The Lactonization of Ring-Substituted Coumarinic Acids. Structural Effects on the Partitioning of Tetrahedral Intermediates in Esterification[1a]

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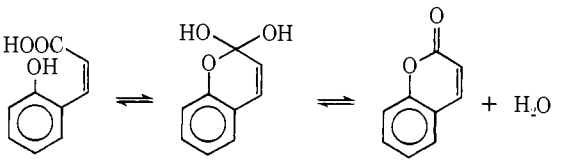
Abstract: The kinetics and equilibria of the lactonization of 13 ring-substituted coumarinic acids have been studied in aqueous solution at pH 0–6 and 30°. The pH–rate profiles have been interpreted in terms of a mechanism including cationic and neutral tetrahedral addition intermediates in acid–base equilibrium. At low pH, the formation of the intermediates *via* acid-catalyzed and uncatalyzed pathways is rate determining. With 12 of the substrates, there occurs, at higher pH, a change in rate-determining step to breakdown of the intermediates *via* acid-, water-, and base-catalyzed paths. The pH values at which the transition in rate-limiting step takes place, as well as the partitioning of the intermediates between reactant and products, are strongly influenced by substituents. Hammett correlations of these and other kinetic constants are discussed. Stabilization of an incipient oxocarbonium ion seems to be an important factor in determining the mode of breakdown of the cationic tetrahedral intermediate.

Although tetrahedral addition intermediates have been found to occur in numerous acyl transfer reactions,[2] there exist relatively few systematic studies of the effect of structural change on the properties of these intermediates in a given system. Among those which may be cited are the hydrolysis of ring- and acyl-substituted anilides,[3] the aminolysis of methyl formate by amines of varying basicity,[4a] and the hydrolysis of acyl-activated thiol esters.[4b] Studies of the hydrolysis of O-substituted acetimidate esters[5] and of a series of N-substituted acetimidates and formimidates[6] were also designed to provide information concerning the pathways of breakdown of tetrahedral intermediates closely related to those formed in nucleophilic attack at the acyl group.

Ester hydrolysis was among the first reactions in which direct experimental evidence was obtained for the existence of tetrahedral intermediates.[7] Although less well studied, the reverse reaction (esterification and lactonization) has recently attracted renewed attention, in part owing to the remarkable rate enhancements achieved in the lactonization of certain phenolic acids[8] and to the interest attendant to the factors which control the high rates of intramolecular reactions.[9] The discovery[10] that the lactonization of coumarinic acid proceeded *via* tetrahedral intermediates which could be readily detected through kinetic means led us to employ this system for detailed study. We intended to ascertain the influence of ring substitution on the



rates and equilibria of ring closure and, particularly, on the partitioning of the several ionic species of the tetrahedral intermediates; this partitioning controls the nature of the rate-determining step of the reaction. We were also interested in determining the similarities and differences between the mechanisms of formation and hydrolysis of coumarins and those of acyclic phenyl esters. The hydrolysis of the latter compounds has been extensively studied,[2] but there appears to be no direct evidence that it proceeds *via* discrete tetrahedral intermediates.

Results

The kinetics of lactonization of a series (**1–13**) of substituted coumarinic acids were studied at pH 0–6 in predominantly aqueous solution, at 30° and μ = 1.0 (LiCl). At pH >2.5, the rate constants, determined spectrophotometrically, were extrapolated to zero buffer concentration. Moderate catalytic effects of formate, acetate, and MES (2-morpholinoethanesulfonate) buffers were observed, with rate increases in 0.1 *M* buffer varying from 10–100% above the rate extrapolated to zero buffer concentration. In most cases, plots of k_{obsd} *vs.* total buffer concentration at fixed

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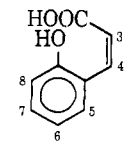
Table II. Rate and Equilibrium Constants for the Lactonization of Coumarinic Acids and the Hydrolysis of Coumarins[a,b]

Coumarinic acid	pK_a	pK'	P^+	P^0	10^2k_1, M^{-1} sec^{-1}	$10^2k_1'$, sec^{-1}	B_H, M^{-1} sec^{-1}	$10^4B_{H_2O}$, sec^{-1}	10^6B_{OH},[c,d] M^{-1} sec^{-1}	k_{OH},[d,e] M^{-1} sec^{-1}	$10^{-6}K_{eq}$
6-OH	3.69	3.24 ± 0.02	0.992 ± 0.0005	0.067 ± 0.005	8.02	0.536	9.28	3.60	3.81	0.207[f]	
5,8-$(CH_3)_2$	3.84	3.78 ± 0.07	0.99935 ± 0.00008	0.28 ± 0.016	6.82	1.25	75.5	35.0	9.13	0.760	12.00
5,7-$(CH_3)_2$	3.93	3.25 ± 0.05	0.993 ± 0.0005	0.080 ± 0.006	10.3	0.756	13.5	6.03	3.56	0.571	6.24
6-CH_3	3.74	2.93 ± 0.04	0.986 ± 0.001	0.090 ± 0.005	7.98	0.612	5.12	5.51	1.85	0.810	2.25
H	3.70	2.63 ± 0.03	0.983 ± 0.001	0.042 ± 0.002	7.78	1.02	4.31	4.32	1.82	1.285	1.42
6-CH_3CONH	3.68	2.03 ± 0.03	0.964 ± 0.002	0.035 ± 0.002	7.62	1.92	1.97	6.65	1.33	2.06	0.645
7-OH	4.10	2.14 ± 0.03	0.972 ± 0.002	0.0071 ± 0.0008	7.98	2.07	2.78	1.44	0.650		
6-Br	3.62	1.63 ± 0.04	0.941 ± 0.004	0.015 ± 0.001	6.83	2.68	1.07	3.99	1.21	3.38	0.358
6-$NH_3^+Cl^-$	3.49[g]	1.14 ± 0.09	0.887 ± 0.01	0.014 ± 0.004	6.60	4.18	0.511	5.85			
6-$CONH_2$	3.63[g]	0.66 ± 0.07	0.767 ± 0.02	0.0038 ± 0.0005	12.2	11.3	0.399	4.27	0.538	4.99	0.108
6-$(CH_3)_3N^+ClO_4^-$	3.43	0.32 ± 0.11	0.71 ± 0.05	0.004 ± 0.0009	6.00	9.77	0.146	4.01	0.580	10.72	0.0588
6-CN	3.46	0.4[h]	0.35 ± 0.08	0.0036 ± 0.0026	19.2	11.9	0.105	4.25	0.667	12.18	0.0548
6-NO_2	3.54						0.043	3.85	0.279	18.20	0.0153

[a] 30°, μ = 1.0 (LiCl). [b] $P^+ = k_3/(k_2 + k_3)$; $P^0 = k_3'/(k_2' + k_3')$; $K' = K_1(k_2' + k_3')/(k_2 + k_3)$; $B_H = k_1P^+(1 - P^0)/(1 - P^+)$; $B_{H_2O} = k_1'P^0$ (see Scheme I). For P^+, P^0, and pK', standard deviations are given. [c] Base-catalyzed lactonization. [d] Based on activity of OH^-. [e] Base-catalyzed hydrolysis. [f] Hydrolysis of anion. [g] Estimated value; see Results. [h] Approximate value.



1, 6-OH
2, 6-CH_3
3, 6-CH_3CONH
4, H
5, 6-Br
6, 6-$CONH_2$
7, 6-NH_3^+
8, 6-$N^+(CH_3)_3$
9, 6-CN
10, 6-NO_2
11, 7-OH
12, 5,7-Dimethyl
13, 5,8-Dimethyl

pH were linear between 0.04 and 0.1 *M*. Where curvature in such plots was observed, only the two lowest buffer concentrations were used to calculate the intercept value. Such curvature was generally small; the extrapolated value at 0.1 *M* buffer, based on the straight line defined by the points at the two lowest buffer concentrations, rarely exceeded the observed values by more than 10%. In selected cases, data obtained at buffer concentrations up to 0.8 *M* confirmed the suggestions of curvature. As in the case of other phenolic acids,[8] the lactonization of coumarinic acids appears to be subject to general acid–base catalysis. A detailed analysis of buffer catalysis in this system will be published separately.

