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

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Abstract ☐ The kinetics of lactonization of α-chloro-, α-bromo-, α-phenyl-, α-methyl-, and β-methylcoumarinic acids and the hydrolyses of their respective 3- and 4-substituted coumarins were studied at all pH values and at various temperatures. The order of hydrogen-ion-catalyzed lactonizations is consistent with α-substituted steric effects which destroy the acid-weakening resonance of the conjugated carboxylic system by disrupting the coplanarity of the carboxylic oxygen. The order of reactivity in alkaline hydrolysis is consistent with inductive effects, *i.e.*, accelerated by electron-withdrawing substituents. The order of reactivity for other derived microscopic rate constants is consistent with the model proposed previously to rationalize the apparent discrepancies between the apparent kinetic and spectral pKa′ values. The intramolecular formation of an anionic orthoacid lactonization intermediate by the attack of a phenate anion on the substituted coumarinic acid carboxyl, its subsequent protonation to the orthoacid $H_2C‡$, and its possible loss of a hydroxyl ion to form coumarin are inhibited by electron-withdrawing groups that modify carboxyl carbon electrophilicity. This order of reactivity for these rate constants are as expected for such mechanisms. The ratio of rates of spontaneous dehydration to hydrogen-catalyzed dehydration of the neutral orthoacid lactonization intermediate, $H_2C‡$, to yield coumarin decreases with electron-donating substituents, as expected by the proposed mechanism since hydrogen-ion attack should be inhibited by electron-withdrawing substituents such as halogens.

Keyphrases ☐ Coumarin hydrolysis—kinetics, mechanism ☐ Lactonization, coumarinic acids—kinetics, mechanism ☐ pKa′ values, apparent—coumarins, coumarinic acids ☐ Substituent effect—coumarinic acid lactonization, coumarin hydrolysis

It was shown (1) that the log k–pH profile for the lactonization of coumarinic acid and the hydrolysis of its lactone, coumarin, and the discrepancy between the spectral (or potentiometric) and apparent kinetic pKa_1' values can be rationalized by a proposed mechanism. This mechanism assumes the intramolecular formation of an orthoacid, $H_2C‡$, which dehydrates both spontaneously and by hydrogen-ion catalysis to give coumarin. The steady-state assumption for $H_2C‡$ permitted the fitting of the log k–pH profile consistent with the analytical pKa_1' value and was consistent with the proposed mechanism.

These present investigations were conducted to determine the pKa′ values, the log k–pH rate profiles, and temperature effects for the hydrolysis of variously 3- and 4-substituted coumarins and for the lactonization of their respective coumaric acids. The purposes were: (*a*) to compare their relative reactivities, (*b*) to compare the extent of the equilibria among all charged forms and the corresponding lactones, and (*c*) to test the proposed mechanism by the expected substituent effects.

EXPERIMENTAL

3-Chlorocoumarin[1] and 3-methylcoumarin[2] were used as received. The 3-phenylcoumarin[3] was recrystallized from dioxane–water and acetone–water mixtures. The preparation of 3-bromocoumarin and 4-methylcoumarin was described previously (1). The reactions were investigated at various pH values between −1 and 13 in hydrochloric acid, phosphate buffer, and sodium hydroxide solutions at temperatures between 8.5 and 50.5° (Tables I–III). All solutions were made up with nitrogen-purged distilled water and, if possible, adjusted to an ionic strength of 0.1 with sodium chloride. The pH at the temperatures of the kinetic runs was read with a Radiometer pH meter and a Sargent combination electrode, or it was calculated (1) from the known activities (2) in strong acid and alkaline solutions. The compositions of the buffer solutions are listed in Tables I–III. Details of specific procedures were the same as those given previously (1).

Lactonization—Generally, 0.05 ml. of about 4×10^{-3} M solution of a coumarin that had been completely solvolyzed in 0.01 M NaOH was added to 3.0 ml. of the appropriate buffer solution to produce a final concentration of about 6.5×10^{-5} M. Only 0.02 ml. of the 4×10^{-3} M solution of 3-phenylcoumarin was used due to its low solubility. The stock solutions of solvolyzed 3-bromocoumarin and 3-chlorocoumarin were prepared immediately before the lactonization studies, since small amounts of bromide and chloride ions were detected in the alkaline solutions after several weeks, even when they were stored under refrigeration. The ring closure of the coumarin derivatives was monitored from the change of the UV absorbance in the manner described previously for coumarin (1), and lactonization was complete in the absence of significant concentrations of coumarinate dianion. The wavelengths used for the kinetic studies were 280 nm. for 3-chlorocoumarin and 3- and 4-methylcoumarin; 280 and 295 nm. for 3-bromocoumarin; and 280 and 310 nm. for 3-phenylcoumarin.

The logarithms of the differences in the final absorbance, A_∞, and the absorbance at any time, A, at a specific wavelength were plotted against time. The apparent first-order rate constants (Tables I and II) were determined from the slopes of these plots in accordance with Eq. 1:

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

Hydrolysis—The hydrolyses of the coumarin derivatives were investigated in the pH region of 11–12.5 (Table III) where complete hydrolysis could be expected. No concentrated stock solution of these substituted coumarins could be prepared because of their low solubilities. These difficulties were circumvented by effecting the ring closure of the respective coumarinic acids in the spectrophoto-

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

Table I—Apparent First-Order Rate Constants, k, in sec.$^{-1}$ for Lactonization of 6.5×10^{-5} M Coumarinic Acids[a] to Their Respective 3- and 4-Substituted Coumarins in HCl Solution

10^2[HCl][b]	pH[c]	3-Chloro	3-Bromo	3-Phenyl	3-Methyl	4-Methyl
				10^3k, 25.5°		
300	−0.59	—	—	—	—	140
200	−0.30	—	—	—	—	77.5
100	0.10	148	—	—	171	35.8
75	0.24	113	144	—	110	21.0
50	0.43	95.1	114	77.8	—	14.0
25	0.73	77.6	80.3	—	55.4	8.70
11	1.05	—	—	27.5	35.1	—
8.2	1.21	54.2	46.9	—	27.0	4.7
4.15	1.44	—	—	17.8	21.8	—
2.9	1.60	35.5	29.2	—	—	—
1.03	2.03	—	—	9.21	—	—
0.97	2.10	15.5	—	—	12.5	2.18
0.425	2.46	8.20	—	4.38	10.5	—
0.265	2.60	—	4.61	—	—	2.03
0.13	2.91	2.34	3.60	—	—	2.02
0.033	3.49	0.733	—	0.329	3.71	—
				10^2k, 17.5°		
400	−0.87	—	—	—	—	13.9
200	−0.31	14.2	19.6	15.3	30.3	4.64
100	0.08	8.03	8.35	8.16	12.8	1.65
50	0.42	4.64	—	—	6.23	—
				10^2k, 12.5°		
400	−0.88	—	—	—	—	9.0
200	−0.32	8.67	12.7	10.5	20.6	2.59
100	0.08	5.42	—	5.2	8.0	1.12
50	0.42	—	2.6	2.89	4.04	—
				10^2k, 8.5°		
400	−0.88	12.7	—	22.8	—	5.54
200	−0.33	5.46	7.52	8.5	16.2	—
100	0.08	3.78	2.95	—	6.39	0.81
50	0.41	—	—	2.37	2.94	0.36

[a] Phenylcoumarinic acid solutions were 2.60×10^{-5} M. [b] NaCl was added to maintain the ionic strength at $\mu = 0.1$ when possible. [c] 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 (2). All other values were measured by a pH meter.

metric cells by mixing 0.05 ml. (0.02 ml. for phenylcoumarin) of the 4×10^{-3} M alkaline solutions of the completely solvolyzed coumarins with 3.0 ml. 0.1 N HCl.

