Concurrent General-Acid and General-Base Catalysis of Esterification[1]

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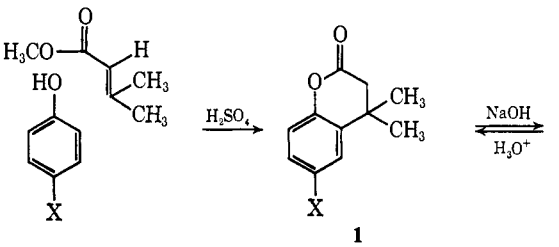
Abstract: The rates of lactonization of a series of β,β-dimethyl(2-hydroxy-5-X)hydrocinnamic acids have been determined as functions of X (eight variations), pH, and buffer components. The rate of hydronium ion catalyzed lactonization increases with the pK of the phenolic nucleophile ($\rho = -1.68$) and shows a solvent–deuterium isotope effect of *ca.* 0.9. In weakly acidic media, lactonization was found to proceed at measurable rates, the reaction being catalyzed concurrently and independently by the acidic and basic buffer species ($\rho_{RCOOH} = -1.50$; $\rho_{RCOO^-} = -0.80$). For X = OCH_3, $k'_{obsd} = 10^{-5}(0.083[H_2O] + 4360[H_3O^+] + 7.20[HCOOH] + 23.2[HCOO^-] + 3.50 \cdot [CH_3COOH] + 27.5[CH_3COO^-])$. No evidence was found for concerted catalysis by both buffer species. The buffer components show kinetic-solvent isotope effects of *ca.* 2. Activation entropies of −20 eu for hydronium ion and −28 eu for buffer acid catalysis were observed. Although the kinetic results, isotope effects, and activation entropies fail to distinguish between rate-determining formation or breakdown of a tetrahedral intermediate, the variations in ρ are considered to favor the latter as the rate-limiting step.

In the course of studies on the conservation of oxidative free energy in covalent bonds,[2] the hypothesis was advanced that a phenolic species, such as ubihydroquinone, is capable of participating in ester formation with a protein carboxyl group, without prior carboxyl activation. The standard free energy of formation of phenyl acetate from its components, in dilute aqueous solution, has been calculated to be +7400 cal/mol.[3] It was envisioned that such a thermodynamically unfavorable process could be compensated, in part, by the entropy advantage and by the conformational restriction generated in a protein–substrate association.[4]

The chemical transformations occurring within a protein–substrate complex are more appropriately simulated by simple intramolecular than by intermolecular model reactions.[5] Accordingly, it is reasonable to attempt to demonstrate the thermodynamic, and perhaps the kinetic, feasibility of our hypothesis by means of intramolecular models for the esterification of phenols with carboxylic acids. Various 3-*o*-hydroxyphenylpropionic acids cyclize completely under appropriate conditions,[6] the parent compound requiring strongly acidic media.[6b] As substitution is introduced to the propionic acid side chain, the rate of lactonization is modestly enhanced,[6c] apparently the result of partial conformational restriction. In the series of compounds used in the present study (**1**, **2**) a *gem*-dimethyl group has been added to the benzylic carbon of the side chain, in the expectation of creating even greater rate enhancement by minimizing nonproductive conformations.



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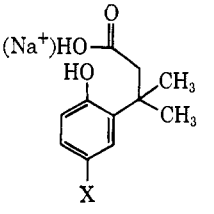

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Among the factors responsible for enzyme catalysis are the ability of various protein functional groups to serve catalytically as general acids and general bases and the high degree of conformational restraint to which the substrate is subjected upon complex formation.[4] This report deals, in part, with the role of acid–base catalysis in intramolecular esterification. In a subsequent paper, the role of conformational restraint as a rate-enhancement factor will be examined.