First-order rate constants for the lactonization of coumarinic acids **1**–**13** are summarized in Table I[11] and four representative examples are shown in Figure 1. Although, in each case, there occurs a steady decrease in the rate of lactonization with increasing pH, the overall shape of the pH–rate profile depends markedly on the nature of the ring substituents.

pK_a values for the carboxyl group of 11 of the coumarinic acids were measured by spectrophotometric titration (Table II) and gave a good correlation with σ^+ constants ($\rho^+ = -0.35$, $r = 0.98$).[12] For 6-NH_3^+ and 6-$CONH_2$ coumarinic acids, pK_a values were estimated from the regression line and the appropriate σ constants.

When the dependence of the rate of lactonization on pH is expressed in terms of neutral substrate (eq 1,

$$k_{obsd}/f = \frac{k_{obsd}}{[H^+]/([H^+] + K_a)} \quad (1)$$

where K_a = dissociation constant of the carboxyl group), a complex variation of rate with pH is seen (Figure 2, solid lines), although the values of k_{obsd} have been corrected for the effects of carboxyl group ionization. Of particular interest is the nonlinear region of acid catalysis. The break in the plot of log k_{obsd}/f *vs.* pH becomes distinctly more pronounced with increasing electron donation by ring substituents (Figures 2 and 3).

Second-order rate constants (Table II, B_{OH}) for the hydroxide-dependent lactonization (in terms of neutral substrate)[13a] at pH >4 were calculated from linear

(11) See the paragraph at end of paper regarding supplementary material.

(12) A ρ value of −0.63 (using σ constants) has been reported for meta-substituted cinnamic acids in 50% aqueous ethanol at 25° [R. Fuchs and J. J. Bloomfield, *J. Org. Chem.*, **31**, 3420 (1966)].

(13) (a) The hydroxide-catalyzed lactonization of the neutral coumarinic acid is of course kinetically equivalent to a reaction of the coumarinate anion and is responsible for the appearance of a pH-independent rate of lactonization at pH > pK_a (Figure 1). (b) The rate constants for the alkaline hydrolysis of **2** and **4** agree well with those reported by K. Bowden, M. J. Hanson, and G. R. Taylor, *J. Chem. Soc. B*, 174 (1968), for 70% dioxane–water. For comparison, the values of k_{OH} in Table II must be converted from an activity to a concentration basis.

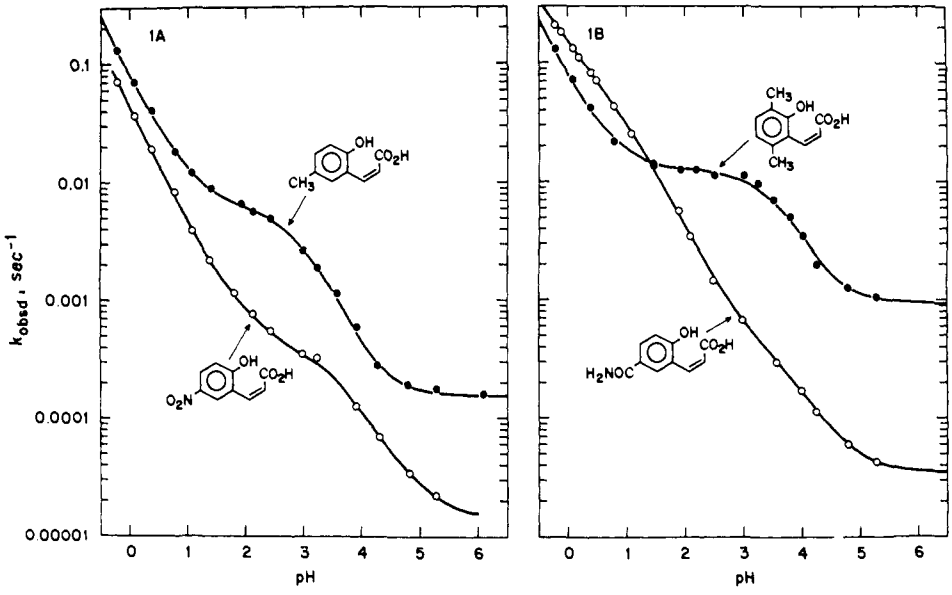


Figure 1. pH–rate profiles for the lactonization of coumarinic acids at 30°, μ = 1.0. Solid lines are calculated as indicated in the text using constants of Table II.

plots of k_{obsd}/f *vs.* $K_w/[H^+]$. The contribution of the hydroxide-dependent term was then subtracted from the pH–rate profile (Figure 2, dashed lines). For most compounds, the resultant profiles display two regions of near unit slope and two regions of lesser slope, sometimes approaching zero.

Second-order rate constants for the base-catalyzed hydrolysis of coumarins (Table II, k_{OH}) were calculated from the slopes of plots of k_{obsd} (measured at 3–5 hydroxide ion concentrations) *vs.* $K_w/[H^+]$. These plots were invariably linear and had zero intercepts, indicating the absence of significant uncatalyzed hydrolysis.[13b] Equilibrium constants (Table II, K_{eq}) for the lactonization reactions were calculated from the ratio of the second-order rate constants for hydroxide-catalyzed lactonization and coumarin hydrolysis and are thus expressed in terms of the conversion of neutral coumarinic acid to lactone.

The solvent deuterium isotope effect in the lactonization of coumarinic acid was determined at several different acid concentrations, allowing the calculation of the effect of the substitution of deuterium for hydrogen both on the low pH acid-catalyzed and pH-independent reactions (Table III).

Table III. Solvent Deuterium Isotope Effect on the Lactonization of Coumarinic Acid[a]

[Acid], M[b]	$k_{obsd}(H_2O)$ $\times 10^3$, sec^{-1}	$k_{obsd}(D_2O)$ $\times 10^3$, sec^{-1}	k_{H_2O}/k_{D_2O}	k_H^+/k_D^+
0.20	34.0	18.3		
0.05	15.3	6.63	3.44	1.59
0.025	12.4	4.46		

[a] 30°, μ = 1.0 (LiCl). [b] HCl or DCl concentration in H_2O or D_2O, respectively.

Discussion

Garrett, and coworkers,[10] made the important observation that the "kinetic pK_a" which governed the rate of lactonization of coumarinic acid was significantly different from the pK_a which could be directly and independently measured. This observation provided the basis for the postulation of a reaction mechanism including a tetrahedral addition intermediate which underwent spontaneous and acid-catalyzed conversions to coumarin. In what follows, we consider a mechanism which differs in some details, though not in essence, from that proposed by Garrett, *et al.*, and draw particular attention to the effects of strutural variation on the pathways of breakdown of the intermediates formed in this system.

General Considerations. When corrected for the effect of carboxyl group ionization, the pH–rate profile for the lactonization of most of the compounds of this study exhibits two regions of acid catalysis separated by a region where the rate of lactonization is less steeply dependent or totally independent of pH (Figures 2 and 3). Such a break in the pH–rate profile is most easily interpreted in terms of a change in the rate-determining step, and hence any proposed mechanism must include at least one intermediate. In a study of a related reaction (the thiolactonization of a mercapto-acid),[14a] a closely similar pH–rate profile was interpreted in terms of a mechanism involving a cationic (T^+) and a neutral (T^0) tetrahedral intermediate in acid–base equilibrium. In what follows, some general kinetic properties of such a mechanism are discussed, prior to consideration of the experimental data.[14b] For the moment, we neglect the base-catalyzed reaction.

According to Scheme I, lactonization proceeds *via* cationic and neutral intermediates present at steady-state concentrations. The nature of the rate-limiting step of the reaction depends on the mode of partitioning of each intermediate. If, for example, the partitioning ratio $P^+ (= k_3/(k_2 + k_3))$ is near unity, the rate-determining step in acid solution will be the formation of T^+,

(14) (a) R. Hershfield and G. L. Schmir, *J. Amer. Chem. Soc.*, 94, 6788 (1972). (b) The assumption of the existence of two intermediates in acid–base equilibrium is convenient but not essential to the kinetic analysis. Other kinetically equivalent formalisms could have been used, such as the existence of T^0 alone, which undergoes decomposition *via* neutral and acid-catalyzed pathways.