This ring closure was completed in a short time (see apparent first-order rate constants of Table I for lactonization in HCl solution), and a 6.5×10^{-5} M solution (2.6×10^{-5} M for phenylcoumarin) of the substituted coumarin was formed and stayed in solution. A calculated amount of 1 M NaOH was then added to give the desired alkaline pH on the basis of the known activities of HCl and NaOH (2). The resultant pH values were checked with a Radiometer pH meter and a Sargent combination electrode, and good agreements were found. The hydrolyses were investigated by recording the change in the UV absorbance at 310 nm. for phenylcoumarin and at 280 nm. for all the other coumarins. The apparent first-order rate constants for the alkaline hydrolysis were calculated in the manner described for the lactonization and are listed in Table III.

Spectrophotometric Determination of the Apparent pKa′ Values—The pKa_1' values of the carboxylic acid groups were determined by adding 0.05-ml. aliquots of the approximately 4×10^{-3} M solution of the completely solvolyzed substituted coumarin to 3.0 ml. of an appropriate buffer solution in the pH range 0–7. The rapid change in the absorbance at a given wavelength due to the ring closure was automatically monitored as a function of time with a Cary 15 re-

Table II—Apparent First-Order Rate Constants, k, in sec.$^{-1}$ for Lactonization of 6.5×10^{-5} M Coumarinic Acids[a] to Their Respective 3- and 4-Substituted Coumarins in Phosphate Buffers[b]

[$H_2PO_4^-$]	[HPO_4^{-2}]	pH[c]	3-Chloro, 10^4k	3-Bromo, 10^4k	3-Phenyl, 10^4k	3-Methyl, 10^3k	4-Methyl, 10^3k
				25.0°			
0.065	0.008	5.09	0.503	—	—	—	1.18
0.065	0.011	6.08	0.332	0.162	0.107	0.348	0.915
0.0167	0.0277	7.02	0.296	0.155	0.115	0.342[d]	0.823
0.00125	0.0329	8.26	—	—	—	0.335[d]	—
				34.5°			
0.065	0.011	6.16	0.75	0.461	0.378	0.915	2.03
0.0167	0.0277	7.15	0.757	0.460	0.377	0.913	2.04
				43.5°			
0.065	0.011	6.18	2.16	1.24	1.19	2.12	4.62
0.0177	0.0277	7.2	2.17	1.24	1.20	2.20	4.63
				50.5°			
0.065	0.011	6.21	4.10	2.67	2.25	4.10	7.88
0.0167	0.0277	7.22	4.24	2.79	2.28	4.00	7.62

[a] Phenylcoumarinic acid solutions were 2.60×10^{-5} M. [b] NaCl was added when needed to maintain the ionic strength at $\mu = 0.1$. [c] pH was measured with a Radiometer pH meter and a Sargent combination electrode. [d] 10^3k = 0.339 (pH 7.02) and 0.341 (pH 8.26) when half the buffer concentrations was used.

Table III—Apparent First-Order Rate Constants, k, in sec.$^{-1}$ for Hydrolysis of 6.5×10^{-5} *M* 3- and 4-Substituted Coumarins[a] in Aqueous Solutions

10^3[NaOH][b]	9.0° pH[c]	9.0° 10^3k	13.0° pH[c]	13.0° 10^3k	17.5° pH[c]	17.5° 10^3k	25.0° pH[c]	25.0° 10^3k
				3-Chloro				
2.0	11.38	14.2	11.25	14.3	11.35	3.11	11.20	25.2
5.0	11.65	27.9	11.62	31.9	11.64	62.5	11.68	102
12.5	—	—	—	—	—	—	12.08	194
20.0	12.23	115	12.22	136	12.20	207	12.3	333
				3-Bromo				
2.0	11.34	10.7	11.40	14.3	11.30	20.5	11.20	18.2
5.0	11.64	24.4	11.68	32.3	11.66	46.7	11.65	74.0
7.9	—	—	—	—	—	—	11.80	110
10.0	—	—	—	—	—	—	11.95	180
20.0	12.22	99.3	12.28	110	12.17	165	12.30	347
				3-Phenyl				
4.5	11.47	0.573	11.55	1.20	11.55	1.95	11.55	2.40
5.5	11.58	0.695	11.74	1.70	11.82	2.32	11.70	4.34
20.0	12.17	3.46	12.22	5.45	12.25	7.50	12.18	13.0
	17.5°		25.0°		32.5°		39.0°	
				3-Methyl				
1.5	—	—	—	—	11.23	2.65	11.20	4.41
4.5	11.52	0.870	—	—	11.52	4.87	11.46	6.90
5.5	11.67	1.47	11.88	3.95	—	—	—	—
20.0	12.25	5.15	12.27	12.2	12.18	17.5	12.21	32.0
25.0	—	—	12.33	12.5	—	—	—	—
				4-Methyl				
1.5	—	—	—	—	—	—	11.10	1.73
2.0	11.52	0.355	—	—	11.30	0.878	11.38	2.10
20.0	12.05	0.700	12.08	1.07	12.13	2.95	12.12	5.10
25.0	—	—	12.30	—	—	—	—	—
30.0	—	—	12.40	2.46	—	—	—	—
40.0	—	—	12.53	2.90	—	—	—	—

[a] 3-Phenylcoumarin solutions were 2.60×10^{-5} *M*. [b] NaCl was added when possible to maintain an ionic strength of $\mu = 0.1$. [c] pH values at NaOH concentrations greater than 0.01 were calculated from pH $= pK_w - \log f'$[NaOH] where the activity coefficient, f', was obtained from the literature (2). All other values were measured by a pH meter.

cording spectrophotometer immediately after mixing in the spectrophotometric cell. The absorbance at time zero, A_0, was obtained by graphical extrapolation (1) for the different pH values. This procedure was carried out at several wavelengths (Table IV) at 25°.

Since the rates of lactonization at pH values >7 were sufficiently slow (Table II), the entire spectra could be monitored at 25° and at a given pH immediately after the solutions of the completely solvolyzed coumarins and the appropriate buffer solutions were mixed at 25°. The change of the UV spectrum of 3-bromocoumarinic acid as a function of pH is shown in Fig. 1 for an example. From these data, the pKa$_2$′ of the phenolic group would be estimated (1).

Spectra of Undissociated Coumarinic Acids and Their Anions—Aliquots of 0.022 ml. (0.011 for phenylcoumarin) of a 1.0×10^{-2} *M* alkaline solution of a completely solvolyzed substituted coumarin were mixed with 3.0 ml. of 0.5 *N* HCl. The rapid change in the absorbance of the 7.30×10^{-5} *M* solutions was automatically recorded with time at each 10-nm. interval between 220 and 380 nm. at 25°. The absorbances at time zero, A_0, were then obtained by graphical extrapolation (1), and these extrapolated spectra of the substituted undissociated coumarinic acids are given in Figs. 2–6.

Table IV—Spectrophotometrically Determined pKa′ Values of 6.5×10^{-5} *M* Coumarinic Acids at 25°

Derived from the Substituted Coumarin	Wavelength, nm. for pKa$_1$′	Wavelength, nm. for pKa$_2$′	pKa$_1$′	pKa$_2$′
3-Bromo	255, 330	230, 295, 340	1.80	9.35
3-Chloro	255, 330	230, 295, 335	2.05	9.60
3-Phenyl	280, 310	245, 310	3.15	9.72
3-Methyl	255, 330	235, 330	3.63	10.00
H[b]	250, 280, 320	238, 290, 335	4.00[b]	9.95[b]
4-Methyl	270, 305, 310	270, 300, 330	4.80	10.70

[a] Phenylcoumarin solutions were 2.60×10^{-5} *M*. [b] See *Reference 1;* potentiometric titration gave 4.00 and 9.90 (1).