Experimental Section[7]

Materials. The substituted phenols used for alkylation were the highest purity commercial products available. *p*-Ethylphenol was recrystallized from hexane, mp 47–48°. 3-Methylcrotonic acid (Aldrich Chemical Co.) was converted into its methyl ester in methanol–sulfuric acid, bp 135–137°.[8] Lactones (**1**) were prepared by condensing the appropriate phenol with methyl 3-methylcrotonate

(1) A preliminary report of this work has been published: S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, 91, 4585 (1969).

(2) (a) J. W. Thanassi and L. A. Cohen, *Biochim. Biophys. Acta*, 172, 389 (1969); (b) J. W. Thanassi and L. A. Cohen, *J. Amer. Chem. Soc.*, 89, 5733 (1967); (c) W. Durckheimer and L. A. Cohen, *Biochemistry*, 3, 1948 (1964); (d) W. Durckheimer and L. A. Cohen, *J. Amer. Chem. Soc.*, 86, 4388 (1964).

(3) J. Gerstein and W. P. Jencks, *ibid.*, 86, 4655 (1964).

(4) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., Inc., New York, N. Y., 1969, Chapter 1.

(5) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 119.

(6) (a) G. L. Schmir, L. A. Cohen, and B. Witkop, *J. Amer. Chem. Soc.*, 81, 2228 (1959); (b) H. Hochstetter, *Ann.*, 226, 355 (1884); (c) O. Neubauer and L. Flatow, *Z. Physiol. Chem.*, 52, 376 (1907).

(7) All analyses were performed by the Microanalytical Section of this laboratory, under the direction of Dr. W. C. Alford. Melting points and boiling points are uncorrected.

(8) M. Halmos and T. Mohàcsi, *J. Prakt. Chem.*, 12, 50 (1960).

Table I. Lactones (1) Obtained by Alkylation of *p*-X-Phenols

X	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
OH[a]	83–85	$C_{11}H_{12}O_3$	68.73	6.29		68.71	6.18	
OCH_3	120 (0.2)	$C_{12}H_{14}O_3$	69.88	6.84		69.78	6.71	
C_2H_5	116–118 (0.5)	$C_{13}H_{16}O_2$	76.44	7.90		76.68	8.06	
H	81–83 (0.15)	$C_{11}H_{12}O_2$	74.97	6.86		75.14	6.79	
F	85–87 (0.2)	$C_{11}H_{11}FO_2$	68.03	5.71		67.95	5.86	
Cl	90–91	$C_{11}H_{11}ClO_2$	62.72	5.26		62.98	5.52	
$N(CH_3)_2$[b]	52–54	$C_{13}H_{17}NO_2$	71.20	7.82	6.39	71.38	7.92	6.65
$N(CH_3)_3{}^+I^-$[b,c]	Dec	$C_{14}H_{20}INO_2$	46.56	5.58	3.88	46.32	5.70	3.81
NO_2[b]	134–135	$C_{11}H_{11}NO_4$	59.72	5.01	6.33	59.68	5.08	6.27

[a] Solid lactones were recrystallized from benzene or hexane. [b] These lactones were obtained by reactions other than direct alkylation (see Experimental Section). [c] Recrystallized from ethanol–ether.

Table II. Salts of Phenolic Acids (2)[a]

X	pK_a	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
OH[b]	4.88	$C_{17}H_{29}NO_4$	65.56	9.39	4.50	65.67	9.66	4.49
OCH_3	5.10	$C_{12}H_{15}O_4Na$	58.54	6.14		58.40	6.24	
C_2H_5	5.19	$C_{13}H_{17}O_3Na$	63.92	7.02		64.08	7.17	
H[c]	4.95	$C_{11}H_{13}O_3Na$	61.10	6.06		61.09	6.41	
F	5.25	$C_{11}H_{12}FO_3Na$	56.41	5.16		56.08	5.43	
Cl[d]	4.91	$C_{17}H_{26}ClNO_3$	62.28	7.99	4.27	62.46	7.80	4.16
NO_2[d]		$C_{17}H_{26}N_2O_5$	60.34	7.74		60.15	7.67	

