.

A good estimate of the pK_a of the conjugate acid of the leaving alkoxide group of the lactone (see compounds **1** and **2**) is 14.5,[18] a value which is well within the range of alcohol acidity of those alkyl esters with poor leaving groups that show a change in rate-determining step. Therefore, an alcohol acidity argument for the lactone cannot explain its phenyl acetate-like aminolysis behavior. An explanation must be sought, therefore, in terms of the special characteristics of the ring. The lactone ring was shown previously to be responsible for the lack of oxygen-18 incorporation into the starting material during the hydrolysis of D-glucono-δ-lactone[2] and γ-butyrolactone,[19] the partitioning of the tetrahedral intermediate being prevented by the more rapid ring opening step. It was suggested that the high rate of ring opening (alkoxide-ion expulsion in aminolysis) is a consequence of increases in rotational degrees of freedom for that step and relief of "cis effect" strain.[2]

In the present study, we have observed $\beta_{nuc} = 0.85 \pm 0.1$ (Figure 4), a value which is very close to that observed for the phenyl acetates (0.9 ± 0.1). This further points to the mechanistic similarities between δ-lactones and phenyl acetates in aminolysis reactions.

Morpholinolysis. An interesting difference between the two systems, on the other hand, is the finding that the first-order term (k_1) of the morpholine reaction is actually a general-base-catalyzed *hydrolysis*. This conclusion is based on a product study and a deuterium solvent isotope effect value of 1.9 ± 0.2. It is known that secondary amines are somewhat less reactive in aminolysis reactions than primary amines of similar basicity[3a,c] and that for secondary amines the general-base-catalyzed reaction (k_2) is more strongly depressed than the uncatalyzed reaction. These observations have been interpreted in terms of a greater steric requirement in the transition state for secondary amines relative to primary.[3c] Because of enhanced crowding by adding a second amine molecule in the transition state of the k_2 reaction, k_2 is diminished even more than k_1. In the lactone morpholinolysis reaction steric crowding is therefore so severe in the transition states of the k_1 and k_2 reactions that morpholinolysis by these pathways are undetectable. General-base-catalyzed hydrolysis becomes a significant competing reaction because the base acts at a distance through bridging water molecules[20] with consequent lower steric requirement. Morpholinolysis occurs only through the hydroxide ion catalyzed pathway because it is a strong base and more importantly, the smallest base present in the morpholine buffers. Therefore, OH^- is capable of trapping the zwitterionic tetrahedral intermediate $T^{\pm}$ by conversion to T^- and then collapse to products (eq 5). This unusual steric



(5)

crowding problem with the lactone arises from the close contact of the morpholine ring(s) with the lactone ring in the transition state. It must also be mentioned that the presence of the three methoxyl groups in the lactone may also contribute to the steric crowding in the morpholine reaction. This latter suggestion is supported by the fact that a k_2 and k_4 term is observed in the morpholinolysis of δ-thiovalerolactone (no ring substitution).[21]

The results of the morpholinolysis experiments of the present work show that, in the absence of a product study, great care should be taken in drawing mechanistic conclusions concerning the reaction associated with k_1. This is particularly important with esters known to be subject to general-base-catalyzed hydrolysis.

Hydroxylaminolysis. The rate expression for the hydroxylaminolysis of tri-*O*-methyl-2-deoxyglucono-δ-lactone as determined in this study is given by

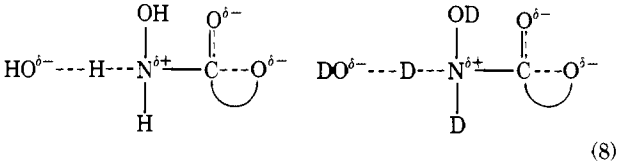
$$k_{obsd} = k_{OH^-}a_{OH^-} + k_2[H_2NOH]^2 + k_3[H_2NOH]a_{OH^-} \quad (6)$$

Plots of $(k_{obsd} - k_{OH^-}a_{OH^-})/[H_2NOH]$ against $[H_2NOH]$ gave parallel lines over the pH range 6.01–7.11 with excellent reproducibility (±3% variation in H_2O; ±1% in D_2O). Bruice and Bruno[22] have found that for the hydroxylaminolysis of δ-valerolactone the rate expression is described by

$$k_{obsd} = k_{OH^-}a_{OH^-} + k_2[H_2NOH]^2 + k_3[H_2NOH]^2a_{OH^-} \quad (7)$$

i.e., these authors observed a hydroxide ion catalyzed reaction proportional to $[H_2NOH]^2$. The different kinetic behavior of the two δ-lactones remains a puzzling problem.