The spectra of their monoanions were obtained in phosphate buffer at pH 7.2. The spectra of their dianions were obtained in 0.1 *N* NaOH. These latter spectra (Figs. 2–6) did not require an extrapolation procedure since there was no significant lactonization during the time interval required to read such spectra under these experimental conditions. The spectral curves for the unsubstituted coumarinic acid were given previously (1).

RESULTS AND DISCUSSION

Estimation of Apparent pKa′ Values—The apparent pKa′ values for the variously substituted coumarinic acids of Table IV were

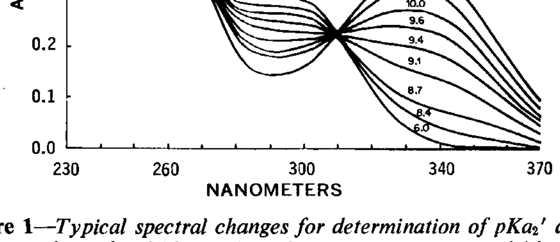


Figure 1—*Typical spectral changes for determination of pKa$_2$′ as a function of pH for 6.25×10^{-5}* M *bromocoumarinic acid (derived from 3-bromocoumarin) in phosphate, borate, and carbonate buffers and in NaOH. The pH values are as indicated.*

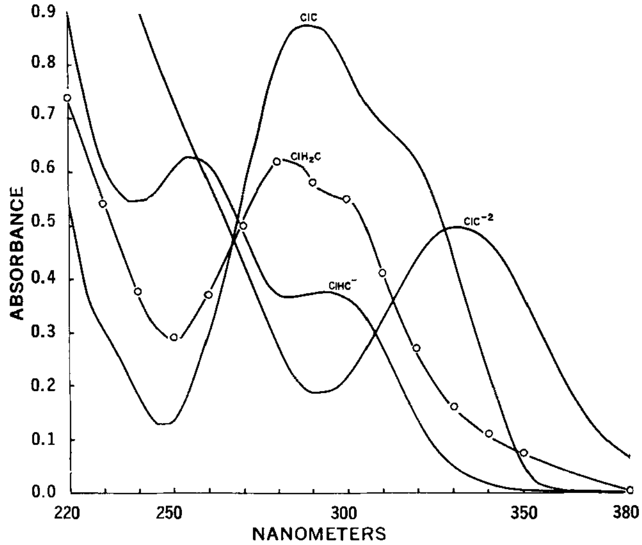


Figure 2—*UV spectra of 7.30 × 10^{-5}* M *undissociated 3-chlorocoumarinic acid, ClH_2C (based on extrapolated time-zero absorbances after introduction of the sodium 3-chlorocoumarinate into 0.5* N *HCl); 3-chlorocoumarinate monoanions, $ClHC^-$ (in phosphate buffer, pH 7.2); 3-chlorocoumarinate dianions, ClC^{-2} (in 0.1* N *NaOH); and 3-chlorocoumarin, ClC (in 0.5* N *HCl). The numbering system used refers to the parent coumarin.*

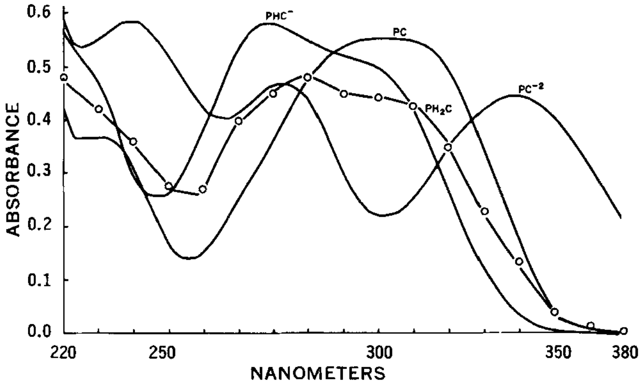


Figure 4—*UV spectra of 3.65 × 10^{-5}* M *undissociated 3-phenylcoumarinic acid, PH_2C (based on extrapolated time-zero absorbances after introduction of the sodium 3-phenylcoumarinate into 0.5* N *HCl); 3-phenylcoumarinate monoanions, PHC^- (in phosphate buffer, pH 7.2); 3-phenylcoumarinate dianions, PC^{-2} (in 0.1* N *NaOH); and 3-phenylcoumarin, PC (in 0.5* N *HCl). The numbering system used refers to the parent coumarin.*

estimated in the manner discussed previously (1) for the several cited wavelengths by use (3) of Eq. 2:

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

where the A_0 values are the time-zero estimates of absorbances at a given pH value, the A_{H_2C} value is the asymptotic absorbance in increasingly acidic solutions and is assigned to the absorbance of the 6.5 × 10^{-5} *M* undissociated substituted coumarinic acid (except at a concentration of 2.6 × 10^{-5} *M* for the phenyl derivative), and A_{HC^-} is the asymptotic absorbance achieved in neutral solution and is assigned to the absorbance of the respective substituted coumarinate monoanion of these same concentrations. These absorbances, A_{HC^-} and A_{H_2C}, at different wavelengths also may be obtained from Figs. 2–6.

It is evident (Table IV) that substituents with a negative inductive effect (−I), such as halogens, increase the acidity of the carboxylic acid groups in the acids derived from the 3-substituted coumarins. The methylcoumarinic acids have higher pKa_1' values because of lessened electron-withdrawing properties (+I) of the methyl group. However, the acid derived from 3-methylcoumarin has a lower pKa_1' than the unsubstituted coumarinic acid, whereas the acid derived from 4-methylcoumarin has a higher pKa_1'. A similar effect has been observed for *o*-methylbenzoic acid (pKa′ 3.91) and *m*-methylbenzoic acid (pKa′ 4.27) as compared to benzoic acid (pKa′ 4.20) and may imply that the disruption of resonance effects, which normally stabilizes the undissociated acid of a conjugated carboxyl, relates the pKa′ values of acids derived from the 3-substituted coumarins (4–6) to these of *ortho*-substituted aromatic acids (7–11). In essence, this implies that these α-substituted coumarinic acids disrupt the coplanarity of the carboxyl with the conjugated systems and disrupt the acid-weakening resonance which can occur more readily in the absence of such vicinal substituents (8).

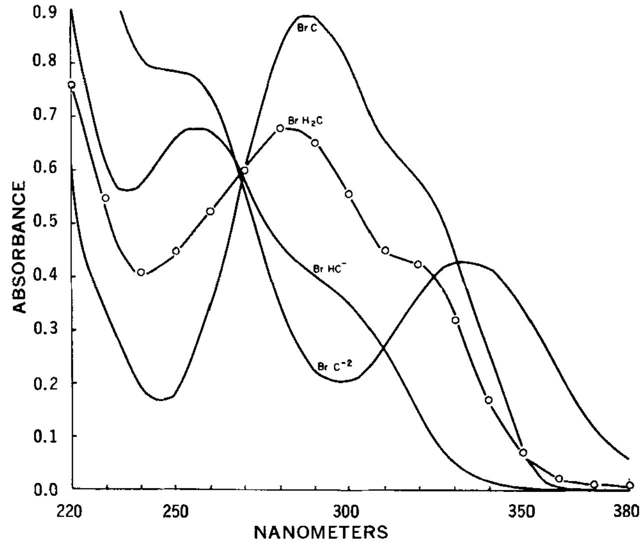


Figure 3—*UV spectra of 7.30 × 10^{-5}* M *undissociated 3-bromocoumarinic acid, BrH_2C (based on extrapolated time-zero absorbances after introduction of the sodium 3-bromocoumarinate into 0.5* N *HCl); 3-bromocoumarinate monoanions, $BrHC^-$ (in phosphate buffer, pH 7.2); 3-bromocoumarinate dianions, BrC^{-2} (in 0.1* N *NaOH); and 3-bromocoumarin, BrC (in 0.5* N *HCl). The numbering system used refers to the parent coumarin.*