[a] Isolated as sodium salts, unless otherwise specified. [b] Triethylammonium salt. [c] pK_a^D in D_2O = 5.42. [d] Cyclohexylammonium salt.

in the presence of sulfuric acid.[9] Yields of purified materials ranged from 10 to 30%; no effort was made to effect improvements. Since direct alkylation failed with *p*-nitrophenol, the 6-nitrolactone (**1**, X = NO_2) was prepared by nitration of the parent lactone (**1**, X = H), by use of fuming nitric acid in acetic anhydride–acetic acid solution at −5°.[10] The assignment of position for the nitro group is based on the analogous nitration of coumarin[11] and on the fact that the ultraviolet spectrum of the hydroxy acid (**2**, X = NO_2), uv max (C_2H_5OH) 333 nm (log ϵ = 3.72), resembles more closely that of 2-methyl-4-nitrophenol than that of 2-methyl-6-nitrophenol.[12]

The dimethylamino lactone (**1**, X = $N(CH_3)_2$) was prepared by catalytic hydrogenation (palladium–charcoal) of an ethanolic solution of the nitro lactone in the presence of slightly more than 2 equiv of aqueous formaldehyde. When hydrogenation was complete (5 equiv, 1 hr), catalyst and solvent were removed and the product was crystallized from hexane, mp 52–54°. The methiodide (**1**, X = $N(CH_3)_3{}^+ I^-$) was obtained by heating a solution of the dimethylamino lactone in methyl iodide at reflux, the product separating rapidly. The methiodide was recrystallized from ethanol–ether. Physical and analytical data for the lactones are reported in Table I.

Phenolic Acid Salts. The lactones were hydrolyzed by heating at reflux their solutions in 50% aqueous ethanol, to which had been added slightly less than 1 equiv of sodium hydroxide. In general, hydrolysis was complete in 2–4 hr. After removal of solvent, the sodium salts were crystallized by careful addition of acetone to their solutions in methanol. In two instances (X = Cl, NO_2), solutions of the lactones in 50% aqueous triethylamine were heated at reflux overnight. After removal of solvent, the residues were dissolved in methanol–acetone and cooled. Excess cyclohexylamine was added and the precipitates were collected by filtration. These salts were recrystallized from methanol–acetone–ether.

Because of its ease of oxidation, the hydroquinone derivative (**2**, X = OH) was prepared under anaerobic conditions. A solution of the lactone (**1**, X = OH) in 50% aqueous ethanol containing a large excess of triethylamine, was heated overnight in a sealed tube from which oxygen had been removed. The tube was chilled and solvent removed by lyophilization. The residue was suspended in acetone, collected by centrifugation, and stored at low temperature. Although the triethylammonium salt is stable in the dry state, ethanolic solutions turned red rapidly at ambient temperature; fresh solutions were prepared prior to kinetic runs.

No attempt was made to isolate salts of the hydroxy acid corresponding to the trimethylammonio lactone (**1**, X = $N(CH_3)_3{}^+$). A solution of the sodium salt was prepared as described above, aliquots being used directly for kinetic runs. Analytical data for salts of the hydroxy acids are given in Table II.

Kinetic Measurements. Buffers were prepared from commercial reagent grade materials, using deionized, distilled water. The pH of each solution was measured on a Model TTT-1c radiometer pH meter, equipped with a scale expander. In selected cases, the pH was measured before and after kinetic runs; in no case was a pH change of greater than 0.02 unit detected. In work utilizing 99.8% D_2O as solvent, the glass-electrode correction formula of Fife and Bruice[13] was employed in the determination of pD.

The rates of lactonization were measured spectrophotometrically by following the appearance of lactone absorption at 240–260 nm,[14] or the disappearance of phenol absorption at 280 nm, using a Model 15 Cary recording spectrophotometer, equipped with an automatic sample-changing accessory. Constant temperature was maintained by circulation of water from a Haake KT41 constant-temperature bath through the sample holder and walls of the spectrophotometer cell compartment. The temperature in the cell compartment was monitored continuously with a Yellow Springs Tele-thermometer, whose output was displayed on a 6-in. recorder. The temperature was maintained to at least 0.05°.

