Kinetics and Mechanisms of Lactonization of Coumarinic Acids and Hydrolysis of Coumarins I

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Abstract □ The lactonization of coumarinic acid and its anions and the hydrolysis of coumarin have been studied in the pH range of −0.3–11 in various buffer solutions between 10 and 25° by spectrophotometric methods. The significant influence of buffer concentration on the apparent first-order rate constant for lactonization was assigned to the acetic acid-catalyzed lactonization of the monoanion, HC^-. The dependency of the apparent first-order rate constants extrapolated to zero buffer concentrations on the hydrogen-ion concentration was derived. It was consistent with hydrogen-ion-catalyzed lactonization and apparent spontaneous lactonization of undissociated coumarinic acid, H_2C, to form coumarin, C, the spontaneous lactonization of the monoanion, HC^-, and the nonreactivity of the dianion, C^{-2}. An apparent discrepancy exists between the kinetic (3.0) and the spectral and potentiometric (4.0) pKa_1' which can only be rationalized by a more complex mechanism. This mechanism assumes the intramolecular formation of an ortho-acid, $H_2C‡$, which dehydrates spontaneously and by hydrogen-ion catalysis to give coumarin. The steady-state assumption for $H_2C‡$ permits the fitting of the log k–pH profiles consistent with the analytical pKa_1' values and is consistent with this mechanism. Coumarin is hydrolyzed by specific hydroxyl-ion-catalyzed solvolysis and has been characterized as a function of pH. The hydrolyses of 3-chlorocoumarin, 3-bromocoumarin, and 3- and 4-methylcoumarin were studied in 30% dioxane for the acid–lactone equilibrium. The halogen substituents showed pronounced accelerating effects consistent with the electronegative group acceleration of hydroxyl-ion attack on the carbonyl carbon, whereas the methyl substituents did not significantly modify the reactivity of coumarin.

Keyphrases □ Coumarinic acids—lactonization □ Coumarins—hydrolysis □ Kinetics, mechanisms—coumarinic acid lactonization, coumarin hydrolysis □ pKa′ values—coumarinic acid □ Buffer effects—coumarinate lactonization □ UV spectrophotometry—analysis

Although the hydrolyses of coumarins (5,6-benzo-α-pyrons) have been studied in alkaline solution (1, 2), the ring closure of the resultant coumarinic acids and their salts to the respective coumarins has not been investigated. The purpose of these studies on the kinetics of lactonization was to determine the relative reactivities of undissociated coumarinic acid and its monoanions and dianions. The rate–pH profile for the hydrolysis

Table I—Apparent First-Order Rate Constants, k, in sec.$^{-1}$ for the Lactonization of Coumarinic Acid

Medium[a]		10.0° pH[b]	10.0° 10^3k	17.5° pH[b]	17.5° 10^3k
10^3 [HCl]					
238		−0.46	57.0	−0.44	129
98.3		0.09	22.2	0.09	40
73.8		0.23	17.2	0.24	27.9
49.2		0.42	11.1	0.43	22.2
24.6		0.72	5.79	0.73	11.4
8.25		1.18	3.13	1.18	6.53
4.13		1.48	2.64	1.48	4.87
0.971		2.11	1.82	2.47	2.28
0.425		2.47	1.44		
[$H_2PO_4^-$]	[HPO_4^{-2}]				
0.065	0.011	6.29	0.0120	6.21	0.0275
0.0167	0.0277	7.23	0.00887	7.11	0.0202
0.00125	0.0329	8.38	0.00795	8.33	0.0193

Medium[a]		25.0° pH[b]	25.0° 10^3k	
10^3[HCl]				
207.5		−0.32	148	
89.7		0.15	64.0	
65.5		0.30	55.7	
45.3		0.47	36.3	
21.7		0.78	20.5	
9.5		1.12	13.9	
3.36		1.57	8.50	
1.04		2.08	5.48	
0.302		2.42	3.82	
[$HC_2H_3O_2$]	[$C_2H_3O_2^-$]		10^3k	
1.48		2.23	6.11	(6.02)[c]
0.183		2.79	3.80	(3.67)[c]
2.2	0.086	3.18	3.47	(2.42)[c]
1.25	0.1	3.50	1.99	(0.92)[c]
0.703	0.1	3.79	1.34	(0.495)[c]
0.269	0.086	4.10	0.640	(0.300)[c]
0.006	0.086	5.38	0.135	(0.115)[c]
[$H_2PO_4^-$]	[HPO_4^{-2}]		10^3k	
0.065	0.011	6.05	0.0995[d]	
0.0167	0.0277	7.07	0.0868	
0.00125	0.0329	8.26	0.0895[e]	
[NaOH]	[HCO_3^-]			
0.005	0.04	9.40	0.0689	
0.013	0.04	9.73	0.0691	
0.020	0.04	10.05	0.0828	
0.0215	0.04	10.11	0.0725	
0.030	0.04	10.50	0.162	
0.030	0.04	10.50	0.128	
0.0315	0.04	10.59	0.238	
0.033	0.04	10.70	0.281	

[a] NaCl was added to maintain the ionic strength at $\mu = 0.1$ when possible. [b] The pH values in HCl at concentrations greater than 0.1 M were calculated from pH = $-\log f$[HCl], where the activity coefficient, f, was obtained from the literature (4). All other values were measured by a pH meter. [c] These apparent first-order rate constants in the acetate buffer region were calculated after correcting for the catalytic effect of the acetic acid in accordance with $k_c = k - f_{HC^-} k'_{HAc}$ [HAc], where $f_{HC^-} = Ka_1'/([H^+] + Ka_1)$, $Ka_1' = 1.00 \times 10^{-4}$, and $k_{HAc} = 3.65 \times 10^{-3}$ l./mole-sec. at 25.0°. [d] At $^2/_3$ and $^1/_3$ of these buffer-ion concentrations, there were no differences among the apparent first-order rate constants. [e] When this phosphate buffer solution was also made 0.1 N in acetate ion, the rate constant was 8.88×10^{-5} sec.$^{-1}$.

Table II—Apparent First-Order Rate Constants, k, in sec.$^{-1}$ for the Hydrolysis of Coumarin

		$[HCO_3^-]^a$												
		0.040								0.000				
[NaOH]		0.006	0.019	0.024	0.026	0.027	0.029	0.031	0.032	0.035	0.0098	0.0375	0.0491	0.075	0.09
pH[b]		9.45	10.00	10.20	10.30	10.35	10.42	10.55	10.65	10.90	11.85	12.50	12.61	12.77	12.88
10^4k	25.0°	0.63	0.72	0.96	1.16	1.22	1.33	1.76	2.45	3.72	—	135	—	254	—
	17.5°	—	—	—	—	—	—	—	—	—	17.1	—	93.0	—	169
	10.0°	—	—	—	—	—	—	—	—	—	9.65	—	59.6	—	119

[a] NaCl added where possible to maintain ionic strength at $\mu = 0.1$. [b] The pH was experimentally determined in the bicarbonate–carbonate buffers but was calculated for the NaOH solutions from $pH = pK_w - \log f'[NaOH]$, where the activity coefficient f' was obtained from the literature (4).

of coumarin and the lactonization of the resultant coumarinates was determined to define the extent of the equilibrium between the open forms and the lactone as a function of pH and the catalytic species that are involved in such transformations. Abernethy (3) stated that the undissociated coumarinic acid has not been isolated nor have sufficiently sophisticated chemical methods been used to reveal directly its transient existence when coumarin is formed on addition of acids to sodium coumarinate. These studies will prove its existence, and the pKa′ values of coumarinic acid determined by kinetic, spectral, and potentiometric methods will be compared.

EXPERIMENTAL

Lactonization—Coumarin[1] was used as received. The reactions were investigated at various pH values between −0.3 and 11 in hydrochloric acid, acetate, phosphate, and carbonate buffers and sodium hydroxide solutions at 10.0, 17.5, and 25.0°. All solutions were made up with nitrogen-purged distilled water. The pH at the temperature of the kinetic experiments was read with a Radiometer pH meter and a Sargent glass electrode or was calculated and extrapolated from the known activities (4) in strong acid and alkaline solutions, *i.e.*, $pH = -\log f[HCl]$ or $pH = pK_w - \log f'[NaOH]$, where the pK_w and activity coefficients f and f' were obtainable at the desired temperatures (4). The ionic strength in all buffer solutions and in hydrochloric acid and sodium hydroxide solutions below 0.1 M was adjusted to $\mu = 0.1$ with sodium chloride.

Generally, 0.05 ml. of about 5×10^{-3} M coumarin, which had been completely solvolyzed in 0.01 N NaOH (pH about 11.9), was added to 3 ml. of the appropriate buffer solution to produce a final concentration in the range of 7.30–8.40 $\times 10^{-5}$ M. The compositions of the buffer solutions are listed in Table I. All solutions of sodium monocoumarinate and dicoumarinate were excluded from light to prevent possible *cis–trans* isomerization and photolytic degradation (1). A Cary model 15 recording spectrophotometer equipped with a repetitive scan accessory, automatic sample changer, and a thermostatically controlled cell compartment was used to follow the reactions. The change of absorbance in the appropriate buffer was automatically recorded either at one wavelength or by repetitive scan techniques. The thermally equilibrated solutions were mixed directly in the 1 × 1-cm. cells of the spectrophotometer. Water was used as the blank.