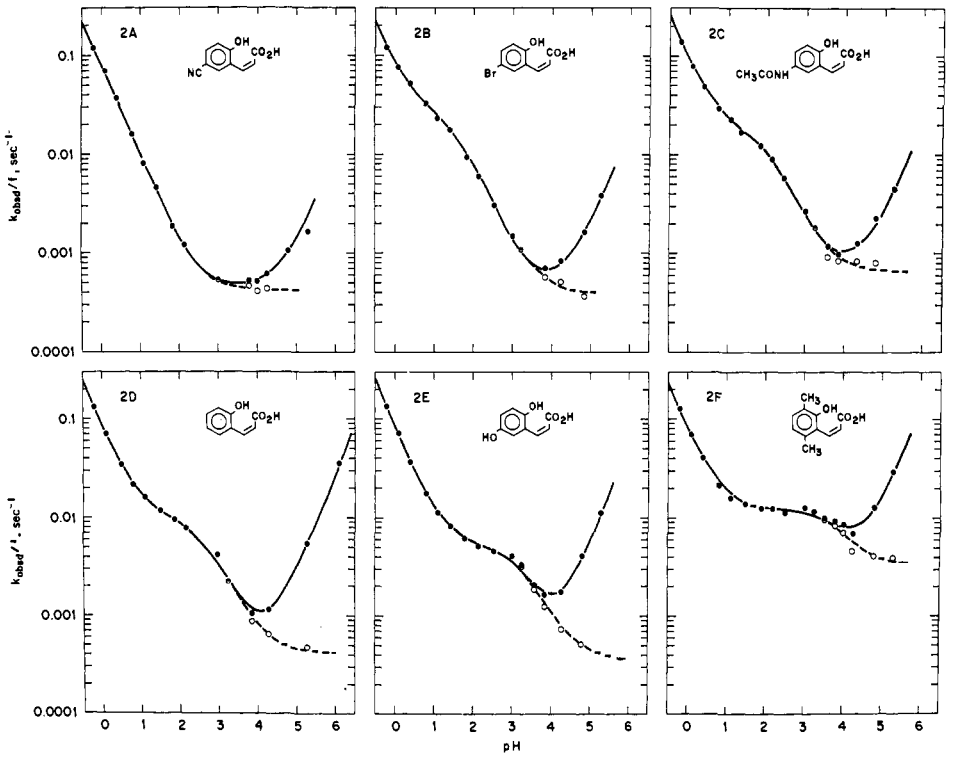


Figure 2. pH–rate profiles for the lactonization of coumarinic acids, expressed in terms of neutral substrate. The solid lines are calculated from eq 2, to which the contribution of the base-catalyzed lactonization has been added. The open circles and dashed lines refer to data from which the hydroxide-dependent reaction has been subtracted (eq 2).

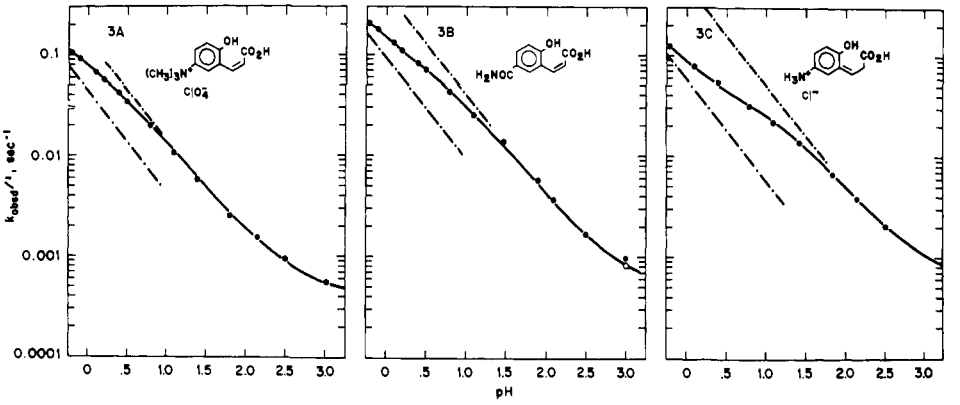
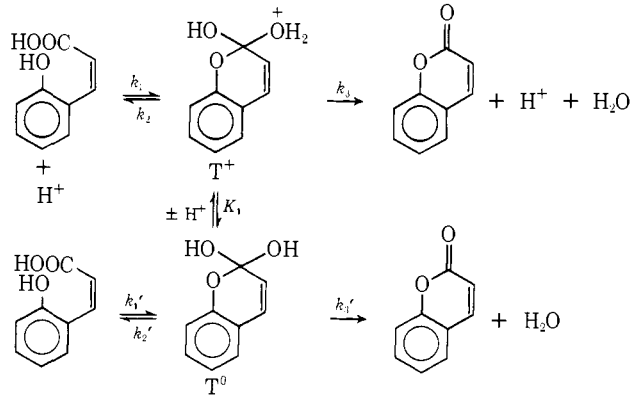


Figure 3. pH–rate profiles for the lactonization of coumarinic acids at 30°, μ = 1.0, expressed in terms of neutral substrate. The solid lines are calculated from eq 2, using constants of Table II. The dashed lines have a slope = −1.0 and represent the calculated values of the terms corresponding to regions A and C of Figure 4.

Scheme I



governed by k_1. If, on the other hand, the partitioning ratio P^0 ($= k_3'/(k_2' + k_3')$) is near zero, the rate-limiting step at higher pH will be the breakdown of the neutral intermediate T^0. A change in rate-limiting step will occur at a pH value (pK') where the reaction pathways involving the two intermediates of different charge contribute equally to the course of the reaction.

The pH–rate profile of a reaction obeying Scheme I is completely determined by the values of four terms only. The steady-state rate equation could be expressed, for example, in terms of k_1, k_1', and the ratios P^+ and P^0. In this work the alternative eq 2 has been chosen, where

$$\frac{k_{obsd}}{f} = \frac{k_1([H^+]P^+ + K'P^0)(H^+ + K'(1 - P^0)/(1 - P^+))}{[H^+] + K'} \quad (2)$$

the dependence of the corrected values of k_{obsd} on pH

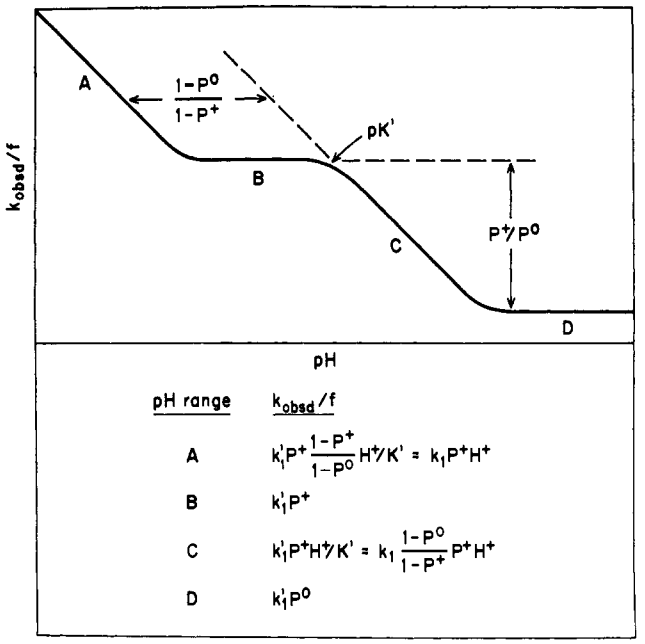


Figure 4. Schematic representation of the dependence of the rate of lactonization according to Scheme I and eq 2. Regions A and C have slope = −1. The terms describing the four regions are defined in the text.

is expressed in terms of k_1, the two partitioning ratios P^+ and P^0, and the constant K' ($= K_1(k_2' + k_3')/(k_2 + k_3)$), whose value indicates the pH where the change in rate-limiting step occurs when $P^+ \neq P^0$. Note that k_1 and k_1' are related by eq 3.

$$k_1/k_2 = k_1'/k_2'K_1 \qquad (3)$$

In the general case, the reaction mechanism of Scheme I and eq 2 generates a pH–rate profile (Figure 4) characterized by two regions of unit slope (acid catalysis) and two regions of zero slope.[15] Consider the extreme situation where P^+ is near unity and P^0 is near zero. The rate-determining step in regions A and B will be the acid-catalyzed and uncatalyzed (or water-catalyzed) formation of intermediates. A change in rate-limiting step occurs at pH = pK', and the rate-determining step in regions C and D is the acid-catalyzed and uncatalyzed breakdown of the intermediate.