The lactonization reaction was initiated by addition of 10–20 μl of *ca.* 5×10^{-2} *M* solution of the salt of the phenolic acid in ethanol to 3 ml of a previously equilibrated solution of buffer in the cuvette. The ionic strengths of all solutions were maintained at 0.3 *M* with NaCl. The rates were generally followed to completion of lactonization, the final spectra invariably duplicating those of equivalent solutions of lactones. Pseudo-first-order rate constants were calculated on a General Electric 265 computer, using a program designed to calculate a least-squares evaluation of a plot of ln $(OD_\infty - OD_0)/(OD_\infty - OD_t)$ *vs.* time. The correlation coefficients were usually greater than 0.9999. The second-order catalytic rate constants were obtained by a least-squares calculation of k_{obsd} *vs.* concentration of catalyst. Activation parameters were obtained

(9) S. Colonge, E. LeSech, and R. Marey, *Bull. Soc. Chim. Fr.*, 776 (1957). The lactones (1) are properly named 4,4-dimethyl-6-X-hydrocoumarins; the corresponding acids (2) are β,β-dimethyl(2-hydroxy-5-X)hydrocinnamic acids.

(10) B. M. Wepster and P. E. Verkade, *Rec. Trav. Chim.*, **68**, 77 (1949).

(11) G. Morgan and F. Micklethwaite, *J. Chem. Soc.*, **85**, 1233 (1904).

(12) V. Balish and M. Uma, *J. Indian Chem. Soc.*, **39**, 810 (1962); W. R. Vaughan and G. K. Finch, *J. Org. Chem.*, 21, 1201 (1956).

(13) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

(14) In the case of the nitro compound, appearance of lactone was followed at 285 nm.

Table III. Rate Constants (M^{-1} sec^{-1}) for Lactonization at 30° (μ = 0.3 M)

X	$10^2k_{H_3O^+}$	$10^2k_{D_3O^+}$	10^5k_{HCOOH}	10^5k_{HCOOH} (D_2O)	$10^4k_{HCOO^-}$	$10^4k_{HCOO^-}$ (D_2O)	$10^5k_{CH_3COOH}$	$10^4k_{CH_3COO^-}$	10^5k_0 [a]
OH	5.33	6.02	9.50	6.23	2.50	0.72	3.72	4.20	4.60
OCH_3	4.36	4.84	7.20		2.32		3.50	2.75	4.64
C_2H_5	4.29		7.58		2.63				
H	2.72	3.12	5.10	2.33	1.72	0.89	2.34	1.96	3.63
F	1.78		3.00		1.61				3.48
Cl	1.07	1.14	2.59		1.20		0.93	1.42	2.78
$N(CH_3)_3^+$	0.16								
NO_2	0.05	0.07							
ρ [b]	−1.68	−1.66	−1.50		−0.75		−1.50	−0.80	−0.55

[a] Sec^{-1}. [b] Based on a least-squares analysis of rate constants.

by computer analysis of plots of ln $k_{cat.}$ *vs.* $1/T$ (°K). In all such calculations, standard deviations were within ±3%.

pK_a Determinations. Owing to the rapid lactonization of the phenolic acids, the pK_a values of the carboxyl groups were determined by the method of half-neutralization in 0.3 M sodium chloride. The results are given in Table II. Reproducibility of the values was ±0.02 pK unit, although accuracy was probably somewhat lower. A moderate error in the pK_a values would have relatively little effect on the overall kinetic constants. As a check, the pK_a value of acetic acid was found to be 4.76 by half-neutralization of sodium acetate in 0.3 M sodium chloride and 5.06 in D_2O. The pK_a value of formic acid was found to be 3.77 in 0.3 M sodium chloride and 4.09 in D_2O.