The plots of the logarithms of the differences in the final absorbance, A_∞, and the absorbance at any time, A, at 280 nm. against time gave straight lines; the rate constants (Table I) were determined from the slopes in accordance with the equation for an apparent first-order reaction:

$$\log |A_\infty - A| = \frac{-kt}{2.303} + \log |A_\infty - A_0| \qquad \text{(Eq. 1)}$$

Typical plots are given in Fig. 1. Kinetic runs exposed to continuous UV irradiation by repetitive scanning had the same final spectra and the same absorbances as those from which aliquots were taken. The fact that the same coumarin spectra resulted with the same absorbance as equimolar coumarin is adequate proof that the solutions were not photolytically degraded in the spectrophotometer during the reaction, that nonlactonizable *trans*-coumarinic acid was not formed on automatic spectrophotometric monitoring of lactonization under the conditions used.

A differential spectrophotometric method was used for kinetic runs above pH values of 9 where the overall absorbance changes were small, since coumarin and coumarinate ions achieved a final equilibrium mixture in the pH 9–10 region. Coumarin, which had been completely solvolyzed at pH 12, was added to the appropriate buffer in what was normally the reference cell. The cell that was normally the sample cell contained material that had been completely reacted to the lactone–anion equilibrium at the same temperature and concentration (8.4×10^{-4} M) and in the same buffer. The differences in the absorbances were thus magnified and were plotted in accordance with Eq. 1. The reason for the reversal of the sample and reference cells was that the finally reacted solutions had greater absorbance because the absorbance of coumarin was greater than that of the anions at the specified wavelength (Fig. 2).

The spectrum (Fig. 2) of the 7.30×10^{-5} M coumarin was recorded in 0.1 N HCl, and that of the equivalent concentration of coumarinate dianion was obtained after complete hydrolysis in 0.01 N NaOH (pH 11.9). The spectrum of the 7.30×10^{-5} M coumarinate monoanion was recorded on the Cary spectrophotometer immediately after mixing 0.05 ml. of 4.45×10^{-3} M coumarin which had been completely solvolyzed in 0.01 N NaOH and 3 ml. of pH 7.07 phosphate buffer solution at 25.0° (Table I). The spectrum of the 7.30×10^{-5} M undissociated coumarinic acid was obtained by mixing 0.05 ml. of the alkaline solution of solvolyzed coumarin and 3 ml. of 0.055 N HCl. The rapid change in absorbance was automatically recorded with time at each of 10-nm. intervals between 220–360 nm. The spectrum of coumarinic acid (Fig. 2) was obtained by graphical extrapolation of the recorded absorbance *versus* time plot to time zero for each wavelength.

Hydrolysis—The hydrolysis of coumarin was investigated in the pH region of 9–13. The compositions of the buffer solutions are listed in Table II. The decreasing absorbances of the 7.55×10^{-5} M solutions were monitored with time and plotted for $\lambda = 280$ nm. in accordance with Eq. 1. At pH values below 9.5, the previously

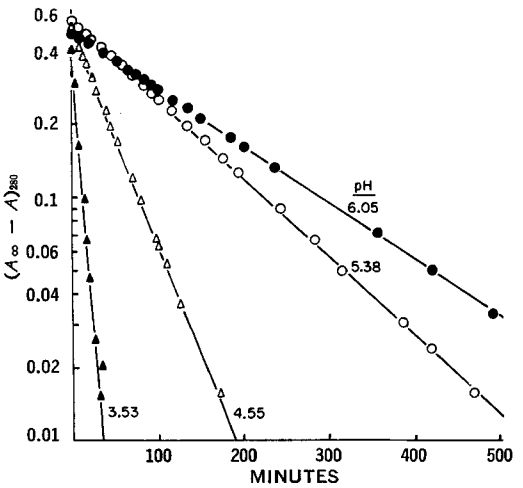


Figure 1—*Typical apparent first-order plots for the lactonization of coumarinic acid in acetate and phosphate buffers at 25° at various pH values ($\mu = 0.1$). The absorbance, A, is at 280 nm. and A_∞ is the absorbance at infinite time.*

[1] Aldrich Chemical Co., Cedar Knolls, N. J.

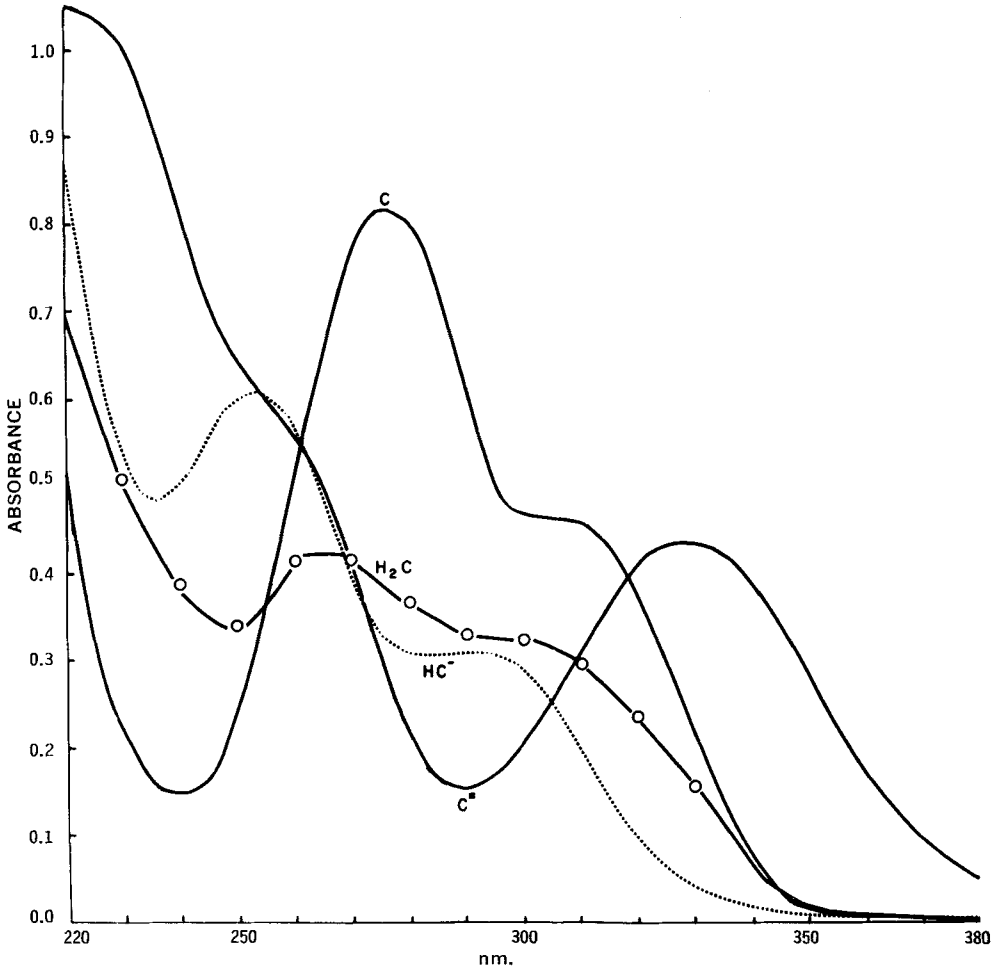


Figure 2—*UV spectra of 7.30 × 10⁻⁵ M undissociated coumarinic acid (based on extrapolated time zero values after introduction of sodium coumarinate in 0.055 N HCl), coumarinate monoanion, HC^- (in phosphate buffer of pH 7.2), coumarinate dianion, C^{-2} (in 0.1 N NaOH), and of coumarin, C (in 0.1 N HCl).*

described differential spectrophotometric method was used. However, the reacting coumarin solution was in the usual sample cell, and the reference cell contained the same concentration of coumarin which had been completely reacted in the same buffer, temperature, and pH value. Typical spectral changes of alkaline-treated (pH 10.35) coumarin are shown in Fig. 3 as a function of time.

The hydrolyses of 3- and 4-substituted coumarins were investigated spectrophotometrically in 30.0% dioxane–water mixtures (v/v) because of the low solubility of these compounds. The compositions of the buffer solutions are listed in Table III, as are the measured apparent pH values. The decreasing absorbances were recorded with time at 280, 290, 295, 280, and 273 nm. for coumarin

Table III—Apparent First-Order Rate Constants, k, in sec.$^{-1}$ for the Hydrolyses of 3- and 4-Substituted Coumarins at 25.0° in Dioxane (30%)–Water Mixtures

Medium[a]							
[NaOH]	[HCO_3^-]	pH[b]	Coumarin, 10^5k	3-Chloro-coumarin, 10^4k	3-Bromo-coumarin, 10^4k	3-Methyl-coumarin, 10^4k	4-Methyl-coumarin, 10^4k
0.0015	0.04	10.05	—	2.88	—	—	—
0.005	0.04	10.3	—	5.33	—	—	—
0.0095	0.04	10.52	—	10.05	1.98	—	—
0.011	0.04	10.6	5.23	—	—	—	—
0.015	0.04	10.78	5.62	14.5	—	—	—
0.0185	0.04	10.97	7.78	—	—	—	—
0.0195	0.04	11.02	—	—	7.16	—	—
0.0225	0.04	11.15	10.6	—	—	—	—
0.027	0.04	11.38	16.5	—	—	—	—
0.0285	0.04	11.45	—	—	—	2.27	—
0.030	0.04	11.53	—	—	—	2.35	—
0.031	0.04	11.6	22.1	—	—	—	—
0.032	0.04	11.65	—	—	—	2.72	—
0.0325	0.04	11.7	—	—	—	3.62	—
0.033	0.04	11.73	29.6	—	—	—	—
0.034	0.04	11.8	—	—	—	—	4.0
0.035	0.04	11.88	—	—	—	—	—
0.1		12.85	—	—	—	—	36.0

[a] NaCl was added when possible to maintain the ionic strength at $\mu = 0.1$. [b] The pH values were measured by a Radiometer pH meter and a Sargent combination electrode.