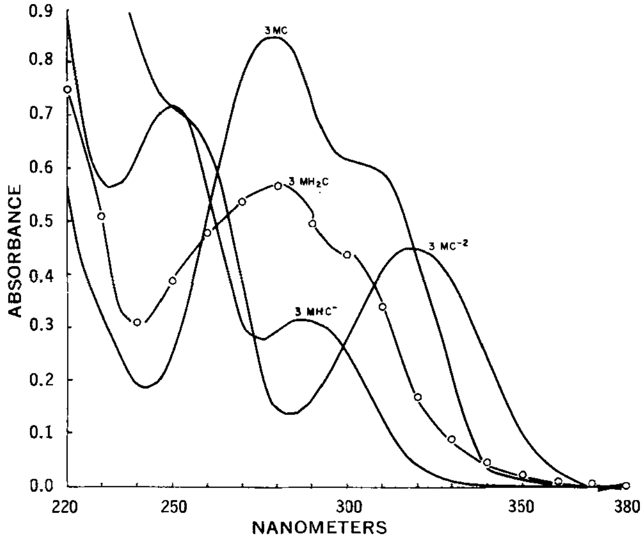


Figure 5—*UV spectra of 7.30 × 10^{-5}* M *undissociated 3-methylcoumarinic acid, $3MH_2C$ (based on extrapolated time-zero absorbances after introduction of the sodium 3-methylcoumarinate into 0.5* N *HCl); 3-methylcoumarinate monoanions, $3MHC^-$ (in phosphate buffer, pH 7.2); 3-methylcoumarinate dianions, $3MC^{-2}$ (in 0.1* N *NaOH); and 3-methylcoumarin, 3MC (in 0.5* N *HCl). The numbering system used refers to the parent coumarin.*

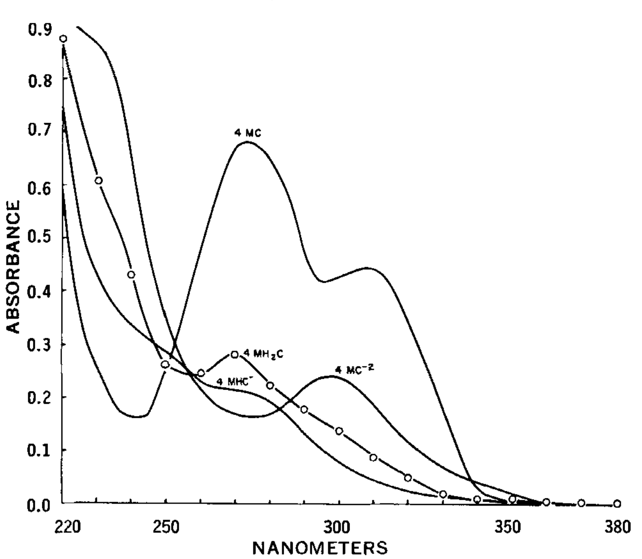


Figure 6—*UV spectra of 7.30 × 10^{-5}* M *undissociated 4-methylcoumarinic acid, $4MH_2C$ (based on extrapolated time-zero absorbances after introduction of the sodium 4-methylcoumarinate into 0.5* N *HCl); 4-methylcoumarinate monoanions, $4MHC^-$ (in phosphate buffer, pH 7.2); 4-methylcoumarinate dianions, $4MC^{-2}$ (in 0.1* N *NaOH); and 4-methylcoumarin, 4MC (in 0.5* N *HCl). The numbering system used refers to the parent coumarin.*

The pKa_1' values of the coumarinic acids derived from the 3-substituted coumarins of Table IV are plotted against the pKa′ values of the comparably *ortho*-substituted benzoic acids (4–6) in Fig. 7 [the pKa_1' value of the coumarinic acid derived from 4-methylcoumarin is plotted against that of *m*-methylbenzoic acid (4–6)]. The reasonably linear relation is demonstrated in Fig. 7 and can be fitted by the expression:

pKa_1' (coumarinic acid from 3-substituted coumarin)

= 1.85 pKa′ (comparably substituted *o*-benzoic acid) − 3.5 (Eq. 3)

The spread among the pKa′ values of the *meta*- (Br, 3.81; Cl, 3.83; and methyl, 4.27) and *para*-substituted benzoic acids (Br, 3.97; Cl, 3.98; and methyl, 4.37) is much less, so that plots of the pKa_1' values of the coumarinic acids derived from 3-substituted coumarins against the pKa′ of comparably substituted *meta*- and *para*-benzoic acids have considerably greater slopes. The slope is 3.64 with an intercept value of −11.9 for the *meta*-substituted benzoic acids, and the point for unsubstituted benzoic and coumarinic acids is widely displaced from the plot.

The pKa_2' values assigned to the phenolic groups of the coumarinic acids derived from the 3-substituted coumarins (Table IV) are also reasonably, linearly related to the pKa_1' of coumarinic acid and to pKa′ values of the similarly substituted benzoic acid, no matter which series of the latter (*ortho*, *meta*, or *para*) is used for the plot. The only widely outlying value in such plots is for the compound derived from 4-methylcoumarin. This implies that the inductive effect of the substituents is readily transmitted through the aryl conjugated system to the phenolic position on the ring (12), since the decrease in pKa_2' cannot be assigned to the increased interaction of the less basic carboxylate anion produced by electron-withdrawing substituents with a phenolic group of invariant acidity.

Log *k*–pH Profiles for Lactonization of Substituted Coumarinic Acids and Their Anions—No significant buffer catalytic effects were observed in phosphate buffer (1) (see *Footnote c* in Table II). The apparent first-order rate constants for the lactonization of the substituted coumarinic acids and their anions should conform to the previously derived (1) equation:

$$k = \{k_{H^+}[H^+] + k_{H_2O}\}f_{H_2C} + \{k_{H^+}'[H^+] + k_{H_2O}'\}f_{HC^-} \quad \text{(Eq. 4)}$$

where the k_i are the individual microscopic rate constants, and

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

and

$$f_{HC^-} = \frac{[HC^-]}{[H_2C] + [HC^-]} = \frac{K_{a_1}'}{[H^+] + K_{a_1}'} \quad \text{(Eq. 6)}$$

are the fractions of the substituted undissociated acid, H_2C, and its monoanion, HC^-, respectively.

Since $k_{H_2O}f_{H_2C}$ and $k_{H^+}'[H^+]f_{HC^-}$ are kinetically equivalent, Eq. 4 can be reduced to:

$$k = \{k_{H^+}[H^+] + k_{H_2O}\}f_{H_2C} + k_{H_2O}'f_{HC^-} \quad \text{(Eq. 7)}$$

An asymptotic slope of unity is approached with decreasing pH in the log *k*–pH profile for each compound (Figs. 8–10) since, with increasing acidity or $[H^+]$, Eq. 7 approaches

$$k = k_{H^+}[H^+] \quad \text{(Eq. 8)}$$

and the second-order rate constants, k_{H^+} (Table V), can be estimated from the intercepts of log *k versus* pH plots (Figs. 8–10) of negative unit slopes in the low pH regions. The value for k_{H_2O} in Eq. 7 was estimated in the pH region below neutrality, where the contribution of the term $k_{H_2O}'f_{HC^-}$ is negligible, by subtracting the calculated $k_{H^+}[H^+]f_{H_2C}$ values from the observed first-order rate