It is readily shown that the separations between regions A and C, and between regions B and D, are solely a function of the ratios P^+ and P^0. In favorable cases (*i.e.*, P^+ near unity and P^0 near zero), estimates of P^+, P^0, and K' may be made by simple inspection of the pH–rate profile. It should be stressed that partitioning ratios of 0.98, 0.99, and 0.999 are easily distinguishable. Thus, when $P^0 \simeq 0$, the separation between regions A and C is approximately given by $1/(1 - P^+)$, so that the above values of P^+ correspond to separations of 1.7, 2, and 3 pH units, respectively. In usual experimental situations, curve-fitting procedures may need to be employed for precise evaluation of the parameters. The kinetic expressions which describe the limiting regions A, B, C, and D are given in Figure 4.

The symmetry properties of eq 2 are such that it is possible to generate identical curves by using either a set of constants (k_1, P^+, P^0) or the set ($1 - P^+$, $1 - P^0$) with k_1 being replaced by $k_1\ P^+/(1 - P^+)$.[14a] Put another way, it is not possible to assign the nature of the rate-limiting step at high and low pH from the kinetics alone. Independent information must be used to decide whether, *e.g.*, the cationic intermediate P^+ is more likely to expel H_2O rather than phenol (*i.e.*, $k_3 > k_2$) or the opposite. For thiol ester hydrolysis and formation, use was made of the known effects of pH on the products of hydrolysis of a ketene *O,S*-acetal to support the conclusion that the cationic intermediate expelled H_2O in preference to mercaptan, while the neutral intermediate broke down mainly with departure of mercaptan.[16] Similar information on the relative leaving abilities of water and phenols is lacking. On the basis of analogy with the thiol system, where the more acidic mercaptan competed favorably with water at high pH but not at low pH, we assume tentatively that the departure of phenol will be preferred over that of water at high pH also. Thus, any kinetically detectable change in rate-limiting step as pH is decreased will be due to a change in favor of water in the relative leaving abilities of phenol and water from a more highly protonated intermediate. The report that the alkaline hydrolysis of phenyl benzoate in $H_2{}^{18}O$ occurs without ^{18}O incorporation into the ester offers some support for this assumption.[17a] Also, on the basis of structure–reactivity relationships, it has been suggested that if the reaction of phenoxide ion with acetic acid occurs *via* an intermediate, the breakdown of the intermediate is probably rate determining.[17b]

Rate and Equilibrium Constants for Lactonization. The pH–rate profiles for the lactonization of coumarinic acids **1–9** and **11–13** were fitted to eq 2 and the constants k_1, P^+, P^0, and K' calculated by a least-squares curve-fitting procedure (Table II). Good agreement was found in all cases between the experimental data and the curves calculated from eq 2 (Figures 2 and 3). In several cases, the pH dependence

(15) G. L. Schmir, *J. Amer. Chem. Soc.*, 90, 3478 (1968).

(16) R. Hershfield and G. L. Schmir, *ibid.*, **95**, 1263 (1972).

(17) (a) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956); (b) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5442 (1970).

Table IV. Rate and Equilibrium Constants for Lactonization of 3-Substituted Coumarinic Acids[a,b]

Compd	P^+	P^0	pK'	10^2k_1, M^{-1} sec^{-1}	10^2k_1, sec^{-1}
3-Br	0.938 ± 0.042	0.42 ± 0.13	1.3[c]	15.9	7.52
3-Cl	0.983 ± 0.003	0.223 ± 0.022	1.72 ± 0.16	8.34	7.20
3-phenyl	0.92 ± 0.009	0.025 ± 0.005	2.12 ± 0.15	18.25	1.71
H	0.980 ± 0.002	0.029 ± 0.008	2.90 ± 0.05	9.5	0.584
3-CH_3	0.953 ± 0.012	0.30 ± 0.03	2.16 ± 0.13	19.0	1.95

[a] At 25°; data taken from ref 10. [b] For definitions of constants, see Scheme I and Table II, footnote *b*. [c] Approximate value.

of k_{obsd} was calculated by computing k_{obsd}/f (eq 2), adding the contribution of base-catalyzed lactonization ($B_{OH}K_w/[H^+]$), and multiplying the resulting values by the mole fraction of the substrate in the acid form. The resulting curves satisfactorily reproduced the experimental observations (Figure 1).

Once the primary constants k_1, P^+, P^0, and K' are deduced from the pH–rate profiles, values of k_1' can be calculated, as well as the values of two terms (B_H and B_{H_2O}) which represent the limiting values of regions C and D in the general pH profile (Figure 4 and Table II).

No evidence for a change in rate-limiting step was noted with 6-nitrocoumarinic acid. After correction for ionization of the carboxyl group, the pH profile was found to fit satisfactorily a simple equation with terms corresponding to acid, base, and uncatalyzed reactions (eq 4). To avoid complications resulting from the

$$k_{obsd} = B_H[H^+] + B_{H_2O} + B_{OH}K_w/[H^+] \quad (4)$$

effect of carboxyl group ionization on the acid–base behavior and electronic properties of the amino group of 6-aminocoumarinic acid, only rate data at pH $\leq$2.5 were used in the kinetic analysis.

Large and regular changes in the partitioning ratio of the cationic intermediate occur with increases in electron withdrawal in the coumarinic acid, with P^+ varying from 0.9994 (k_3/k_2 = 1600) for 5,8-dimethylcoumarinic acid to 0.35 (k_3/k_2 = 0.54) for 6-cyanocoumarinic acid. Thus, while for most of the coumarinic acids the rate-limiting step at pH < pK' is the formation of the intermediate, both steps have become about equally rate determining with the 6-cyano substrate. The steady decrease in P^+ (and consequently in the k_3/k_2 ratio) is illustrated by the decreasing separation between regions A and C with increasing electron withdrawal (Figure 2, 2F → 2A). The merger of the two regions of acid catalysis is shown on an expanded scale in Figure 3, where the dashed lines represent the limiting value of regions C and A calculated using the least-squares parameters derived from the curve-fitting procedure.

The partitioning ratio, P^0, of the neutral intermediate also decreases steadily with electron withdrawal, ranging from 0.28 (k_2'/k_3' = 2.6) with the 5,8-dimethyl derivative to 0.0036 (k_2'/k_3' = 280) with 6-cyanocoumarinic acid. Thus, at pH > pK', the rate-limiting step for essentially all the compounds is largely the breakdown of intermediates, although with the 5,8-dimethyl compound, both formation and decomposition of the intermediate contribute substantially to the rate-limiting step. It should be noted that when P^0 is >0.1, there exists the possibility of a second (partial) change in the rate-limiting step if the base-catalyzed lactonization proceeds *via* an anionic intermediate whose partitioning ratio is nearly zero. A small error in the value of P^0 calculated for 5,8-dimethylcoumarinic acid may have been introduced by this factor.

The pH value (pK') at which the transition in rate-limiting step occurs decreases steadily with electron withdrawal, covering the range of pH 3.78 to 0.4. Two factors, therefore, appear to account for the observation that no change in the rate-limiting step is seen with 6-nitrocoumarinic acid: the low value of P^+ (<0.35), and the low value of pK' (<0.4). For this compound, it appears that breakdown of intermediates is largely rate determining throughout the entire pH range, since both T^+ and T^0 expel primarily phenol in preference to water. It should be noted that the increasing values of P^0 with electron donation suggest that with a somewhat greater degree of electron donation than obtained with 5,8-dimethylcoumarinic acid, P^0 may become sufficiently close to unity so that, again, no change in rate-limiting step would be seen. In this case, both T^+ and T^0 would expel mainly water, and formation of intermediates would remain rate limiting throughout. At both extremes of substituent variation, the lactonization reaction appears to proceed *via* a single, albeit different, rate-limiting step over the pH range of this study.

The kinetic constants obtained in this work for the lactonization of the parent coumarinic acid agree reasonably well with those which can be calculated from the data published by Garrett, *et al.*,[10a] for the same reaction at 25° and μ = 0.1 (Table IV).[18] Similar analysis of the data[10b] for four side-chain substituted coumarinic acids reveals no discernible pattern in P^+ and P^0 and a regular decrease in pK' with increasing electron withdrawal.[19a]

Although the kinetic data offer no direct information concerning the existence of intermediates in the base-catalyzed lactonization (at pH >4, Figure 2), it is probable that an anionic intermediate T^- is formed (eq 5 and 6). Its partitioning ratio P^- ($= k_3''/(k_2'' + k_3'')$) is expected to be small, so that $k_2'' > k_3''$, and the rate-limiting step in this pH range is the breakdown of T^-.

(18) The difference between the pK_a value of 4.0 reported[10a] for coumarinic acid and that of 3.70 found here is most likely the result of the use of 1.0 *M* LiCl in the present work.