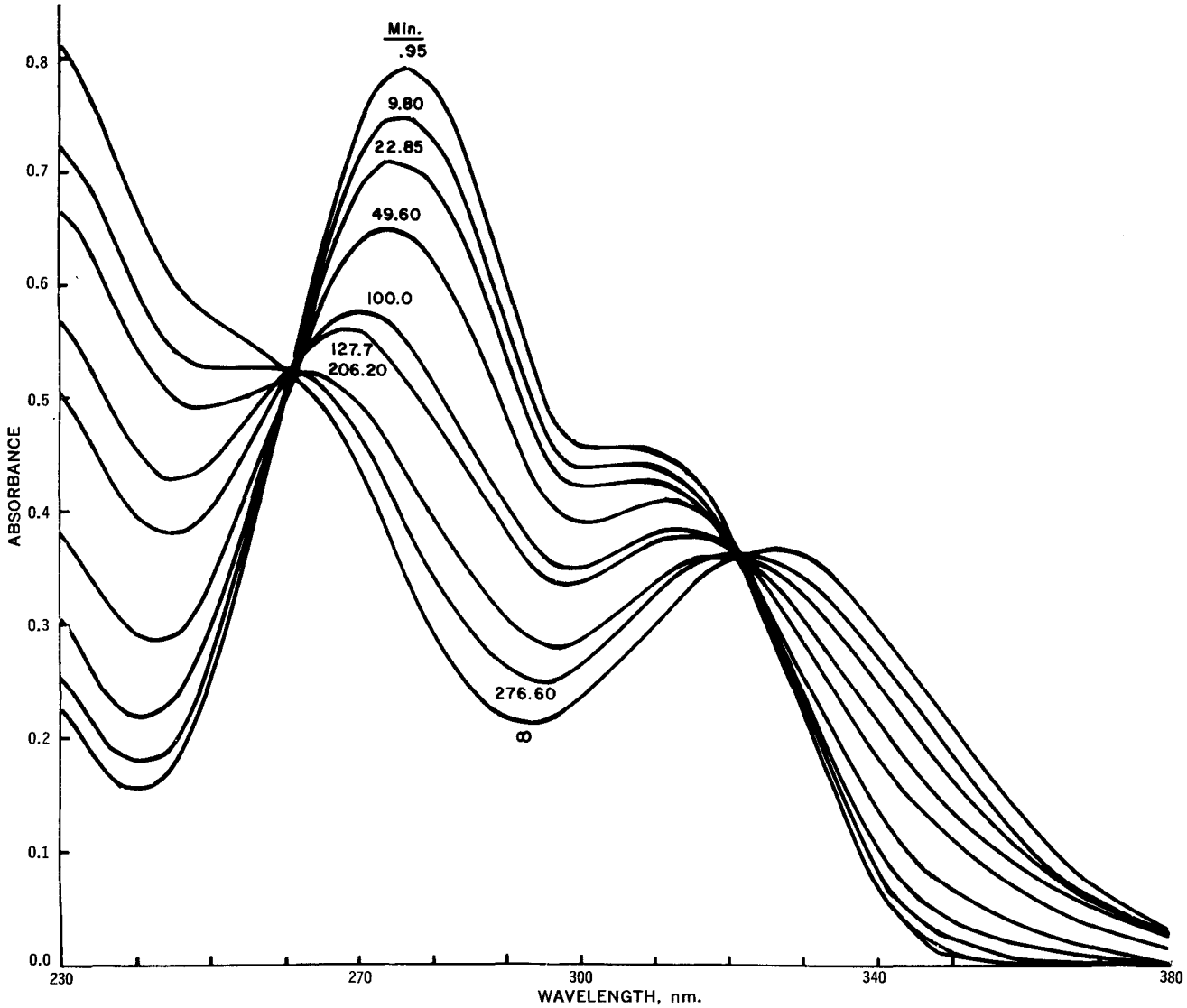


Figure 3—*Typical spectral changes for the hydrolysis of 7.55 × 10⁻⁵ M coumarin in carbonate buffer, pH 10.35, μ = 0.1, at 25°. The curves are labeled as to minutes after the start of the reaction.*

(for comparison), 3-chlorocoumarin[2], 3-bromocoumarin, 3-methylcoumarin[3], and 4-methylcoumarin[4], respectively. The plots of the logarithm of the differences of the absorbance at time zero, A_0, and the absorbance at any time, A, gave straight lines in accordance with Eq. 1. The coumarin compounds were obtained from the stated companies and were used as received. 3-Bromocoumarin was synthesized by the method of Ghiya and Marathey (5) and used after recrystallization in 0.001 *N* acetic acid (m.p. 109° uncorrected). 4-Methylcoumarin was prepared by the methods of Woodruff (6) and used after recrystallization in petroleum ether–benzene (1:1) mixture (m.p. 83–84°).

Spectrophotometric Determination of pKa′ Value of Coumarinic Acid—The UV spectra of mixtures of completely solvolyzed coumarin in 0.01 *N* NaOH with appropriate buffers (pH 1–7, Table I) at a final concentration of 7.30×10^{-5} *M* were recorded at 250, 280, and 320 nm. by the Cary recording spectrophotometer as a function of time immediately after mixing in the spectrophotometric cells. The apparent first-order rate plots for the lactonization in the different buffer solutions (Fig. 1) permitted extrapolation of the log $|A_\infty - A|$ values to an intercept value of log $|A_\infty - A_0|$, so that the absorbance values, A_0 at time zero, could be estimated for the various buffer solutions of Table I. Plots of these time zero absorbances assigned to equilibrium mixtures of coumarinic acid and its anion before lactonization are shown in Fig. 4. Similar plots of time zero absorbances assigned to equilibrium mixtures of coumarinate monoanion and dianion also are shown in Fig. 4.

Potentiometric Determination of pKa′ Values of Coumarinic Acid—A 0.5-ml. aliquot of a solution of 0.100 *M* coumarin, completely solvolyzed in 0.300 *N* NaOH, was diluted to 30.0 ml. with nitrogen-purged 0.1 *M* KCl solution. Different varying known amounts (0–100 μl.) of 0.5 *N* HCl were added to 3.00-ml. aliquots, and the pH of each aliquot was recorded immediately using a Radiometer pH meter and a Sargent combination electrode (S-30070-10). Similarly, as a blank, a 0.5-ml. aliquot of 0.100 *N* NaOH was diluted to 30.0 ml. with 0.1 *N* KCl solution, the microliters of 0.5 HCl added, and the pH read.

RESULTS AND DISCUSSION

Estimation of Apparent pKa′ Values—Apparent pKa values were estimated (7) at a specific wavelength by

$$\log \left| \frac{A_{HC^-} - A_0}{A_0 - A_{H_2C}} \right| = pKa' - pH \qquad \text{(Eq. 2)}$$

where the A_0 values are the time zero estimates of absorbances at a given pH value, A_{H_2C} is the asymptotic absorbance in increasingly acidic solutions and is assigned to the absorbance of 7.30×10^{-5} *M* undissociated coumarinic acid (Fig. 2 at pH 1.0), and A_{HC^-} is the asymptotic absorbance achieved in neutral solution and is assigned

[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] K & K Laboratories Inc., Plainview, N. J.
[4] Pfalz and Bauer, Flushing, N. Y.