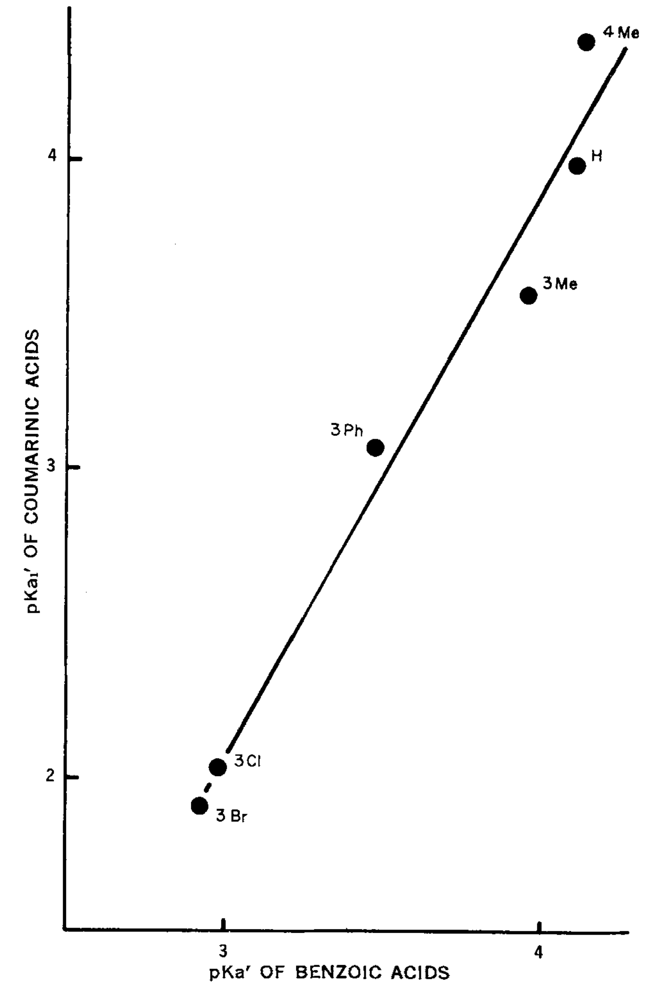
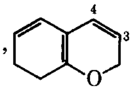
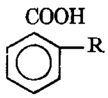


Figure 7—*Plot of pKa′ values of coumarinic acids derived from the 3- or 4-substituted coumarins, i.e.,*  *, against the pKa′ values of* ortho-*benzoic acids*  *with the same substituents. The exception is that the pKa′ for the acid derived from 4-methylcoumarin is plotted against the pKa′ for* m-*toluic acid.*

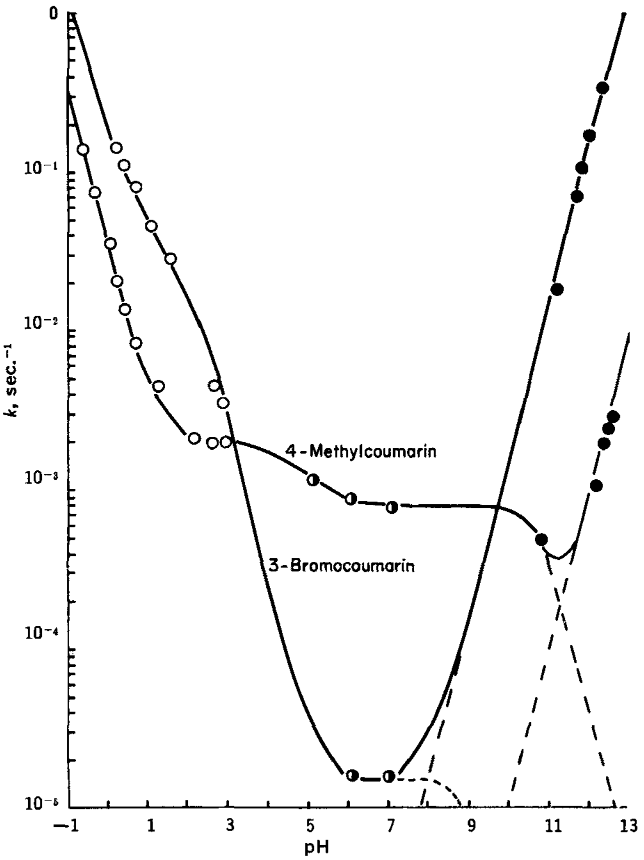


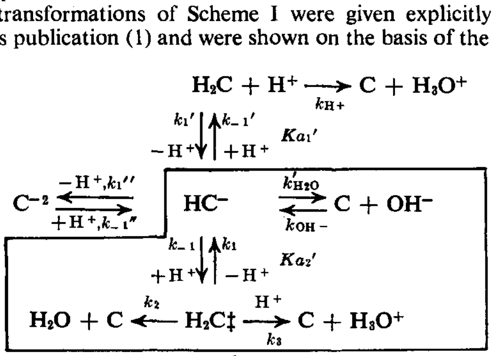
Figure 8—*Log* k-*pH profiles at 25° for hydrolyses of 3-bromocoumarin and 4-methylcoumarin and lactonization of their respective coumarinic acids. Key:* ○, *lactonization in hydrochloric acid;* ◑, *lactonization in phosphate buffer; and* ●, *hydrolysis in sodium hydroxide solutions.*

constants, so that for pH values less than 7

$$k - k_{H^+}[H^+]f_{H_2C} = k_{H_2C}f_{H_2C} \qquad \text{(Eq. 9)}$$

Various pKa_1' values were assumed for each compound for the calculations of the f_{H_2C} and f_{HC^-} values (Eqs. 5 and 6) to give the best fits for the log k-pH plots of Figs. 8–10. The apparent kinetic pKa_1' values for the coumarinic acids derived from the substituted coumarins were: 3-chloro, 1.52; 3-bromo, 1.7; 3-phenyl, 1.8; 3-methyl, 2.96; and 4-methyl, 3.67. The rate constants, k_{H^+}, k_{H_2O}, and k'_{H_2O}, of Eq. 7 that give best fits in Figs. 8–10 are given in Table V. The apparent kinetic pKa_1' values differ markedly from the respective spectral pKa_1' values (Table IV), in the same manner that the apparent kinetic pKa_1' of 3 and the spectral and potentiometric pKa_1' values of 4 differed for unsubstituted coumarinic acid (1). These discrepancies can be rationalized (1) on the basis of Scheme I for the lactonization of a coumarinic acid, H_2C, in equilibrium with its monoanion, HC^-, and dianion, C^{-2}, to its respective coumarin, C, where $H_2C‡$ is the monoester of an orthoacid in Scheme II. The blocked area in Scheme I includes the transformations expanded in Scheme II.

The transformations of Scheme I were given explicitly in the previous publication (1) and were shown on the basis of the steady-



Scheme I

state assumption, $d[H_2C‡]/dt \sim 0$, to result in the kinetic dependency:

$$k = k_{H^+}[H^+]f_{H_2C} + k'_{H_2O}f_{HC^-} + \frac{(k_2 + k_3[H^+])K_{a_1}'k_{-1}}{k_1 + k_2 + k_3[H^+]} f_{H_2C} \qquad \text{(Eq. 10)}$$

which, on comparison to Eq. 7, states that

$$\frac{(k_2 + k_3[H^+])K_{a_1}'k_{-1}}{k_1 + k_2 + k_3[H^+]} = k_{H_2O} \qquad \text{(Eq. 11)}$$