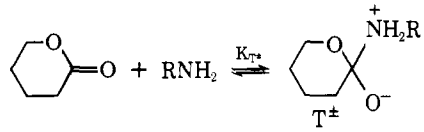
Aminolysis Isotope Effects. The observed isotope effects are quite similar to previously determined values for the respective terms associated with other ester aminolysis reactions. However, the value of 0.6 for k_3^H/k_3^D in the hydroxylamine reaction was unexpected. This value stands in marked contrast to the value of 1.4 for k_3^H/k_3^D observed in the morpholinolysis reaction of the present work and 2.2 for the k_3^H/k_3^D in the methylaminolysis of phenyl acetate.[3d] It is possible that this inverse isotope effect represents a fundamentally different mechanism than the one envisioned in Scheme I. The hydroxide-catalyzed reaction as formulated in Scheme I consists of a rate-determining proton transfer between $T^{\pm}$ and OH^- in a *stepwise* fashion to give T^-, which then rapidly collapses to products.[6] The concerted mechanism is ruled out for the k_3 (and k_2) reaction with most amines and general bases because of unfavorable entropic and enthalpic requirements for coupled multiatom transfers between three properly positioned molecules in the transition state of the concerted mechanism. In the hydroxylaminolysis, however, since the zwitterionic intermediate $T^{\pm}$ has a very low pK_a', it is possible that proton transfer between the strong base OH^- and $T^{\pm}$ provides sufficient free-energy advantage to permit the observation of the concerted mechanism shown in eq 8. Also, the instability of a de-



(8)

veloping T^- in δ-lactones provides an additional free-energy advantage. Although the concerted mechanism for the hydroxide ion catalyzed hydroxylaminolysis may appear reasonable, it does not provide a priori a unique[23] or even a particularly satisfactory resolution of the difficulty associated with the inverse solvent deuterium isotope effect, $k_3^H/k_3^D \simeq 0.6$. It is worth noting that another way out of this dilemma is to assume a stepwise mechanism involving a preequilibrium proton transfer from the hydroxylamine-δ-lactone addition intermediate $T^{\pm}$ to OH^-, followed by a relatively slower breakdown of the anionic tetrahedral intermediate T^- to the ring-opened product. An attractive feature of the latter mechanism can be found in the observation that the dealdolization of diacetone alcohol, a reaction involving preequilibrium proton transfer to OH^- followed by a rate-determining decomposition of the alkoxide, also exhibits an inverse isotope effect of similar magnitude, $k_{OH^-}/k_{OD^-} \simeq 0.67$.[24,25]

Reactivity. It is known that the extra hydrolytic reactivity of δ-lactones compared to straight-chain esters is due to the cis conformation of the ring and the removal of eclipsing in the ground state by changing the hybridization of the exocyclic carbon–oxygen double bond from sp^2 to sp^3 upon addition of the nucleophile.[2,26] These two forces are also operating to increase the reactivity toward aminolysis. Diminution of ground-state strain of the exocyclic sp^2 bond by addition of the amine nucleophile, coupled with partial relief of cis conformational strain in the zwitterionic tetrahedral intermediate relative to the lactone, serves to increase the aminolysis rate by increasing the equilibrium constant $K_{T^{\pm}}$ for formation of the intermediate compared to straight-chain esters.



(9)

Removal of the cis conformation of the lactone structure and an increase in the number of rotational degrees of freedom in the ring-opened alkoxide ion accelerate the breakdown of T^- relative to that of straight-chain esters. The extra steric crowding in the transition states of δ-lactone aminolysis compared to those of straight-chain esters, however, would tend to diminish somewhat this reactivity.

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(25) Perhaps the preequilibrium proton transfer is from the hydroxyl group of the hydroxylamine to OH^- to give the reactive species H_2NO^- as the nucleophile. [The pK_a value for the reaction $H_2NOH \rightleftharpoons H^+ + H_2NO^-$ is 13.7 at 25 °C; M. N. Hughes, H. G. Nicklin, and K. Shrimanker, *J. Chem. Soc. A.*, 164 (1971).] This would lead to oxygen attack on the δ-lactone to form the corresponding *O*-acyl hydroxylamine. Such a mechanism would also produce an inverse isotope effect. However, our kinetics do not exhibit a slow breakdown of the unstable *O*-acyl hydroxylamine to the final hydroxamic acid product (W. P. Jencks, *J. Am. Chem. Soc.*, **80**, 4581, 4585 (1958)).
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