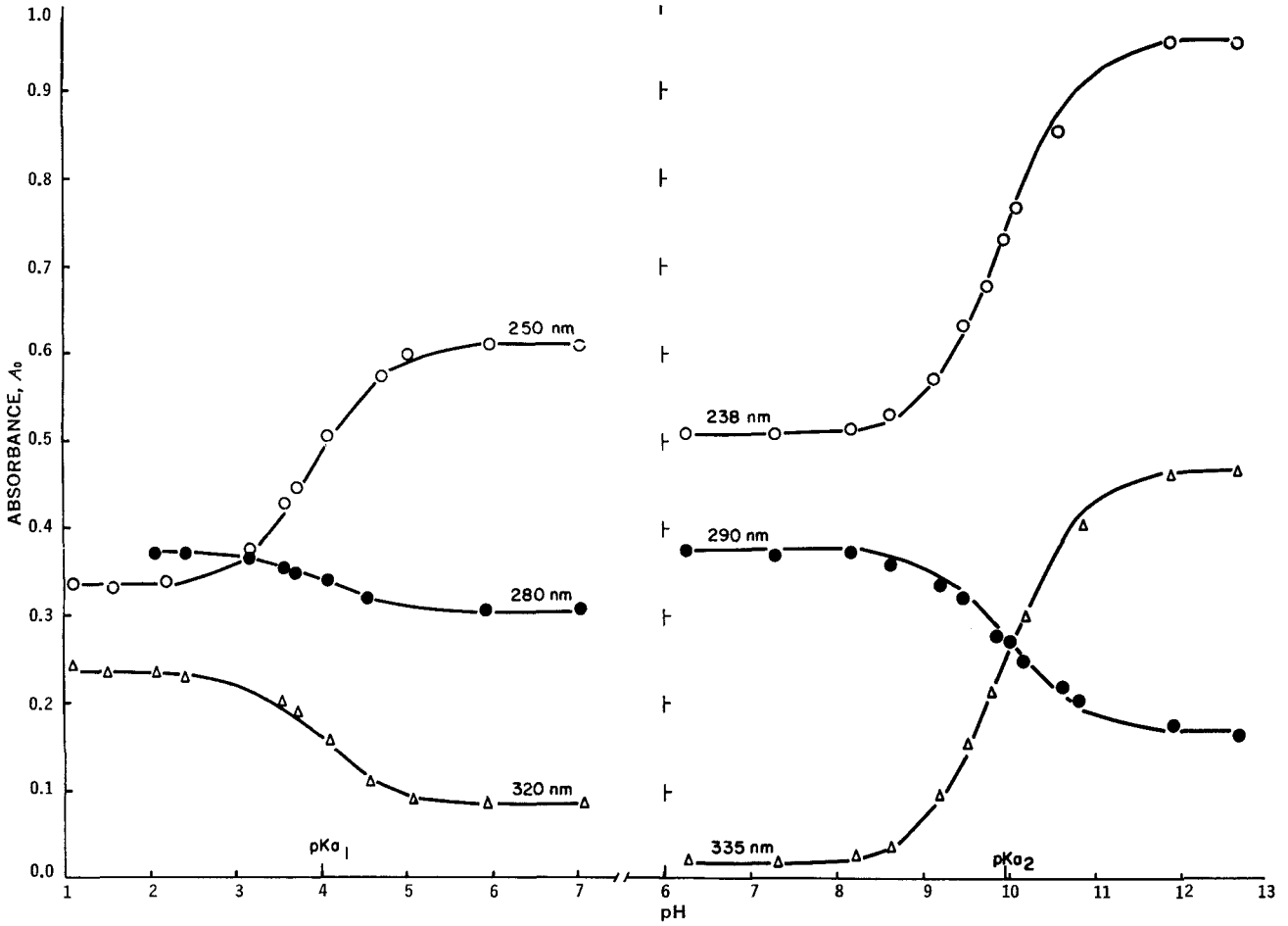


Figure 4—*Spectrophotometric titration curves for coumarinic acid at 25° at several wavelengths. The pKa_1' was made at 7.30×10^{-6} M and the pKa_2' was determined at 7.86×10^{-5} M. Absorbances were determined from extrapolated time zero values.*

to the absorbance of 7.30×10^{-5} *M* coumarinate monoanion. The obtained pKa_1' value was 4.00 at 25.0°. Similar studies were made at 238, 290, and 335 nm. after mixing solvolyzed coumarin and the appropriate buffers (Table I) in the pH range 6–13. The calculated pKa_2' from an expression similar to Eq. 2 for the dissociation of the phenolic monoanion to the coumarinate dianion was 9.95 at 25.0°. This was estimated as 10.7 by Mattoo (1). However, inspection of Mattoo's spectral Fig. 2 (1) does not show a clear isosbestic point. Since the monoanion lactonizes in this pH region, spectral reading should be made immediately or the spectrum of coumarin will interfere with the analyses. The spectral evidence was inconsistent with the previously (1) postulated dimers (Figs. 2 and 4) and yielded a pKa′ of 9.95 in the present studies.

The immediately read pH values of 3.0-ml. acidified aliquots of 0.00167 *M* coumarinic acid obtained from alkaline-solvolyzed coumarin when plotted against the microliters of 0.5 *N* HCl added provided the potentiometric titration curves of Fig. 5. The difference between the numbers of milliliters necessary to adjust these aliquots and a blank solution of the alkali used to a given pH are given as a difference curve in Fig. 5. The pH values of half-neutralization can be observed from this difference curve (8, 9) and used to estimate pKa′ as 4.00 and pKa_2' as 9.90. The asymptotic value in the acidic region was based upon the fact that 10 μl. of HCl had to be consumed for complete liberation of the coumarinic acid. Of course, the greatest error in pH measurement is in the region of pH 3.0, since the half-life for ring closure below pH 3.0 is less than 5.0 min.

Buffer Effects on Rates of Coumarinate Lactonization—The apparent first-order rate constants, *k*, for the lactonization of coumarinic acid (H_2C) and its anions (HC^- and C^{-2}) vary markedly with pH (Table I and Fig. 1). It was necessary to quantify any possible buffer effects on rate so that exact equations could be written for rate-constant dependence on pH. Significant buffer effects were observed in the acid region with acetate buffers (Table I and Fig. 6) but not with phosphate buffers (Table I, footnote *e*).

There was no significant difference in the rate of lactonization between a phosphate buffer solution (pH 8.26) of hydrolyzed coumarin (*i.e.*, as the monoanion) and when the same solution was 0.1 *M* in acetate ion, Ac^- (Table I, footnote *e*).

Thus, any catalytic effect of $k'_{Ac^-}[Ac^-][HC^-]$ is negligible, and the observed acetate buffer catalytic effects in the pH range 2.2–5.4 (Table I and Fig. 6) must be restricted to acetate-ion-, Ac^-, catalyzed lactonization of the coumarinic acid, H_2C (or its kinetically equivalent acetic acid-, HAc, catalyzed lactonization of the coumarinate monoanion, HC^-) and/or the nonkinetically equivalent acetic acid-, HAc, catalyzed lactonization of the undissociated coumarinic acid, H_2C.

The apparent first-order rate constant, *k*, for the lactonization of coumarinic acid, H_2C, and its anion HC^- can be constructed (10) at pH values below 9 as

$$k = \{k_{H^+}[H^+] + k_{HAc}[HAc] + k_{Ac^-}[Ac^-] + k_{H_2O}\} f_{H_2C} + \{k_{H^+}'[H^+] + k'_{HAc}[HAc] + k'_{Ac^-}[Ac^-] + k'_{H_2O}\} f_{HC^-} \quad \text{(Eq. 3)}$$

where

$$f_{H_2C} = \frac{[H_2C]}{[H_2C] + [HC^-]} = \frac{[H^+]}{[H^+] + K_{a_1}'} \quad \text{(Eq. 4)}$$

and

$$f_{HC^-} = \frac{[HC^-]}{[H_2C] + [HC^-]} = \frac{K_{a_1}'}{[H^+] + K_{a_1}'} \quad \text{(Eq. 5)}$$

are the fractions of total coumarinic acid, undissociated and anionic, respectively, and the k_i's are the indicated microscopic catalytic rate constants. These simple expressions for f_{H_2C} and f_{HC^-} can be used when K_{a_1}' and K_{a_2}' differ widely and when the dianion concentration, $[C^{-2}]$, is negligible (10) as it is in this case. The term $k'_{Ac^-}[Ac^-]$ has previously been shown to be negligible, and the