The values of k_{H^+} were readily obtained from the intercepts of the linear asymptotes of the log k-pH plots, with a slope of -1 at the pH values below 2 (Figs. 8–10). The value of k'_{H_2O} was estimated from the plateau in the log k-pH profile reached in the neutral pH region, 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 defined (1) in the mildly acidic pH region from consideration of Eqs. 7 and 11 as:

$$k' = k - (k_{H^+}[H^+]f_{H_2C} + k'_{H_2O}f_{HC^-}) = \frac{(k_2 + k_3[H^+])k_{-1}K_{a_1}'}{(k_1 + k_2) + k_3[H^+]} f_{H_2C}$$

$$= \frac{Q + P[H^+]}{1 + P[H^+]} k_{-1}K_{a_1}'f_{H_2C} \qquad \text{(Eq. 12)}$$

where

$$Q = k_2/(k_1 + k_2) \qquad \text{(Eq. 13)}$$

and

$$P = k_3/(k_1 + k_2) \qquad \text{(Eq. 14)}$$

Thus, at high $[H^+]$ concentrations or at pH values less than 2, where

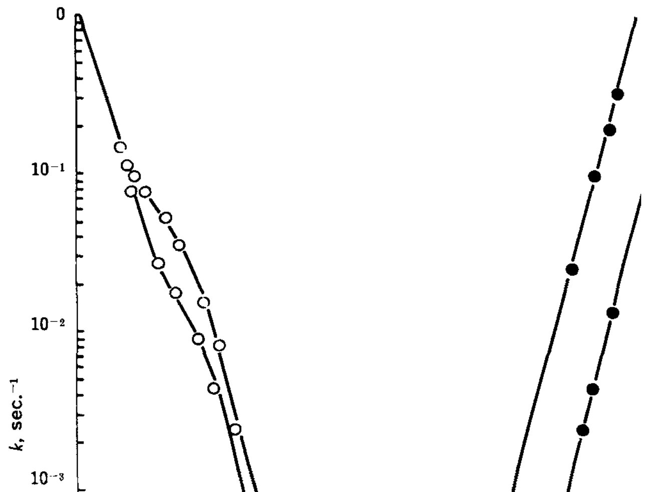
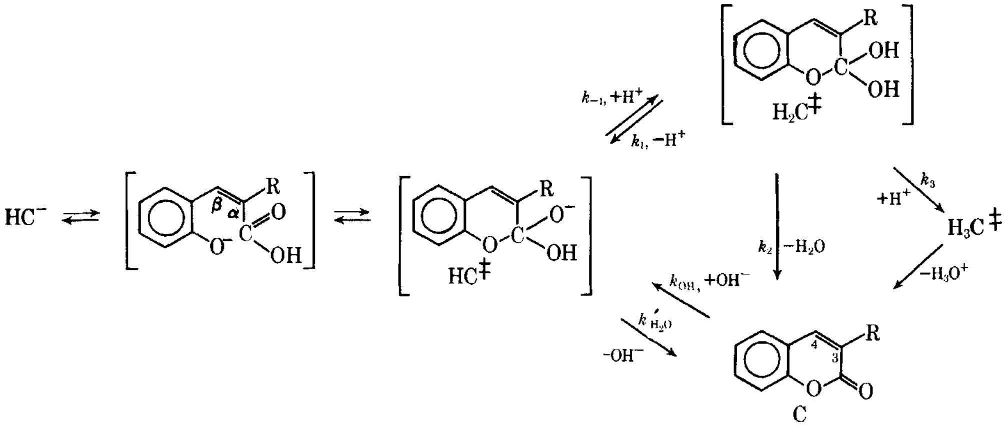


Figure 9—*Log* k-*pH profiles at 25° for hydrolyses of 3-chlorocoumarins and 3-phenylcoumarins and lactonization of their respective coumarinic acids. Key:* ○, *lactonization in hydrochloric acid;* ◑, *lactonization in phosphate buffer; and* ●, *hydrolysis in sodium hydroxide solutions.*



Scheme II

$f_{H_2C} \rightarrow 1$ and

$$(Q + P[H^+])/(1 + P[H^+]) = (k_2 + k_3[H^+])/(k_1 + k_2 + k_3[H^+]) \rightarrow 1 \quad \text{(Eq. 15)}$$

then,

$$\lim_{[H^+]\rightarrow\infty} k' = k_{-1}K_a' = k_{H_2O} \quad \text{(Eq. 16)}$$

and k_{-1} may be estimated (Table V) from the known K_{a_1}' and the apparent k_{H_2O} values, where the latter was obtained from the best fit of Eq. 7.

Thus, at low $[H^+]$ concentrations, possibly at pH values greater than 6, where $k_3[H^+] \ll k_2$,

$$\lim_{[H^+]\rightarrow 0} k' = \left(\frac{k_2}{k_1 + k_2}\right) k_{-1}K_{a_1}'/f_{H_2C} = Qk_{-1}K_{a_1}'/f_{H_2C} \rightarrow Qk_{-1}[H^+] \quad \text{(Eq. 17)}$$

since, from Eq. 4, $f_{H_2C} \rightarrow [H^+]/K_{a_1}'$ at $[H^+] \rightarrow K_{a_1}'$. Thus, Q, as defined in Eq. 13, may be estimated (Table V) since k_{-1} (Eq. 16), K_{a_1}', and $[H^+]$ are known.

At intermediate pH values, possibly at pH values in the range of the pKa_1', the more exact Eq. 12 holds, where k_{-1} (Eq. 16) and $Q = k_2/(k_1 + k_2)$ (Eq. 17) have been estimated (Table V) and all other factors such as $[H^+]$, K_{a_1}', and f_{H_2C} (Eq. 5) are known. The values of P may be calculated from

$$P = \frac{k' - Qk_{-1}K_{a_1}'/f_{H_2C}}{(k_{-1}K_a'/f_{H_2C} - k')[H^+]} \quad \text{(Eq. 18)}$$

and are given in Table V.

The curves drawn through the points in Figs. 8–10 are based on the evaluated values of Q, P, k_{-1}, k_{H^+}, and k'_{H_2O} as given in Table V and may be compared with the curve previously published for coumarin (1).

Estimates of k_{H^+} and k'_{H_2O} (Table V) were determined from studies at various temperatures (Tables I and II). The thermodynamic parameters obtained from the slopes and intercepts of the Arrhenius plots are given in Table VI.

Hydrolyses of Substituted Coumarins and Monoanion and Dianion–Coumarin Equilibria—The plots of log k *versus* pH for the hydrolyses of the coumarins to coumarinate dianions are linear and of the slope of unity above the pH = $pKa_2' + 1.5$ (Figs. 8–10) in accordance with

$$-\frac{d[C]}{dt} = \frac{d[H_2C]_T}{dt} = k[C] = k_{OH^-}[OH^-][C] \quad \text{(Eq. 19)}$$

Thus, after logarithmic transformation,

$$\log k = \log k_{OH^-} - pK_w + pH \quad \text{(Eq. 20)}$$

The values of k_{OH^-} (Table V) can be estimated from the extrapolated intercepts of the alkaline branch of the profiles (Figs. 8–10) for the several temperatures studied. The thermodynamic parameters (Table V) were estimated from the slopes and intercepts of the Arrhenius plots.

In the pH region of the pKa_2' of the various coumarinic acids (Table IV), the apparent first-order rate constant, k, was expected to be the sum or the backward and forward rate constants (1) for hydrolysis and lactonization, respectively, since k was estimated from Eq. 1 and in this region the asymptotic absorbance is the sum of the equilibrated lactone, monoanion, and dianion. Thus,

$$k = k'_{H_2O}f_{HC^-} + k_{OH^-}[OH^-] \quad \text{(Eq. 21)}$$

where hydroxide-ion attack on coumarin may form HC‡ (Scheme II) and thus HC^- (Schemes I and II) in the reverse reaction of the net pH-independent loss of hydroxide ion for the coumarinate monoanion to yield coumarin.