(19) (a) The kinetic analysis of Garrett, *et al.*,[10] includes an acid-catalyzed reaction at lowest pH which does not explicitly involve the formation of a tetrahedral intermediate (step k_{H^+} in Schemes I of ref 10a and 10b). For this reason, the derived kinetic constants (Table V in ref 10b) are not all directly comparable with those of Table IV in the present paper, which are based on the same data. The terms K', P^0, $k_1'P^+$, and k_1P^+ of this work are respectively identical with the terms $1/P$, Q, $K_{a1}'k_{-1}$, and k_{H^+} of Garrett, *et al.*,[10] and may be compared. The differences which are principally found in the terms K' and P^0 probably arise from the different curve-fitting procedures used, as well as from the difficulty in substracting the k_{H^+} (or k_1P^+) term (region A) from the remainder of the pH profile when the several regions are not well separated. (b) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 211; (c) *ibid.*, p 178.

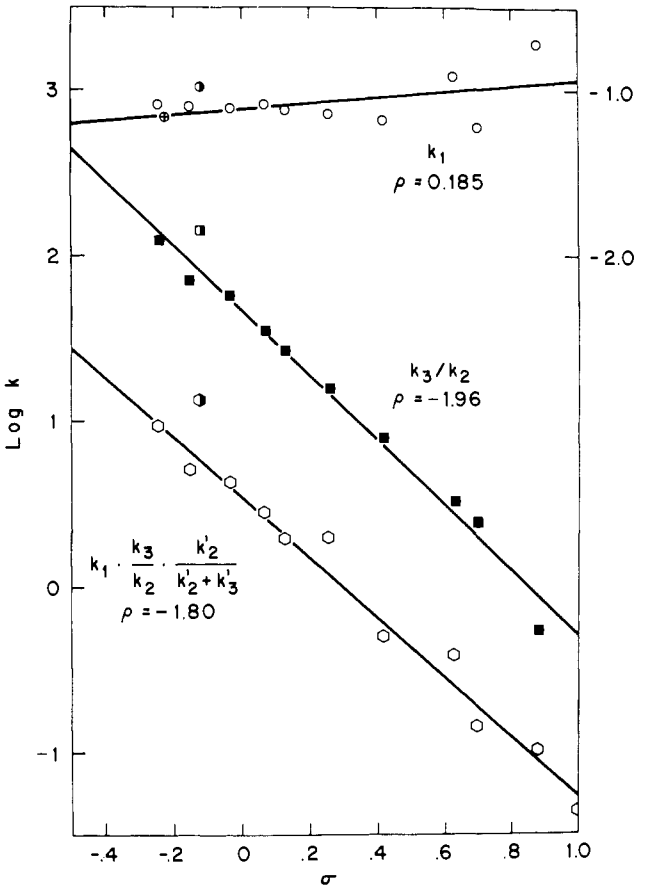
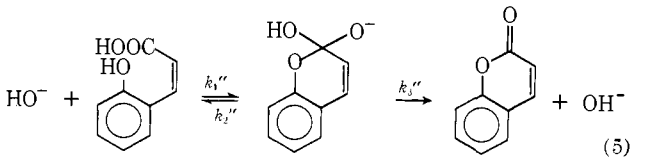


Figure 5. Hammett plots for acid-catalyzed reactions: (⊕) 5,8-dimethylcoumarinic acid; (half-shaded symbols) 5,7-dimethylcoumarinic acid. These two compounds were not used in the least-squares calculation of ρ.



(5)

$$\frac{k_{obsd}}{f} = \frac{k_1'' k_3''}{k_2'' + k_3''}[OH^-] = B_{OH}[OH^-] \qquad (6)$$

The assumption underlying the calculation of the equilibrium constants for the lactonization reaction (see Results) is that the same reaction step is rate-determining under the different conditions where the rates of the forward and reverse reactions were measured. Although base-catalyzed lactonization was measured at pH 4–6 and base-catalyzed hydrolysis at pH 10.5–12.5, it is likely that this assumption is valid and that no further change in rate-limiting step takes place at pH >4.

Structure–Reactivity Relationships. The kinetic and equilibrium constants obtained for 11 6- and 7-substituted coumarinic acids (Table II) were employed to construct Hammett plots (Figures 5–7); the derived ρ values (least squares) are listed in Table V. As stated above, only four independent kinetic constants can be obtained from the kinetic data for lactonization at pH <4, and therefore, only four independent Hammett relationships can be established. A number of other relationships, however, follow directly from these.

The effects of ring substituents on the kinetics and equilibria of the lactonization of coumarinic acids

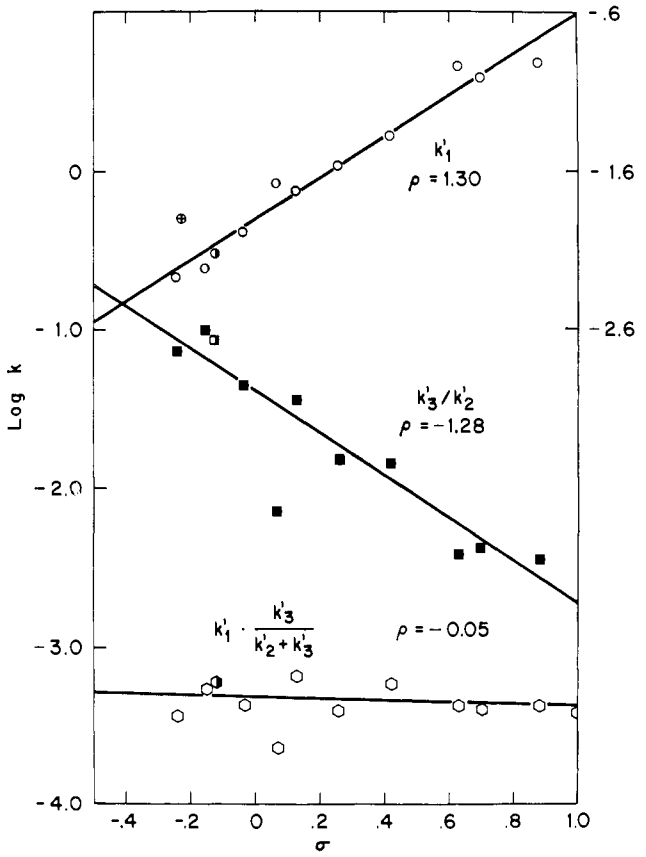


Figure 6. Hammett plots for pH-independent reactions: (⊕ and half-shaded symbols) see legend to Figure 5.

Table V. $\sigma\rho$ Correlations for Rate and Equilibrium Constants for Esterification of Phenols

	$\rho^{a,b}$	r^c	ρ^d	ρ^e
pK_a[f]	−0.35	0.98		
K'	2.75	0.99		
k_3/k_2	−1.96	0.99		
k_3'/k_2'	−1.28	0.90		
k_1	0.185	0.47		
k_1'	1.30	0.98		
B_H	−1.80	0.99	−1.55[g]	−1.68[h]
B_{H_2O}	−0.05	0.25	−0.32[i]	−0.55[j]
B_{OH}	−0.66	0.88	−0.61[k]	
k_{OH}	1.43[l]	0.99	0.725, 0.954[m]	
K_{eq}	−1.75	0.99	−1.33[n]	

[a] This study. [b] σ values calculated from pK_a of corresponding phenol and the regression line $pK_a = 9.92 - 2.23\sigma$ [A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961)]. σ values for 6-NH_3^+ and 6-CH_3CONH groups were taken as 0.42 and 0.13, respectively, from the least-squares fit of the k_3/k_2 data to σ; σ^-(*p*-$CONH_2$) = 0.63 (ref 19b); a σ value of −0.24 was used for 6-OH group; σ(*p*-NO_2) = 1.00 [T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964)]. [c] Correlation coefficient. [d] Reaction of phenols with acetic acid at 25° in H_2O, except where indicated. [e] Lactonization of *o*-hydroxy-β,β-dimethyldihydrocinnamic acids, 30°, ref 8a. [f] Correlated with σ^+ (ref 19b, p 204). [g] Acid-catalyzed reaction. From $\rho = -0.20$ for acid-catalyzed hydrolysis of aryl acetates in 60% acetone (ref 19b, p 180) and $\rho = -1.33$ for formation of phenyl acetates from phenols and acetic acid (data from ref 23). [h] Acid-catalyzed lactonization. [i] Uncatalyzed reaction. Data taken from ref 17b. [j] Uncatalyzed lactonization. [k] Hydroxide-catalyzed reaction of phenols with acetic acid. From equilibrium dependence and ρ of 0.725 for hydroxide-catalyzed hydrolysis of phenyl acetates. [l] σ values based on ionization of benzoic acids (ref 19b, p 173). [m] Dependence of hydroxide-catalyzed hydrolysis of phenyl acetates on σ^- ($r = 0.977$) and σ ($r = 0.988$), respectively; data from ref 24. [n] Equilibrium constant; data from ref 23.