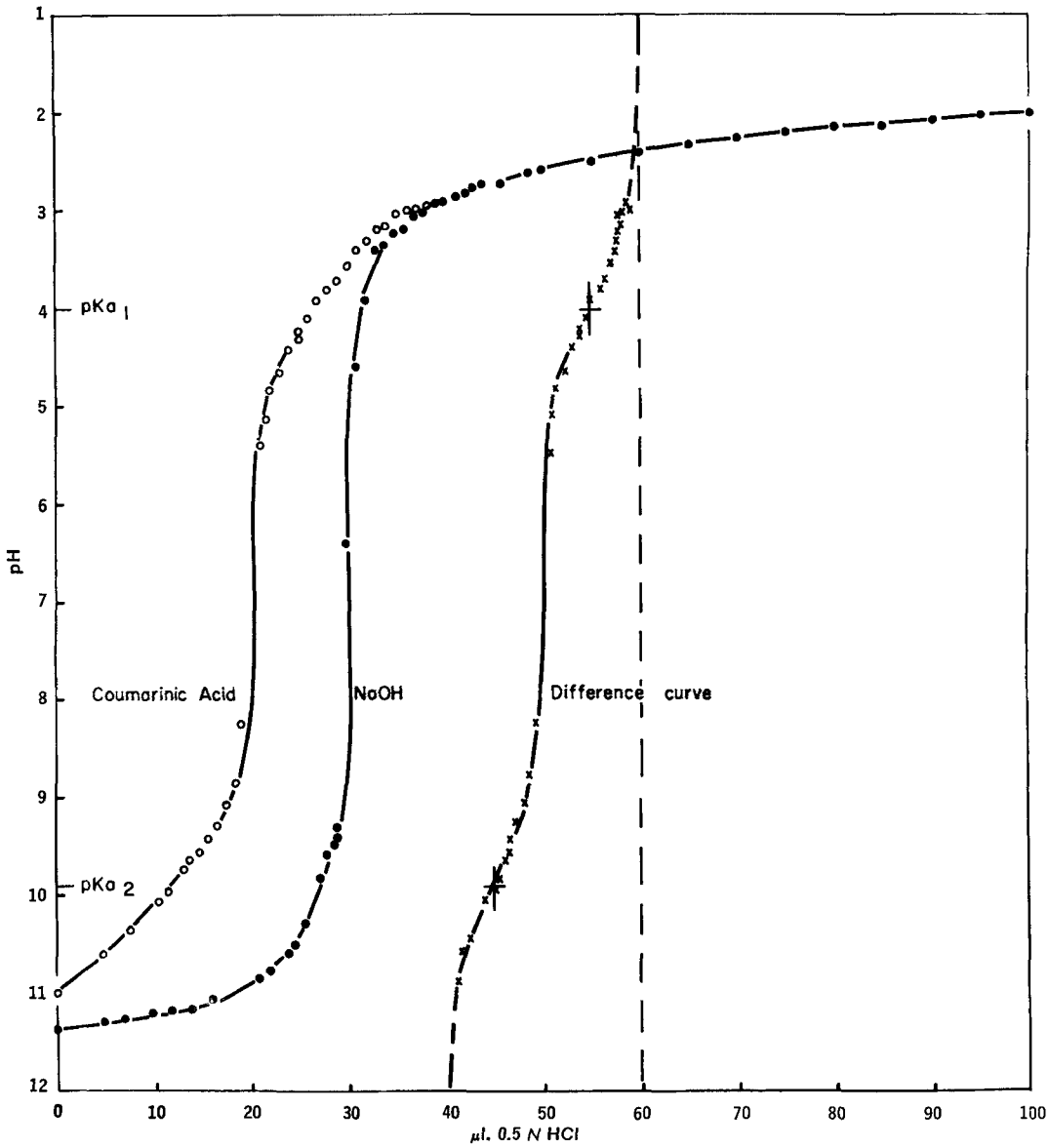


Figure 5—*Potentiometric titration curve for coumarinic acid at 25°. The titration curve of coumarinic acid is for 3 ml. of 1.67 × 10⁻³ M completely solvolyzed coumarin in 5.0 × 10⁻³ N NaOH, μ = 0.1. The blank titration curve is for 3 ml. 5.0 × 10⁻³ N NaOH, μ = 0.1.*

terms k_{Ac^-} [Ac⁻] f_{H_2C} and k'_{HAc}[HAc] f_{HC^-} are kinetically equivalent, as are $k_{H_2O}f_{H_2C}$ and $k_{H'}$ [H⁺] f_{HC^-}, so that Eq. 3 can be reduced to

$$k = \{k_{H^+}[H^+] + k_{HAc}[HAc] + k_{H_2O}\}f_{H_2C} + \{k'_{HAc}[HAc] + k'_{H_2O}\}f_{HC^-} \quad \text{(Eq. 6)}$$

At any constant [H⁺], this equation becomes

$$k = k_{HAc}[HAc]f_{H_2C} + k'_{HAc}[HAc]f_{HC^-} + (k_0 + k_0') \quad \text{(Eq. 7)}$$

where at constant pH, the constants

$$k_0 + k_0' = \{k_{H^+}[H^+] + k_{H_2O}\}f_{H_2C} + k'_{H_2O}f_{HC^-} \quad \text{(Eq. 8)}$$

where f_{H_2C} and f_{HC^-} of Eqs. 4 and 5 are also constants at constant [H⁺].

Since $K_{a_1}' = \{[H^+][HC^-]\}/[H_2C]$ and $K_{HAc} = \{[H^+][Ac^-]\}/[HAc]$, then

$$k'_{HAc}[HAc]f_{HC^-} = k'_{HAc}[HAc]\frac{[HC^-]}{[H_2C] + [HC^-]} = \frac{k'_{HAc}K_{a_1}'[HAc]}{[H^+]}\left\{\frac{[H_2C]}{[H_2C] + [HC^-]}\right\} = \frac{k'_{HAc}K_{a_1}'}{[H^+]}[HAc]f_{H_2C} \quad \text{(Eq. 9)}$$

If Eq. 7 is valid, substitution of Eq. 9 permits reduction of Eq. 7 to

$$k = (k_{HAc} + k'_{HAc}K_{a_1}/[H^+])f_{H_2C}[HAc] + (k_0 + k_0') \quad \text{(Eq. 10)}$$

Thus, a plot of the apparent first-order rate constant, k, *versus* f_{H_2C}[HAc] at any specific pH value should be a straight line of slope $(k_{HAc} + k'_{HAc}K_{a_1}'/[H^+])$ and intercept $(k_0 + k_0')$. The slope should decrease with increasing [H⁺] or decreasing pH values if acetic acid catalyzes the lactonization of the coumarinate monoanion. Similarly,

$$k_{HAc}[HAc]f_{H_2C} = k_{HAc}[HAc]\frac{[H_2C]}{[H_2C] + [HC^-]} = \frac{k_{HAc}[H^+][HC^-]}{K_{a_1}\{H_2C + HC^-\}} = \frac{k_{HAc}[HAc][H^+]}{K_{a_1}}f_{HC^-} \quad \text{(Eq. 11)}$$

If Eq. 7 is valid, substitution of Eq. 11 reduces Eq. 7 to

$$k = \left(k'_{HAc} + \frac{k_{HAc}[H^+]}{K_{a_1}}\right)f_{HC^-}[HAc] + (k_0 + k_0') \quad \text{(Eq. 12)}$$

Thus, a plot of the apparent first-order rate constant, k, *versus* f_{HC^-}[HAc] at any specific pH value should be a straight line of slope $(k'_{HAc} + k_{HAc}[H^+]/K_{a_1}')$ and intercept $(k_0 + k_0')$. The slope should increase with increasing [H⁺] or decreasing pH values if acetic acid catalyzes the lactonization of undissociated coumarinic acid.

The facts that slopes of k *versus* f_{H_2C}[HAc] do decrease with increasing pH in accordance with Eq. 10 and that slopes of k *versus* f_{HC^-} [HAc] do not significantly change with pH (Fig. 6) in accordance with the postulates of Eq. 12 prove that acetic acid does catalyze the lactonization of coumarinate monoanion but does not catalyze the lactonization of undissociated coumarinic acid.

The plots of Fig. 6 can be rationalized only on the presumption that the supposed catalytic rate constant, k_{HAc}, from acetic acid-

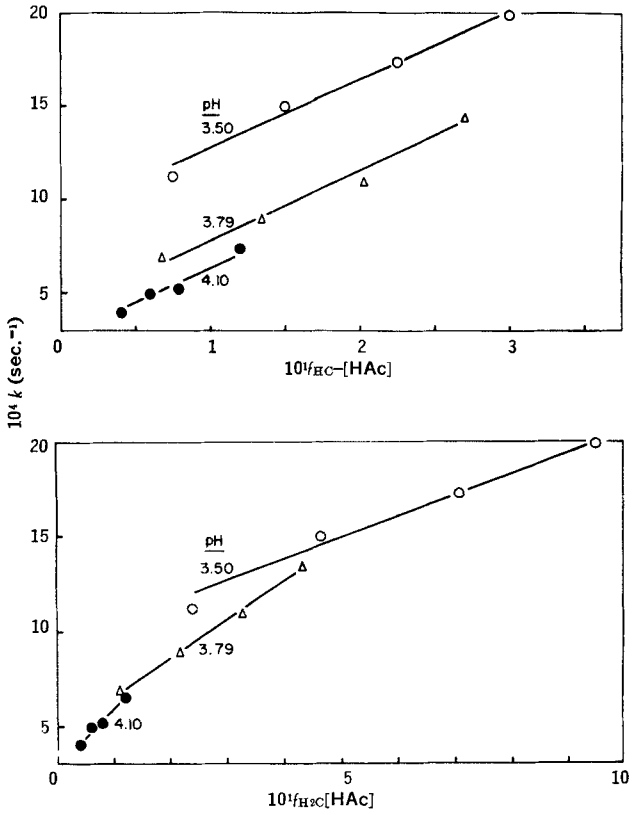


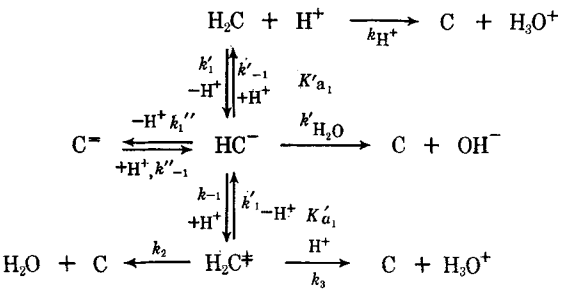
Figure 6—*Apparent first-order rate constants for the lactonization of coumarinic acid at 25°, μ = 0.1, as a function of the product of the concentration of acetic acid and the fraction as coumarinate monoanion (top) and the fraction of the undissociated coumarinic acid (bottom) at various pH values.*

catalyzed lactonization of undissociated coumarinic acid in Eqs. 7 and 9–12 is negligible. The values of $k_0 + k_0'$ can be obtained from the intercepts of the plots of Fig. 6 in accordance with Eqs. 10 and 12. The value of the catalytic rate constant, k'_{HAc}, for acetic acid-catalyzed lactonization of coumarinate monoanion, as determined from the parallel slopes of Fig. 6 in accordance with Eq. 12, is 3.65×10^{-3} l./mole-sec. at 25.0°. The observed apparent first-order rate constants at any pH can be corrected for this acetic acid catalysis by

$$k = k_{observed} - k'_{HAc} f_{HC^-}[HAc] \qquad \text{(Eq. 13)}$$

These are the k values for known $[H^+]$ and [HAc] values plotted in the log k–pH profiles of Fig. 7, where the apparent K_{a_1}' value of $10^{-4.00}$ was taken for the calculation of f_{HC^-} from Eq. 5.