The dashed lines coming from the left in Figs. 8–10 show the decrease in the $k'_{H_2O}f_{HC^-}$ term for the lactonization of the mono-

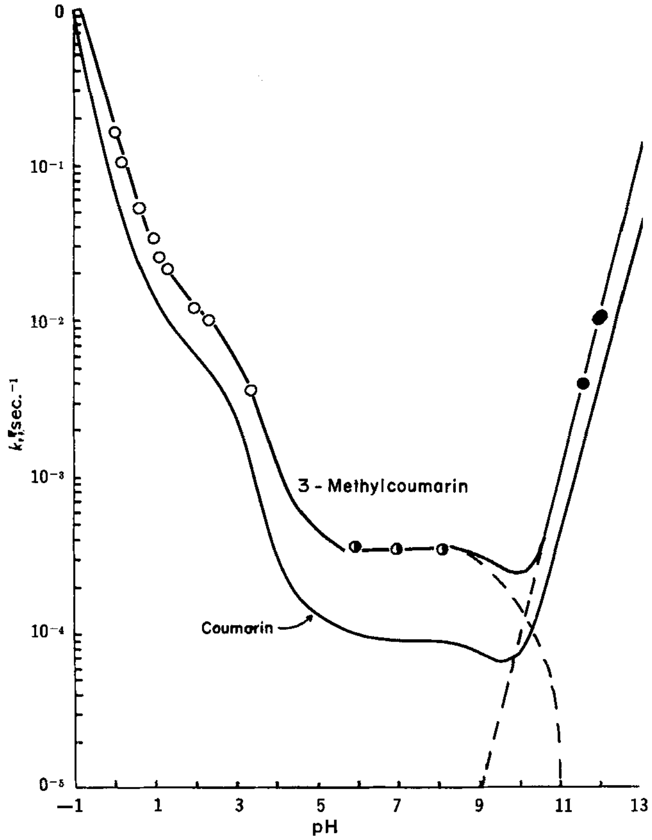


Figure 10—*Log* k–*pH profiles at 25° for hydrolyses of 3-methylcoumarin and lactonization of its coumarinic acid. Key:* ○, *lactonization in hydrochloric acid;* ◑, *lactonization in phosphate buffer; and* ●, *hydrolysis in sodium hydroxide solutions. The solid line is given for coumarin (1) to serve as a reference.*

Table V—Microscopic Rate Constants[a] for Lactonization of Coumarinic Acids[b] and Hydrolysis of Coumarins

Temperature	3-Chloro	3-Bromo	3-Phenyl	3-Methyl	H[c]	4-Methyl
			$10^2k_{H^+}$			
8.5°	2.60	3.50	3.75	7.60	—	0.890
10.0°	—	—	—	—	2.20	—
12.5°	4.20	5.50	5.50	9.75	—	1.20
17.5°	7.00	9.30	8.40	15.8	4.50	2.00
25.0°	14.0	17.0	18.0	25.0	10.0	3.60
			$10^3k_{H_2O}$			
25.0°	65.0	50.0	18.0	14.0	5.0	2.1
			$10^5k'_{H_2O}$			
10.0°	—	—	—	—	0.80	—
17.5°	—	—	—	—	2.40	—
25.0°	3.00	1.50	1.10	34.2	9.20	85.0
34.5°	7.53	4.60	3.78	91.5	—	203
43.5°	21.6	12.4	11.9	259	—	462
50.5°	41.7	27.3	22.6	405	—	775
			k_{OH^-}			
9.0°	6.40	5.50	0.220	—	—	—
10.0°	—	—	—	—	0.140	—
13.0°	8.00	6.20	0.340	—	—	—
17.5°	12.5	10.3	0.400	0.290	0.250	0.060
25.0°	18.0	16.0	0.800	0.520	0.450	0.100
32.5°	—	—	—	1.20	—	0.220
39.0°	—	—	—	2.10	—	0.300
			k_{-1}			
25.0°	7.30	3.14	25.5	59.8	50.0	133
			Q			
25.0°	0.274	0.795	0.0392	0.217	0.080	0.90
			$10^{-2}P$			
25.0°	0.23	0.44	0.66	6.07	8.8	92
			$10^3Q/P = 10^3k_2/k_3$			
25.0°	12	18	0.59	0.36	0.09	0.10

[a] Apparent first-order rate constants, k, in sec.$^{-1}$ for lactonization can be defined in terms of the various constants as:

$$k = k_{H^+}[H^+]f_{H_2C} + k_{H_2O}f'_{H_2C} + k'_{H_2O}f_{HC^-} = k_{H^+}[H^+]f_{H_2C} + \frac{Q + P[H^+]}{1 + P[H^+]} k_{-1}K_{a_1}'f_{H_2C} + k'_{H_2O}f_{HC^-}$$

where

$$\frac{Q + P[H^+]}{1 + P[H^+]} = \frac{(k_2 + k_3[H^+])}{k_1 + k_2 + k_3[H^+]}$$

$Q = k_2/(k_1 + k_2)$, 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 profiles on the presumption of an apparent kinetic pKa_1' different from the spectral pKa_1' (Table V). $f_{H_2C} = [H^+]/([H^+] + K_{a_1}')$ and $f_{HC^-} = K_a'/([H^+] + K_{a_2}')$ in the pH region <(pKa_1' + pKa_2')/2 and $f_{HC^-} = [H^+]/([H^+] + K_{a_2}')$ in the pH region > (pKa_1' + pKa_2')/2. All rate constants are in l./mole-sec., except k_{H_2O} and k'_{H_2O} which are in sec.$^{-1}$. [b] The substituents are numbered with respect to the parent coumarins to avoid confusion. If numbered with respect to the coumarinic acid series, the numbers would have to be diminished by a unit, or α and β could be used for the coumarinic acids derived from 3- and 4-substituted coumarins, respectively. [c] Included for comparison; see *Reference 1.*

anion, HC^-, where

$$f_{HC^-} = \frac{[H^+]}{[H^+] + K_{a_2}'} \quad \text{(Eq. 22)}$$

for pH values > (pKa_1' + pKa_2')/2.

The dashed lines coming from the right in Figs. 8–10 show the decrease of the k_{OH}-$[OH^-]$ term of Eq. 21 with decreasing pH. The equilibrium constant, K, for the monoanion and dianion–coumarin equilibria was defined (1) as

$$K = \frac{[C]_{eq.}}{[HC^-]_{eq.} + [C^{-2}]_{eq.}} = \frac{k'_{H_2O}f_{HC^-}}{k_{OH}\text{-}[OH^-]} \quad \text{(Eq. 23)}$$

where the subscript "eq." refers to the respective equilibrium concentrations and where the amount of undissociated acid, H_2C, is assumed to be negligible in the pH region where the coumarins exist in equilibrium with their nonlactonized open forms. Some values of this equilibrium constant at various pH values at 25° are given in Table VII.

Substituent Effects on Microscopic Rate Constants—Substituent Effects on Acid-Catalyzed Lactonization, k_{H^+}—It appears that any of the studied substituents in the α-position of coumarinic acid (*i.e.*, derived from coumarins substituted in the 3-position) accelerates hydrogen-ion-catalyzed lactonization (k_{H^+}, Table V). This contrasts with the steric inhibition of the rates of acid-catalyzed esterifications of *ortho*-substituted benzoic acids (9) but is consistent with the acceleration by similar *ortho*-substituents of the lactonization of 6- (or 3-) substituted 2- (hydroxymethyl-)benzoic acids (11).