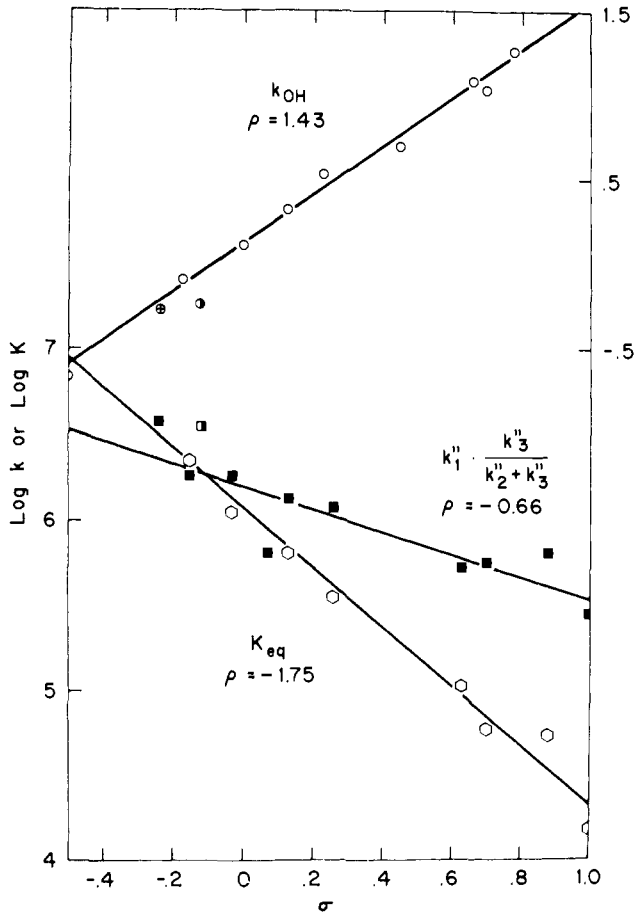
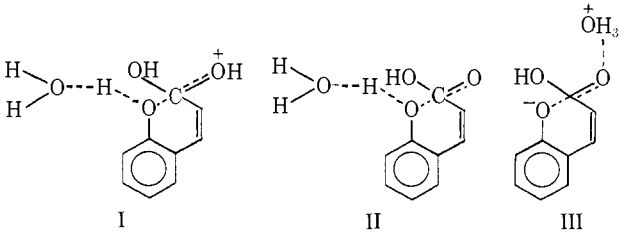


Figure 7. Hammett plots for base-catalyzed hydrolysis of coumarins (○); base-catalyzed lactonization (■); and equilibrium constants for lactonization (⬡); for ⊕ and half-shaded symbols, see legend to Figure 5.

appear to manifest themselves mainly in terms of interaction at the phenolic oxygen atom. No significant improvements in correlation were obtained when a four-parameter σ–ρ treatment was attempted, although it has been reported[13c] that such a treatment could be applied to the alkaline hydrolysis of coumarins and that effective transmission of electronic effects occurred through both phenolic oxygen and the olefinic side chain. It may be that some of the scatter in the plots of Figures 5–7 is the result of some transmission through the side chain, although the major effect is at the phenolic oxygen.

a. Acid-Catalyzed Reactions (Figure 5). The rate (k_1) of the acid-catalyzed formation of T^+ is nearly independent of substituent. It is possible that the development of positive charge on the attacking phenolic oxygen is counteracted by partial proton removal by a water molecule (I). Alternative mechanisms, such as the specific or general acid-catalyzed attack of the phenolic group on the carbonyl group, without significant breaking of the phenolic O–H bond, would require a negative ρ value. The ratio k_3/k_2, which describes the partitioning of T^+, shows a strong negative dependence on σ. Increasing electron density at the phenolic oxygen will facilitate the departure of water (k_3). It seemed reasonable to expect, however, that increasing the basicity of the phenolic oxygen would favor its expulsion from T^+ relative to the expulsion of water, owing to the greater relative concentration of the protonated leaving group, thus resulting in a small overall ρ value. The contrary finding suggests that stabilization of the developing oxocarbonium ion by the remaining groups is more important in determining leaving ability than the relative basicities of the potential leaving groups. A similar proposal was offered to explain the effects of acyl group variation on the pathways of breakdown of the intermediates formed in thiol ester hydrolysis.[4]



I II III

The substituent dependence of lactonization in the region where the rate-limiting step is acid-catalyzed breakdown of the intermediate (region C; B_H in Table II) follows immediately from the preceding. The kinetic term for this part of the pH profile (Figure 4) is given by $k_1k_3k_2'/k_2(k_2' + k_3')$ which is approximately equal to k_1k_3/k_2, since $k_2' > k_3'$ for most of the compounds. The steep negative ρ value for this region of the profile (Figure 5) is thus determined mainly by the large negative ρ for the ratio k_3/k_2.

b. Neutral Reactions (Figure 6). The substituent dependence of the rate constant k_1' ($\rho = +1.3$) for the uncatalyzed (or water-catalyzed) formation of T^0 suggests a transition state (II) characterized by very little O–C bond formation and extensive removal of the phenolic proton by a water molecule (ρ for the complete ionization of substituted phenols is $+2.1$).[19c] Alternatively, there may occur complete proton removal from the phenol with some O–C bond formation and general acid catalysis by the solvated proton (III). A pathway involving lactonization of a zwitterionic species is ruled out by the requirement of a rate constant exceeding 10^{14} sec^{-1}. The observed solvent deuterium isotope effect ($k_{H_2O}/k_{D_2O} = 3.44$) for the pH-independent lactonization of **4** in the pH range of rate-limiting formation of intermediates is consistent with the participation of water molecules in the transition state for this step. The negative ρ value for k_3'/k_2' indicates that with T^0 as with T^+, expulsion of water relative to that of phenol is favored by electron donation. Electron-rich substituents would be expected to reduce k_2' (note that the transition state for this step is also given by II or III with extensive bond cleavage between carbon and phenolic oxygen and little or no protonation of the latter) and possibly to slightly favor departure of water (increase in k_3').

The water-catalyzed, rate-limiting decomposition of the intermediate (region D) is found to be independent of substituent ($\rho = -0.05$). In this pH range, the kinetic term $k_1'P^0 = k_1'k_3'/(k_2' + k_3')$ is approximately equal to $k_1'k_3'/k_2'$, and the absence of substituent effect is the consequence of the cancellation between the attack step k_1' ($\rho = +1.30$) and the partitioning step k_3'/k_2' ($\rho = -1.28$).

The pH at which the transition in the rate-limiting step occurs decreases rapidly with electron withdrawal, with $\rho = +2.75$ for K' (plot not shown). Quali-

tatively, this behavior follows from the already established substituent effects on the component terms of this complex constant. Since for most of the substrates, $k_3 > k_2$ and $k_3' < k_2'$, the constant K' is approximately given by K_1k_2'/k_3. It has already been suggested that electron donation will decrease k_2' and increase k_3, and since K_1 will certainly be decreased also, all three effects act in the same direction to decrease K'. More precisely, K' is approximately equal to the product of three terms $(k_1'k_2/k_1k_3)$, whose substituent dependence is known and accounts quantitatively for the observed variation of K' with σ.

The hydroxide-dependent breakdown of the intermediate is somewhat accelerated by electron donation ($\rho = -0.66$), suggesting that expulsion of hydroxide ion is more important than the ease of removal of the hydroxylic proton. The alkaline hydrolysis of coumarins presumably represents rate-determining attack of hydroxide ion on the carbonyl group; its substituent dependence ($\rho = +1.43$) is less pronounced than that reported[13c] for hydrolysis in 70% dioxane–water ($\rho = +2.34$).