The Log *k*–pH Profile for Lactonization of Coumarinic Acid and Its Anions—The apparent first-order rate constants plotted in the log k–pH profiles of Fig. 7 below the pH of 9.0, after correction for



Scheme I

general acid catalysis as by Eq. 13, may conform to the dependency of

$$k = \{k_{H^+}[H^+] + k_{H_2O}\} f_{H_2C} + \{k_{H^+}'[H^+] + k'_{H_2O}\} f_{HC^-} \qquad \text{(Eq. 14)}$$

Since $k_{H_2O} f_{H_2C}$ and $k_{H^+}'\,[H^+]\, f_{HC^-}$ are kinetically equivalent, Eq. 14 can be reduced to

$$k = \{k_{H^+}[H^+] + k_{H_2O}\} f_{H_2C} + k'_{H_2O} f_{HC^-} \qquad \text{(Eq. 15)}$$

The asymptotic slope of unity is approached with decreasing pH in Fig. 7 since Eq. 15 approaches $k = k_{H^+}[H^+]$ with increasing $[H^+]$. Thus the log k values at pH = 0 provide estimates of the k_{H^+} values (Table IV) for several temperatures.

The remainder of the log k–pH profile of Fig. 7 for lactonization was fitted by adjusting values of k_{H_2O} and k'_{H_2O} in Eq. 15 and assuming various values of K_{a_1}' for the calculation of the f_{H_2C} and f_{HC^-} values from Eqs. 4 and 5. To obtain a reasonable fit, it was necessary to assume a kinetic pK_{a_1}' of 3.00 for Eqs. 4 and 5 (Fig. 7). This differs significantly from the determined spectral (Fig. 4) and potentiometric (Fig. 5) pK_{a_1}' of 4.0. The derived parameters of Eqs. 13 and 15 are given in Table IV, as well as the Arrhenius and absolute rate thermodynamic factors obtained from the Arrhenius plots of Fig. 8.

Possible Explanation to Reconcile Apparent Kinetic, Spectral, and Potentiometric pK_{a_1}'s of Coumarinic Acid—A possible reconciliation of this discrepancy between the apparent kinetic pK_{a_1}' of 3.0 and the spectrophotometric and potentiometric titration pKa's of 4.0 may be based on an explanation similar to that offered by Eriksson (11) for similar discrepancies between kinetic and titrimetric pKa′ values observed in the alkaline solvolyses of substituted anilides and barbituric acids.

The simplest mechanistic scheme to explain the observations on lactonization of coumarinic acid, H_2C, to coumarin, C, can be given as Scheme I.

The total rate of loss of coumarinic acid to coumarin in all its forms, *i.e.*,

$$[H_2C]_T = [H_2C] + [HC^-] + [H_2C\ddagger] + [C^{-2}] \qquad \text{(Eq. 16)}$$

can be expressed as

$$-d[H_2C]_T/dt = k[H_2C]_T = -(d[H_2C]/dt + d[HC^-]/dt + d[H_2C\ddagger]/dt + d[C^{-2}]/dt) \qquad \text{(Eq. 17)}$$

Table IV—Microscopic Rate Constants[a] and Thermodynamic Parameters for the Lactonization of Coumarinic Acid and the Hydrolysis of Coumarin

Temperature	$10^2 k_{H^+}$	$10^3 k_{H_2O}$	k_{-1}	$10^{-2}P$	$10^2 Q$	$10^4 P/Q$[b]	$10^3 k_{HAc}$	$10^5 k'_{H_2O}$	k_{OH^-}
10.0°	2.2	1.9	19	5.4	5.8	0.93	—	0.80	0.14
17.5°	4.5	2.9	29	12.0	7.0	1.7	—	2.4	0.25
25.0°	10.0	5.0	50	8.8	8.0	1.1	1.2	9.2	0.45
ΔEa	17.8	10.9	10.9	—	—	—	—	22.8	13.2
log pZ[c]	12.0	9.2	5.7	—	—	—	—	12.5	9.9
$\Delta S\ddagger$ (e.u.)[d]	−5.5	−15.3	−34.5	—	—	—	—	−3.0	−18.0

[a] The apparent first-order rate constants, k, in sec.$^{-1}$ for the lactonization can be defined in terms of the various constants as: $k = k_{H^+}[H^+] f_{H_2C} + k_{H_2O} f'_{H_2O} + \{k'_{H_2O} + k'_{HAc}[HAc]\} f_{HC^-} = k_{H^+}[H^+] f_{H_2C} + (Q + P[H^+])/(1 + P[H^+]) k_{-1} Ka_1' f_{H_2C} + \{k'_{H_2O} + k'_{HAc}[HAc]\} f_{HC^-}$, where $(Q + P[H^+])/(1 + P[H^+]) = \{(k_2 + k_3[H^+])\}/(k_1 + k_2 + k_3[H^+])$, $Q = k_2/(k_1 + k_2)$, and $P = k_3/(k_1 + k_2)$. The f'_{H_2C} is an artificial expression of the fraction undissociated consistent with the log k–pH profile on the presumption of a kinetic pKa at 3 rather than at the true value of 4, $f_{H_2C} = [H^+]/([H^+] + Ka_1')$ and $f_{HC^-} = Ka_1'/([H^+] + Ka_1')$ in the pH region <7 and $f_{HC^-} = [H^+]/([H^+] + Ka_2')$ in the pH region >7, where $Ka_1' = 1.00 \times 10^{-4}$ and $Ka_2' = 1.48 \times 10^{-10}$ at 25.0°. All rate constants are in l./mole-sec. except k_{H_2O} and k'_{H_2O} which are in sec.$^{-1}$. [b] $P/Q = k_3/k_2$. [c] Ea in kcal./mole and log pZ are obtained from the slopes and intercepts of the Arrhenius plots of log k *versus* $1/T$ (Fig. 7), where T is the absolute temperature and $k = pZ\, e^{-\Delta Ea/RT}$. [d] Where $k = kT/h\, e^{-\Delta S\ddagger/R}\, e^{-\Delta H\ddagger/RT}$ and $\Delta H\ddagger = \Delta Ea - 0.6$ kcal.

where k is the apparent first-order rate constant and

$$-d[H_2C]/dt = (k_{H^+}[H^+] + k_1')[H_2C] - k_{-1}'[H^+][HC^-] \quad \text{(Eq. 18)}$$

$$-d[HC^-]/dt = (k_{-1}'[H^+] + k_1'' + k_{H_2O}' + k_{-1}[H^+])[HC^-] - k_1[H_2C\ddagger] - k_1'[H_2C] - k_{-1}''[H^+][C^{-2}] \quad \text{(Eq. 19)}$$

$$-d[C^{-2}]/dt = k_{-1}''[H^+][C^{-2}] - k_1''[HC^-] \quad \text{(Eq. 20)}$$

$$-d[H_2C\ddagger]/dt = (k_1 + k_2 + k_3[H^+])[H_2C\ddagger] - k_{-1}[H^+][HC^-] \quad \text{(Eq. 21)}$$

so that from Eqs. 17–21,

$$k = k_{H^+}[H^+][H_2C]/[H_2C]_T + k_{H_2O}'[HC^-]/[H_2C] + (k_2 + k_3[H^+])[H_2C\ddagger]/[H_2C]_T$$
$$= k_{H^+}[H^+]f_{H_2C} + k_{H_2O}'f_{HC^-} + (k_2 + k_3[H^+])f_{H_2C\ddagger} \quad \text{(Eq. 22)}$$

where f_{H_2C} and f_{HC^-} are defined by Eqs. 4 and 5, respectively, if $f_{H_2C\ddagger}$ is of negligible quantity. This latter postulate is consistent with the steady-state assumption that $d[H_2C\ddagger]/dt \sim 0$; when this condition is imposed on Eq. 21,