Reactivity in acid-catalyzed ester formation is decreased by conjugation of the carbonyl group of the esterifiable carboxyl with aromatic rings or double bonds (13) and is a phenomenon similar to the decreased acidity of a conjugated carboxyl group by such resonance interaction (8). Space-filling substituents on adjacent carbons (as in α-substituted coumarinic acids) or on neighboring

Table VI—Arrhenius Energies of Activation, ΔE_a, and Entropies of Activation, $\Delta S‡$

	k_{H^+}	k'_{H_2O}	k_{OH^-}	k_{H^+}	k'_{H_2O}	k_{OH^-}
		ΔE_a(kcal.)[a]			$\Delta S‡$(e.u.)[b]	
3-Chloro	16.5	21.2	11.8	−9.0	−11.2	−15.0
3-Bromo	16.4	22.3	12.9	−8.8	−7.7	−15.0
3-Phenyl	15.3	23.2	10.6	−11.8	−5.2	−28.7
H[c]	17.8	22.8	13.2	−5.5	−3.0	−18.0
3-Methyl	12.6	19.1	16.3	−25.6	−12.4	−23.3
4-Methyl	13.9	17.3	14.8	−20.5	−16.9	−28.5

[a] ΔE_a is obtained from the slopes of the Arrhenius plots of log k *versus* $1/T$, where T is the absolute temperature. [b] Where $k = (kT/h)e^{\Delta S‡/R}\,e^{-\Delta H‡/RT}$, and $\Delta H‡ = \Delta E_a - 0.6$. [c] Included for comparison; see *Reference 1.*

Table VII—Equilibrium Constants[a] for Monoanion and Dianion–Coumarin Equilibria as Function of pH at 25°

pH	3-Chloro	3-Bromo	3-Phenyl	Coumarin	3-Methyl	4-Methyl
8.0	1.62	8.95×10^{-1}	13.5	2.10×10^{2}	6.16×10^{2}	8.50×10^{3}
9.0	1.28×10^{-1}	6.50×10^{-1}	1.15	1.83×10^{1}	4.10×10^{1}	8.33×10^{2}
9.5	2.86×10^{-2}	1.99×10^{-2}	2.70×10^{-1}	4.80	7.08	2.53×10^{2}
10.0	4.73×10^{-3}	1.69×10^{-3}	4.62×10^{-2}	9.60×10^{-1}	9.24×10^{-1}	7.06×10^{1}
10.5	5.8×10^{-4}	1.96×10^{-4}	4.05×10^{-3}	1.40×10^{-1}	1.04×10^{-1}	1.65×10^{1}
11.0	6.22×10^{-6}	2.03×10^{-5}	6.61×10^{-4}	1.70×10^{-2}	1.08×10^{-2}	2.80
12.0	6.03×10^{-8}	2.10×10^{-7}	7.15×10^{-6}	1.30×10^{-4}	1.09×10^{-4}	4.08×10^{-2}

[a]
$$K = \frac{[C]_{eq.}}{[HC^-]_{eq.} + [C^{-2}]_{eq.}} = \frac{k'_{H_2O} f_{HC^-}}{k_{OH^-}[OH^-]}$$

where $[C]_{eq.}$ is the equilibrium concentration of coumarin; $[HC^-]_{eq.}$ and $[C^{-2}]_{eq.}$ are the equilibrium concentrations of the coumarinate monoanion and dianion, respectively; and the fraction of the total coumarinic acid, $[HC^-] + [C^{-2}]$, as the monoanion is $f_{HC^-} = ([H^+]/[H^+] + K_{a_2}')$ and the fraction as the dianion is $f_{C^{-2}} = K_{a_2}'/([H^+] + K_{a_2}')$.

carbons (as in *ortho*-substituted benzoic acids) interfere with the coplanarity of carboxyl oxygens and the conjugated system, where such coplanarity is so necessary for resonance interaction. The result is to force these carboxyl oxygens out of the plane of the conjugated system, thus diminishing "the acid-weakening" resonance effect (8), and to make it more difficult to produce the alternative protonated resonant forms which serve to decrease the concentrations of protonated carboxyl forms necessary for the mechanistic sequence in acid-catalyzed esterification.

This steric effect that weakens resonance is not widely different from that which would be predicted (14) and is consistent with the order of reactivity for k_{H^+} (Table V), the rate constant for the acid-catalyzed lactonization of coumarinic acids derived from substituted coumarins: 3-methyl > 3-phenyl ~ 3-bromo > 3-chloro > H > 4-methyl. The 3-methyl and 3-phenyl compounds may be transposed from the prediction.

Substituent Effects on k_{-1}, the Rate Constant Representative of Both Degree of Cyclization of Coumarinate Monoanion (HC^-) and Rate of Proton Association of Resultant Anionic Orthoacid Intermediate ($HC‡ + H \rightarrow H_2C‡$)—The observed sequence for k_{-1}, representative of the degree of cyclization of the coumarinate monoanion, HC^-, and the rate of association of the resultant orthoacid monoanion, HC‡, with a proton to form the reactive orthoacid intermediate, $H_2C‡$ [Schemes I and II and (1)], can be attributed mainly to inductive effects. The k_{-1} sequence (Table V) for the coumarinic acids derived from substituted coumarins is: 4-methyl > 3-methyl ≥ H > 3-phenyl ≫ 3-chloro > 3-bromo (where the double inequality represents a 10-fold greater magnitude). Assuredly, electron-withdrawing groups such as halogens in the α-position (derived from 3-substituted coumarins) would inhibit the phenate-anion attack on a more electronegative carboxyl carbon and also would increase the acidity of the resultant orthoacid ($H_2C‡$) to result in lessened associations of the orthoacid anions (HC‡) with protons. Both of these effects in the sequence of Schemes I and II would result in lessened amounts of reactive intermediate, $H_2C‡$, with increasing electron-withdrawing substituents affecting the electronegativity of the carboxyls of the coumarinic acids.

Substituent Effects on k'_{H_2O}, the Rate Constant for Lactonization of Coumarinate Monoanion—The sequence of reactivities for k'_{H_2O} for coumarinate monoanions derived from the substituted coumarins is (Table V): 4-methyl > 3-methyl > H > 3-chloro > 3-bromo ≥ 3-phenyl and is not too different than the sequence for k_{-1}. This is reasonable since both rate constants may be affected by electron-withdrawing groups inhibiting the phenate-anion attack on a less positive carboxyl carbon (Schemes I and II). The subsequent step in the solvolytic process characterized by k'_{H_2O}, the possible loss of hydroxyl ion from the resultant anionic orthoacid to give the respectively substituted coumarin (see Schemes I and II), will certainly be more favored by more electron-donating groups such as alkyls.

Substituent Effects on $Q/P = k_2/k_3$, the Ratios of Rate Constants of Dehydration, $H_2C‡ \xrightarrow[-H_2O]{k_2} C$, to Protonation, $H_2C‡ \xrightarrow[H^+]{k_3} H_3C‡ \xrightarrow{-H_3O^+} C$, for Reactions of Orthoacid Reaction Intermediate—The magnitudes of these ratios decrease in the order: 3-bromo ≥ 3-chloro ≫ 3-phenyl > 3-methyl ≥ H ~ 4-methyl (Table V). This sequence is consistent with the fact that with constant rates of dehydration, the reaction pathway (Schemes I and II) dependent on the ease of protonation of the orthoacid, $H_2C‡$, should increase with the greater electron-donating properties of substituents such as alkyls. The phenyl compound is slightly displaced from prediction in this sequence, but its lessened k_2/k_3 ratio may be rationalized. Although the phenyl substituent decreases the rate of protonation, k_3, of the orthoacid, $H_2C‡$, the possible spontaneous dehydration, k_2, may be retarded by an intramolecular association of the carboxyl carbon's alcohol groups and the adjacent phenyl ring and thus minimize the k_2/k_3 ratio change.

Substituent Effects on k_{OH^-}, the Bimolecular Rate Constant for Hydroxyl-Ion-Catalyzed Solvolysis of Coumarins—These rate constants decrease in the order: 3-chloro ≥ 3-bromo ≫ 3-phenyl > 3-methyl ~ H > 4-methyl (Table V). The electron-withdrawing halogen and phenyl substituents facilitate the attack of hydroxyl ions on the coumarin carboxyl carbon, whereas electron-donating alkyl substituents are less favorable. Steric hindrance of this attack may be significantly important only for the 3-phenylcoumarin and could account for the relatively large decrease in its solvolytic rate constant (Table V). As has been already found for hydrolysis in dioxane (30%) and water mixtures (1), the 3-methyl derivative appears to hydrolyze faster than coumarin at 17.5 and 25.0°. However, it has the higher heat of activation; at lower temperatures, *e.g.*, < 15°, the 3-methylcoumarin is relatively much less susceptible to hydroxyl-ion attack.

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