The lactonization of substituted *o*-hydroxyphenylpropionic acids occurs *via* acid-catalyzed and pH-independent pathways but does not exhibit a change in the rate-limiting step with pH.[8a] Arguing on the basis of substituent effects, Milstien and Cohen assigned the rate-limiting step of this reaction to the breakdown of a tetrahedral intermediate, although the kinetics of the reaction did not require the existence of an intermediate. Their conclusion is supported by comparison of their ρ values to those ascribed to rate-limiting decomposition of intermediates in the present work (Table V). Furthermore, ρ values calculated for the acid-, water-, and base-catalyzed reactions of substituted phenols with acetic acid closely resemble those measured for the corresponding steps in the lactonization of coumarinic acids, in the pH ranges where the rate-limiting step is thought to be the decomposition of the intermediate (Table V). It is likely that, if the reaction of phenol with acetic acid proceeds through a discrete intermediate, its decomposition is rate determining throughout the entire pH range; if no intermediate is formed, the transition state may resemble that for breakdown of the intermediate.[17b]

It has been stressed that ρ or β values are measures of the change in charge of atoms near the substituent and do not necessarily indicate the extent of bond changes or the exact position of the transition state along the reaction coordinate.[20a-c] This point is illustrated by the ρ values of -0.05 and -0.66 for water- and base-catalyzed reactions which might have been thought to have proceeded little or not at all toward lactone (ρ for complete acyl transfer is -1.75), although it is very likely that these steps represent the decomposition of the tetrahedral intermediate.[20d]

It is not clear why a change in rate-determining step with pH does not seem to occur in the lactonization of *o*-hydroxyphenylpropionic acids[8] or in the hydrolysis of acyclic phenyl esters. This special property of coumarinic acids may be related to the presence of unsaturation in the side chain. Departure of water from the tetrahedral intermediate results in the formation of a oxocarbonium ion stabilized by extended allylic resonance. In the absence of such unusual stabilization, phenol may leave almost exclusively at all pH values to allow the greater stabilization offered by the two remaining hydroxyl groups. As a result, the rate-limiting steps in the lactonization of saturated phenolic acids and in the hydrolysis of phenyl acetates would remain, respectively, the departure and attack of water. The high thermodynamic stability of the coumarins compared to simple phenyl esters may also favor the expulsion of water from the cyclic tetrahedral intermediates. The planarity of the product, with the consequent extended π overlap, would be partially lost on expulsion of phenol and would provide a driving force for expulsion of water from the intermediate.

An estimate of the large rate accelerations obtained in the intramolecular lactonization of coumarinic acid can be made by comparison to the rates of reaction of phenol with acetic acid. For the reactions subject to acid, water, and base catalysis, the "effective molarities" of the intramolecular process are 4×10^{10}, 1.7×10^{9}, and 4×10^{11} M, respectively.[21] The ratio of the equilibrium constants for the intra- and intermolecular reactions is 3.8×10^{11} M.

The ratio of the rates of lactonization of the very highly reactive *o*-hydroxy-*o*-methyl-β,β-dimethylphenylpropionic acid[8c] to those of 4 are 6×10^{5}, 1.4×10^{2}, and 8 for the acid-, water-, and base-catalyzed reactions, respectively.[21a] It is worth noting that although the lactonization of coumarinic acids occurs some 10^{10} times faster than the esterification of phenol, the sensitivity to changes in electron density at the reaction center is approximately the same for both systems. Several recent publications[17b,20a-c,25] have pointed out that, in reactions where proton transfers are necessary, there need not be a continuous variation in either the size or sign of ρ values with increasing reactivity (Leffler–Hammond effect), and arguments dependent on this assumption may be invalid.

Experimental Section

Coumarin, 6-methylcoumarin, and 7-hydroxycoumarin were obtained from Aldrich Chemical Co. 7-Hydroxycoumarin was recrystallized from ethyl acetate–heptane.

6-Nitro- and 6-aminocoumarin hydrochloride were prepared by the method of Morgan and Micklethwait.[26] **6-Acetamidocoumarin** was prepared by the addition of 5.6 g (0.072 mol) of acetyl chloride to a stirred solution of 9.7 g (0.06 mol) of 6-aminocoumarin and 4.75 g (0.06 mol) of pyridine in 100 ml of 1:1 chloroform–dichloro-

(20) (a) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968); (b) A. R. Fersht, *ibid.*, **93**, 3504 (1971); (c) C. K. Johnson and K. Schofield, *ibid.*, **95**, 270 (1973). (d) With the base-catalyzed reaction, the comparison of ρ values depends on the assumed mechanism. If this reaction were viewed as the attack of phenoxide ion on the carboxyl group, the resulting ρ = *ca.* -2.6 could be compared with ρ = *ca.* -3.75 for complete acyl transfer to phenoxide ion.

(21) (a) The kinetic data used for 4 were those for rate-limiting breakdown of the intermediate. (b) The rate of acid-catalyzed formation of phenyl acetate (1×10^{-10} M^{-2} sec^{-1}) was calculated from the rate of acid-catalyzed hydrolysis[22] and the equilibrium constant.[23] The rate of reaction of phenol with acetic acid was taken from ref 20b. The rate of the hydroxide-catalyzed formation of phenyl acetate (4.7×10^{-6} M^{-2} sec^{-1}) was calculated from the rate constant for alkaline hydrolysis[24] and the equilibrium constant.

(22) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc., London*, **141**, 1801 (1938).

(23) J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 4655 (1964).

(24) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).

(25) (a) F. G. Bordwell and W. J. Boyle, *ibid.*, **93**, 511, 512 (1971); **94**, 3907 (1972); (b) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H. W. Leung, and R. McDonald, *ibid.*, **95**, 160 (1973); (c) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

(26) G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc., London*, **85**, 1230 (1904).

methane at 0°. After being stirred for 1 hr at room temperature, the solution was filtered, extracted successively with dilute aqueous HCl, $NaHCO_3$, and water, then dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The residue was recrystallized from benzene.

6-Cyanocoumarin was synthesized from 6-aminocoumarin by a modification of the procedure of Dey and Salal.[27] A solution of 1.75 g of $NaNO_2$ in 8 ml of H_2O was added to 4 g of 6-aminocoumarin in 20 ml of concentrated HCl at 0–5°. After a few minutes, the solution was neutralized by the addition of Na_2CO_3 and added to 100 ml of H_2O containing 32 g of NaCN and *ca.* 40 g of Cu^ICl[28] at 50°. The solution was heated to 90°, allowed to come to room temperature, and stored for 12 hr. The solid product was collected by filtration and extracted with ethanol overnight in a Soxhlet extractor. The solid obtained after evaporation of the ethanol was recrystallized from ethanol–H_2O. A mass spectrum showed a molecular ion at 171 (*m/e*).

Coumarin-6-carboxylamide was synthesized from 6-cyanocoumarin according to the procedure of Dey and Salal;[27] mass spectrum: molecular ion at 189 (*m/e*). *Anal.* Calcd for $C_{10}H_7NO_3$ (189.17): C, 63.5; H, 3.70; N, 7.41. Found: C, 63.39; H, 3.87; N, 7.13.

6-Hydroxycoumarin was prepared according to DeGraw and Tsakotellis.[29]

6-Coumaryltrimethylammonium iodide was prepared by the procedure of Morgan and Micklethwait,[26] except that an additional equivalent of methyl iodide was added after 3 hr at reflux and refluxing was continued overnight. **6-Coumaryltrimethylammonium perchlorate** was prepared by stirring 0.22 g of the iodide salt with 0.140 g of $AgClO_4$ in 50 ml of methanol, filtration, evaporation of the filtrate, and recrystallization of the residue from 90% aqueous ethanol.

5,7-, and 5,8-dimethylcoumarin were prepared by a modification of the general procedure of Clayton;[30] 0.1 mol of the appropriate phenol and 0.1 mol of either malic acid or ethyl acetoacetate were heated in 30 cm^3 of concentrated H_2SO_4 at 50–80° for 2–3 hr with stirring. When bubbling had subsided, the solution was allowed to cool, poured on crushed ice, and filtered. The solid product was dissolved in aqueous NaOH, precipitated by addition of 3 *M* HCl, collected by filtration, and extracted overnight with petroleum ether in a Soxhlet extractor, and the solvent removed under vacuum. The remaining white solid was recrystallized from ethanol.

6-Bromocoumarin was prepared by the procedure of Pearson, *et al.*[31] Melting point values for the coumarins prepared for this study are recorded in Table VI.