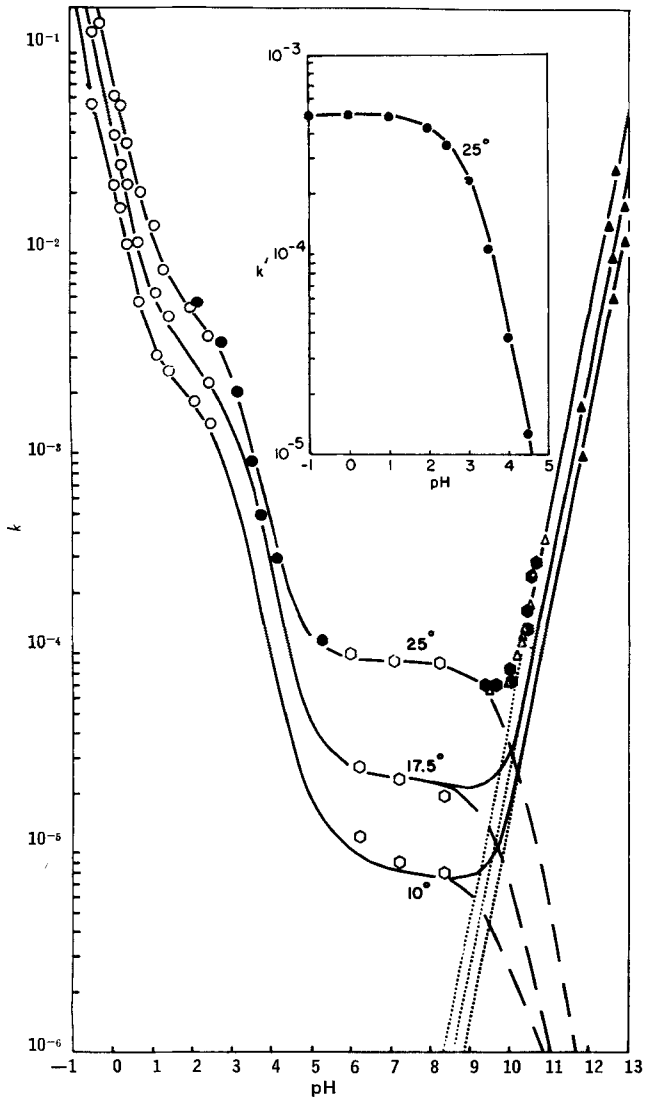


Figure 7—*Log* k–*pH profile for the lactonization of coumarinic acid and the hydrolysis of coumarin at 25.0, 17.5, and 10.0°. Key:* ○, *lactonization in HCl;* ●, *extrapolated from acetate buffer and acetic acid without general acid catalysis;* ○, *lactonization in phosphate;* ●, *lactonization in carbonate buffer;* △, *hydrolysis in carbonate buffer; and* ▲, *hydrolysis in NaOH. The inset is a plot of log* k′ versus *pH at 25.0° where* $k' = k - (k_{H^+}[H^+]f_{H_2C} + k'_{H_2O}f_{HC^-})$. *The drawn lines are calculated from the derived microscopic rate constants.*

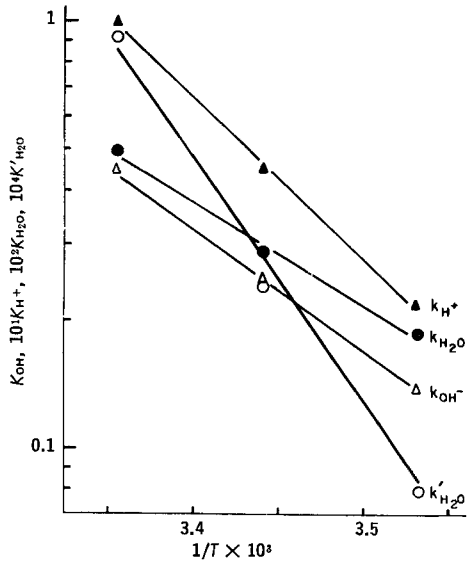


Figure 8—*Arrhenius plots of the microscopic rate constants for the lactonization of coumarinic acid and the hydrolysis of coumarin.*

$$[H_2C\ddagger] = [HC^-]k_{-1}H^+/(k_1 + k_2 + k_3[H^+]) \quad \text{(Eq. 23)}$$

so that Eq. 22 may be transformed into

$$k = k_{H^+}[H^+]f_{H_2C} + k_{H_2O}'f_{HC^-} + \frac{(k_2 + k_3[H^+])k_{-1}[H^+]}{k_1 + k_2 + k_3[H^+]}f_{HC^-} \quad \text{(Eq. 24)}$$

Since

$$[H^+]f_{HC^-} = K_{a_1}'f_{H_2C} \quad \text{(Eq. 25)}$$

the last term of Eq. 24 may be equated to

$$\frac{(k_2 + k_3[H^+])K_{a_1}'k_{-1}}{k_1 + k_2 + k_3[H^+]}f_{H_2C} \quad \text{(Eq. 26)}$$

which shows Eq. 24 to be equivalent to Eq. 15.

The value of k_{H^+} can be readily obtained from the intercept of the linear asymptote of the log k–pH plot with a slope of 1 at the pH values below 2 (Fig. 7). The value of k'_{H_2O} can be estimated from the plateau in the log k–pH profile reached between pH 6 and 8 where only the coumarinate monoanion, HC^-, exists and before the formation of a significant amount of nonlactonizable coumarinate dianion, C^{-2}, lowers the monoanion's apparent rate of lactonization. Thus, an apparent rate constant, k', can be calculated for the pH region between 2 and 6 and would be defined by consideration of Eqs. 24–26 as

$$k' = k - (k_{H^+}[H^+]f_{H_2C} + k_{H_2O}'f_{HC^-}) = \frac{(k_2 + k_3[H^+])k_{-1}K_{a_1}'}{(k_1 + k_2) + k_3[H^+]}f_{H_2C}$$
$$= \frac{Q + P[H^+]}{1 + P[H^+]}k_{-1}K_{a_1}'f_{H_2C} \quad \text{(Eq. 27)}$$

where

$$Q = k_2/(k_1 + k_2) \quad \text{(Eq. 28)}$$

and

$$P = k_3/(k_1 + k_2) \quad \text{(Eq. 29)}$$

Thus, at high $[H^+]$ concentrations or at pH values less than 2 where $f_{H_2C} \rightarrow 1$ and

$$(Q + P[H^+])/(1 + P[H^+]) = (k_2 + k_3[H^+])/(k_1 + k_2 + k_3[H^+]) \rightarrow 1 \quad \text{(Eq. 30)}$$

then,

$$\lim_{[H^+]\rightarrow\infty} k' = k_{-1}K_a' = k_{H_2O} \quad \text{(Eq. 31)}$$

and k_{-1} may be estimated (Table IV) from the known K_{a1}' and the apparent k_{H_2O} values, where the latter was obtained from the best fit of Eq. 15 and is 5×10^{-3} at 25°.

Thus, at low $[H^+]$ concentrations, possibly at pH values greater than 5, where $k_3[H^+] \ll k_2$

$$\lim_{[H^+]\to\infty} k' = \left(\frac{k_2}{k_1 + k_2}\right) k_{-1}K_{a1}'f_{H_2C} = Qk_{-1}K_{a1}'f_{H_2C} \to Qk_{-1}[H^+] \qquad \text{(Eq. 32)}$$

since from Eq. 4, $f_{H_2C} \to [H^+]/K_{a1}'$ at $[H^+] \ll K_{a_1}'$. Thus Q, as defined in Eq. 28, may be estimated (Table IV) since k_{-1} (Eq. 31), K_{a_1}', and $[H^+]$ are known.

At intermediate pH values, possibly at pH values between 2 and 5 where the more exact Eq. 27 holds, where k_{-1} (Eq. 31) and $Q = k_2/(k_1 + k_2)$ (Eq. 32) have been estimated (Table IV) and all other factors such as $[H^+]$, K_{a_1}', and f_{H_2C} (Eq. 4) are known, the value of P may be calculated as

$$P = \frac{k' - Qk_{-1}K_{a_1}'f_{H_2C}}{(k_{-1}K_a'f_{H_2C} - k')[H^+]} \qquad \text{(Eq. 33)}$$

and is given in Table IV.

The curves drawn through the points in Fig. 7 are based on the evaluated values of Q, P, k_{-1}, k_{H^+} and k'_{H_2O} given in Table IV.

Mechanism in Explanation of Kinetic Dependencies—The kinetic transformations of Scheme I are consistent with the fitting of the log k–pH profiles of Fig. 7 on the basis of the kinetic dependencies of Eqs. 22 and 24–27. These relations may have the mechanistic bases outlined in Scheme II which are consistent with the classical explanations of esterification (12).

The sequence I–IV, Scheme II,

$$H_2C + H^+ \rightleftarrows [H_3C^+] \rightleftarrows [H_3C\ddagger] \xrightarrow{-H_3O^+} C \qquad \text{(Eq. 34)}$$

is typical of hydrogen-ion attack on carbonyl to produce a protonated monoester of an orthoacid, $H_3C\ddagger$ (III), which dehydrates to coumarin, C (IV), and is consistent with a rate dependency of the apparent first-order rate constant on $k_{H^+}[H^+]f_{H_2C}$. The ionization equilibria of coumarinic acid, H_2C (I), provide a monoanion, HC^- (V), and a dianion, C^{-2} (IX), where the latter may be completely stabilized against intramolecular esterification by repulsion of its two negative charges. The coumarinic acid and/or its monoanion can form the anionic orthoacid, $HC\ddagger$ (VII), by intramolecular nucleophilic attack of phenate anion on carboxyl (VI → VII) after intramolecular general base attack of the monoanion (V → VI) or direct dissociation of the coumarinic acid (I ⇆ VI). Of course, the direct closure of the coumarinate monoanion (V → VIII) is a possibility. The anion orthoacid, $HC\ddagger$ (VII), may directly dissociate into hydroxyl ion and coumarin (VIII → IV). This is a relatively slow process and is consistent with the observed dependency of the apparent first-order rate constant on $k'_{H_2O}f_{HC^-}$ to form coumarin (Eq. 15). The anion orthoacid, $HC\ddagger$ (VII), may equilibrate with its conjugate monoesterified orthoacid, $H_2C\ddagger$ (VIII), which may spontaneously dehydrate to coumarin (VIII → IV) with first-order rate constant k_2 or be attacked by hydrogen ion with a second-order rate constant k_3 to form the more highly unstable protonated monoester of the orthoacid $H_3C\ddagger$ (III), which more readily forms coumarin (VIII → III → IV). These sequences are consistent with the complex dependency of the apparent first-order rate constant as represented by Eq. 27 on the premise of the steady-state approximation that $H_2C\ddagger$ (VIII) is highly unstable and in low concentration and that $k_3/k_2 = P/Q$ is in the ratio of 10,000:1.

Reactivity of Coumarin and Coumarinate Anion in Alkaline Solutions—If the coumarinate dianion C^{-2} (IX) is unreactive, due to the repulsion of the phenate and carboxylate anions, the apparent first-order rate constant for lactonization will plateau in the pH range 6–8 (Fig. 7) at a value of k'_{H_2O}, where all the coumarinic acid is in the monoanionic form, and will decrease in accordance with $k'_{H_2O}f_{HC^-}$ above pH values of 8 (dashed lines in Fig. 7). The plots of log k *versus* pH for the hydrolysis of coumarin to coumarinate dianion are linear above pH 10 in accordance with the expression

$$\frac{-dC}{dt} = \frac{d[H_2C]_T}{dt} = kC = k_{OH^-}[OH^-]C \qquad \text{(Eq. 35)}$$

where, on a logarithmic transformation,

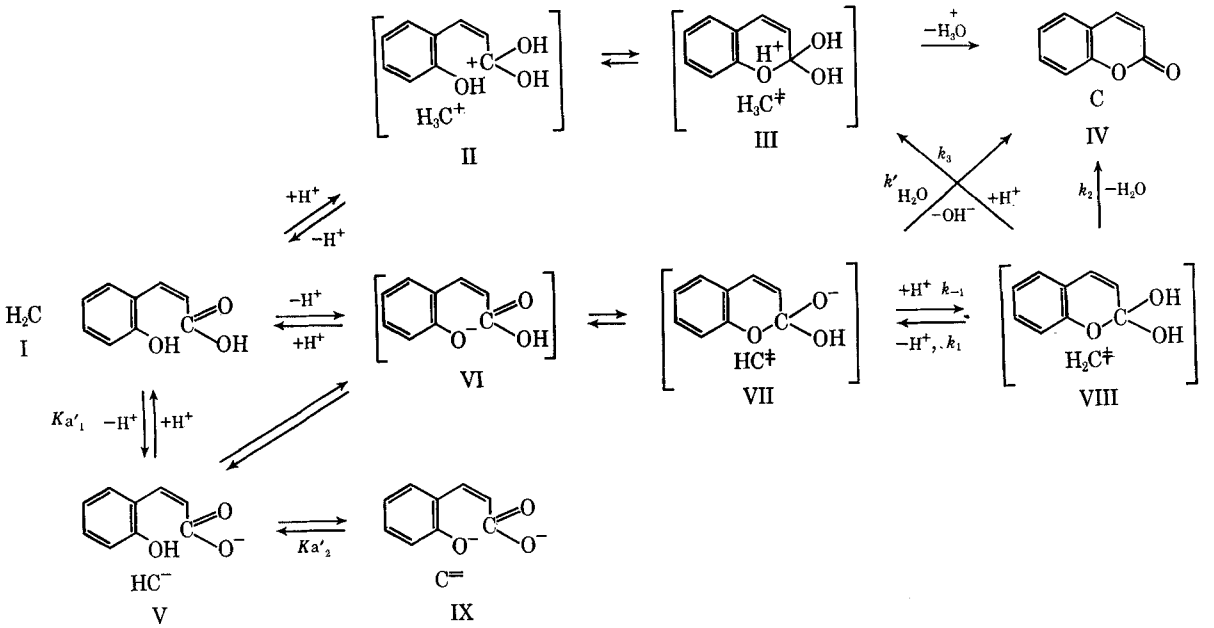
$$\log k = \log k_{OH^-} pK_w + \text{pH} \qquad \text{(Eq. 36)}$$

where the k_{OH} values (Table IV) are estimated from the intercepts. The sums of the observed apparent first-order rate constants for lactonization and hydrolysis are drawn in the pH region 8.5–11.5 and are consistent with the plotted overall apparent first-order rate constants obtained from appropriate plots of the spectral data in accordance with Eq. 1. This is consistent with a rate of achievement of a coumarinic acid monoanion and dianion–coumarin equilibrium, where the overall apparent first-order rate constant, k, to achieve this equilibrium in this pH region is actually

$$k = k'_{H_2O}f_{HC^-} + k_{OH}[OH^-] \qquad \text{(Eq. 37)}$$

since only nonreactive dianion, C^{-2}, and reactive monoanion, HC^-, are present in this pH region.

The equilibrium constant can be defined as a function of hydrogen- and hydroxyl-ion concentrations when Eqs. 17 and 35 are equated,



Scheme II

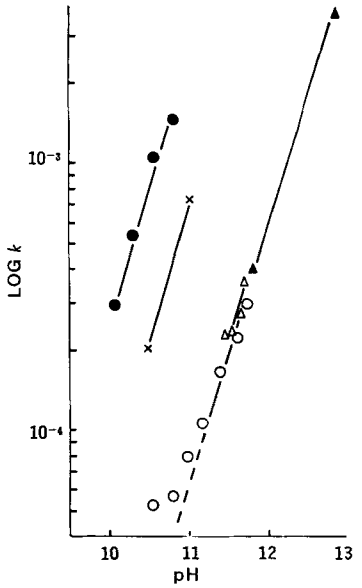


Figure 9—*Log* k–*pH relationship for the hydrolysis of 3-chlorocoumarin* (●), *3-bromocoumarin* (×), *3-methylcoumarin* (△), *coumarin* (○), *and 4-methylcoumarin* (▲) *in dioxane* (*30%, v/v*)–*water at 25°.*

Eqs. 18–26 and the fact that C^{-2} has been shown to be nonreactive are considered, and the resulting expression is rearranged to

$$K = \frac{[C]_{eq.}}{[H_2C]_{T_{eq.}}} = \frac{[C]_{eq.}}{[H_2C]_{eq.} + [HC^-]_{eq.} + [C^{-2}]_{eq.}} = \frac{k'_{H_2O}f_{HC^-} + \left(k_{H^+}[H^+] + \frac{(k_2 + k_3[H^+])k_{-1}K_{a1}'}{k_1 + k_2 + k_3[H^+]}\right) f_{H_2C}}{k_{OH^-}[OH^-]} \quad \text{(Eq. 38)}$$

where the subscript "eq." refers to the respective concentrations at equilibrium. However, coumarin and coumarinic acid ions only exist in solution together in the pH region 8.5–11.5 (Fig. 7), where f_{H_2C} is negligible, so that the equilibrium constant of Eq. 38 for lactonization simplifies to

$$K = k'_{H_2O}f_{HC^-}/k_{OH^-}[OH^-] \quad \text{(Eq. 39)}$$

Some typical values of this equilibrium constant at 25.0° and at various pH values are: 7.0 (pH), 2200 (*K*); 8.0, 210; 9.0, 18.3; 9.5, 4.8; 10.0, 0.96; 10.5, 0.142; and 11.0, 0.017.

Hydrolysis of 3- and 4-Substituted Coumarins in 30% (v/v) Dioxane–Water—Halogen substitution in the 3-position has a pronounced accelerating effect on hydrolysis (Table III). This can be rationalized by the electron-withdrawing action of these atoms, which is greater for the chloro than for the bromo compound. This property should and does promote the attack of the hydroxyl ions on the carbonyl carbon. Methyl substitutions for hydrogens in both the 3- and 4-positions do not significantly affect hydrolysis rates. This can be clearly seen from the bimolecular rate constants, k_{OH^-}, for the hydrolysis, determined from the intercepts of the unit slope plots of log *k versus* pH, plotted in accordance with Eq. 36 (Fig. 9). The k_{OH^-} (l./mole-sec.) values at 25.0° in 30.0% (v/v) dioxane–water were 2.5 for 3-chloro-, 0.7 for 3-bromo-, 0.07 for 3-methylcoumarin, 0.065 for coumarin, and 0.058 for 4-methylcoumarin. Further investigations of the reactivity of these compounds are planned in aqueous solutions.

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