Table VI

Coumarin derivative	Mp (lit.), °C	λ_1, nm[a]	λ_2, nm[b]	λ_3, nm[c]
6-OH	253–255 (247–248)[d]	278	240	280
5,8-$(CH_3)_2$	121 (122–123)[e]	310	285	255
5,7-$(CH_3)_2$	133–134	310	285	256
6-CH_3		279	285	255
H		280	285	250
6-CH_3CONH	221–222 (216–217)[f]	285	242	280
7-OH		325		320
6-Br	166–168 (165–166)[g]	286		254
6-NH_3^+Cl	163–168 (163–164)[h]	280		
6-$CONH_2$	251–252 (203)[i]	320	305	320
6-$(CH_3)_3N^+ClO_4^-$	252–253[j]	275	240	251.5
6-CN	224–226 (220)[i]	254	294	263
6-NO_2	193–195 (181–182)[h]	263	265	315

[a] Wavelength used for lactonization kinetics. [b] Wavelength for pK_a determination. [c] Wavelength used to follow coumarin hydrolysis. [d] Reference 29. [e] Reference 30. [f] L. Gattermann, *Chem. Ber.*, **27**, 1927 (1894). [g] D. E. Pearson, W. E. Stamper, and B. R. Suthers, *J. Org. Chem.*, **28**, 3147 (1963). [h] Reference 26. [i] Reference 27. [j] Iodide salt, mp 214–215; reported mp 202–207 (ref 26).

Deuterium chloride (38% in D_2O, >99% D) and deuterium oxide (99.7% D) were obtained from Merck Sharp and Dohme of Canada, Ltd.

Kinetic Measurements. Buffers and inorganic salts were used without further purification. Glass-distilled water was used in the preparation of aqueous solutions. The lactonization of all coumarinic acids was studied at 30° in aqueous solution containing 0.1% ethanol, μ = 1.0, adjusted with LiCl. Solutions used in the hydrolysis of coumarin derivatives contained 0.5% acetonitrile. Constant pH was maintained with HCl at pH <2.5; at higher pH, formate, acetate, and MES (2-morpholinethanesulfonate) buffers were used at concentrations generally between 0.04 and 0.1 *M*. The hydrolysis of substituted coumarins was studied in 0.005–0.2 *M* NaOH (μ = 1.0, LiCl). In 0.005–0.01 *M* HCl solutions (30°, μ = 1.0, LiCl) the equation pH = −log [HCl] − 0.21 is obeyed and was used in the calculation of pH below pH 2.1. At pH >2, a Radiometer TTT1c meter equipped with scale expander was used to measure pH. In dilute NaOH solution (0.002–0.02 *M*, 30°, μ = 1.0) the measured pH obeyed the equation pH = 13.28 + log [OH] and the activity of hydroxide ion was calculated assuming $K_w = 1.48 \times 10^{-14}$. This equation was used to calculate the activity of hydroxide ion for concentrations of hydroxide ion up to 0.2 *M*.

Rates of lactonization and hydrolysis of all coumarinic acids were determined spectrophotometrically at the wavelengths listed in Table VI. Stock solutions for lactonization experiments were prepared by dissolving 0.1–0.2 mmol of coumarin derivative in 1 ml of ethanol in a 5-ml volumetric flask, adding 0.3–0.6 mmol of NaOH, diluting to the mark with 1.0 *M* LiCl, and warming until complete solution was effected. In most cases, these solutions could be stored in a refrigerator for several days without deterioration. The 6-OH and 7-OH derivatives were hydrolyzed for at least 1 hr in 0.1 *M* NaOH before use and fresh stock solutions were prepared daily. For coumarin hydrolysis experiments, stock solutions of *ca.* 0.01 *M* coumarin in acetonitrile were used. In either case, reactions were initiated by the addition of 0.015 ml of stock solution to 3 ml of aqueous buffer equilibrated at 30° in the cell compartment of a Cary 15 spectrophotometer. Reactions were followed to at least 3 half-lives and generally to greater than 6. For reactions in which an infinity reading was not obtained, a modified Guggenheim treatment[32] was used to calculate the infinity value. Rate constants were then calculated using the integrated form of the first-order rate equation and were generally reproducible to better than 3%.

pK_a Determinations. The pK_a values of the coumarinic acid carboxyl groups were determined by spectrophotometric titration at 30°, μ = 1.0 (LiCl), using absorbance data which had been extrapolated to zero time. Table VI records the wavelengths used for each compound. The data were plotted using eq 7 where A_2 and

$$\log (A_2 - A_0)/(A_0 - A_1) = pK' - pH \qquad (7)$$

A_1 are the absorbances of the dissociated and undissociated acids, respectively, and A_0 is the absorbance at a given pH. Where A_2 could not be directly measured because of interference from ionization of the phenolic group (6-NO_2, 6-$(CH_3)_3N^+$, 6-CN), the method of Reed and Berkson[33] was used to estimate A_2.

Curve Fitting Procedure for pH–Rate Profiles. Least-squares values and standard deviations of the parameters k_1, P^+, P^0, and K' (eq 2) were calculated by means of an iterative computer program written following the method outlined by Usher, *et al.*[34] The weighting estimates used by Usher, *et al.*,[34a] were adopted, and calculations were performed by means of an IBM 370/155 computer.

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Supplementary Material Available. Table I will appear following

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Secondary Deuterium Isotope Effects for Addition of Nitrogen Nucleophiles to Substituted Benzaldehydes[1a]

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Abstract: Kinetic secondary deuterium isotope effects, k_D/k_H, for the water-catalyzed addition of semicarbazide to a series of substituted benzaldehydes are near 1.30 and are independent of the nature of the polar substituent; corresponding values for the same reaction catalyzed by the hydrated proton and other acids are near 1.21. Values of k_D/k_H for the water-catalyzed addition of phenylhydrazine to substituted benzaldehydes decrease from 1.28 to 1.16 as the nature of the polar substituent is varied from *p*-methoxy to *p*-nitro. The corresponding values for the same reaction catalyzed by the hydrated proton decrease from 1.21 to 1.13 for the same substituents. These results indicate that the extent of carbon–nitrogen bond formation in the transition state for addition of nucleophiles to the carbonyl group is a function of the reactivity of substrate, nucleophilic reagent, and the strength of the catalyzing acid. The secondary deuterium isotope effect on the equilibrium constant for carbinolamine formation from benzaldehyde and hydroxylamine is near 1.36, larger than the largest of the kinetic effects observed. Under conditions in which carbinolamine dehydration is rate determining, values of k_D/k_H for the overall rate of semicarbazone formation from benzaldehydes decrease from 1.31 to 1.20 as the nature of the polar substituent varies from hydrogen to *p*-nitro. This result demonstrates that the extent of carbon–oxygen bond cleavage in the transition state for carbinolamine dehydration is a function of the nature of the polar substituent of the substrate. Moreover, for those substituents which are not strongly electron withdrawing, the transition state closely resembles the carbinolamine itself.

One of the central questions in physical organic chemistry is the relationship between substrate structure and transition-state structure. This subject has been treated theoretically several times[2-6] and a number of experimental approaches, including study of linear free energy relationships and isotope effects, have been brought to bear on it. Among these, α-deuterium isotope effects have proved useful indicators of transition-state structures in several cases.[7] For example, measurement of the α-deuterium isotope effects for the hydrolysis of acetals and orthoformates revealed a marked change in the degree of carbon–oxygen bond cleavage in the transition state as a function of substrate structure, clarifying structure–reactivity relationships for these hydrolyses.[8]

Simple carbonyl addition reactions provide one of the most versatile settings in which to study the relationship between substrate and transition-state structure. For example, the addition of amines to carbonyl compounds proceeds with rate-determining attack of the nucleophilic reagent under acidic conditions and with rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions.[9,10]

$$>C{=}O + RNH_2 \rightleftharpoons -\overset{\overset{OH}{|}}{\underset{\underset{H}{|}}{C}}-N(H)-R \rightleftharpoons >C{=}N-R + H_2O$$

Consequently, through appropriate choice of experimental conditions, one can probe the transition-state structure for both steps employing a single set of compounds.

As a specific set of reactants, substituted benzaldehydes have been chosen as the carbonyl component and semicarbazide and phenylhydrazine as amines. This provides for study of the effect of variation in reactivity of both substrate and nucleophile on transition-state structure. Moreover, with these reactants, the addition step exhibits a pH-independent reaction as well as specific and general acid catalysis.[11,12] Consequently, the strength of the acid catalyst is an additional variable whose effect on transition-state

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