Results

Hydronium Ion Catalysis. Catalysis of lactonization by hydronium ion was examined in the range of 0.01–0.3 M hydrochloric acid. In this region, all the compounds studied obey the rate law for simple hydronium ion catalysis (eq 1) where k_0 is the rate constant for the

$$k_{obsd} = k_0 + k_{H_3O^+}[H_3O^+] \quad (1)$$

spontaneous or water-catalyzed reaction and $k_{H_3O^+}$ is the second-order rate constant for hydronium ion catalysis. No corrections were made for ionization of the substrates since, at the lowest concentration of acid employed, all the compounds were less than 1% ionized. Plots of k_{obsd} *vs.* [HCl] are shown in Figure 1 for eight

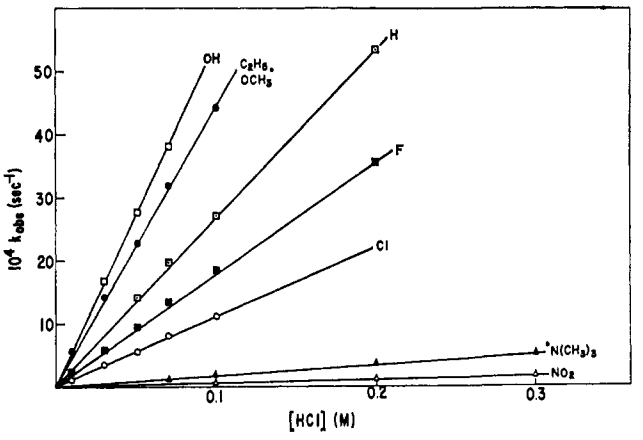


Figure 1. Observed rates of lactonization of **2**, as a function of acid concentration and the nature of the *para* substituent.

variations of X in **2**. The kinetic results, in both H_2O and D_2O, are presented in Table III. In general, $k_{H_3O^+}$ was obtained from duplicate runs at five to six acid strengths and $k_{D_3O^+}$ from four to five values of $[D_3O^+]$. Values of the specific rate constants were obtained by computer regression analysis, with correlation coefficients all >0.995. The values of k_0 are much smaller than those of $k_{H_3O^+}$ and usually not significantly greater than zero.[15] The solvent isotope effect was found to be *ca.* 0.9 for the compounds studied (Table VI), a value consistent with that for other cases of hydronium ion catalysis.[16]

The rate of acid-catalyzed lactonization decreases as the substituent *para* to the phenolic hydroxyl becomes more electron withdrawing. A Hammett plot of log $k_{H_3O^+}$ *vs.* σ (Figure 2) provides a linear correlation with

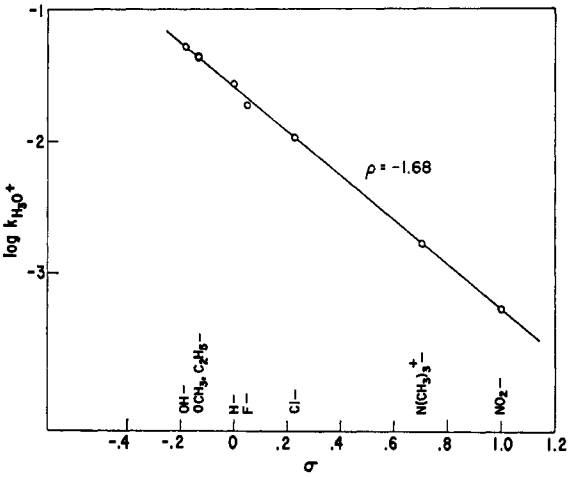


Figure 2. Hammett plot of the catalytic rate constants for the lactonization of **2** in acidic media *vs.* σ for the *para* substituent.

a slope, ρ, of −1.68. The σ values used were calculated from the dissociation constants of the corresponding phenols and the regression line, pK_a = 9.92 − 2.23σ (Table IV).[17,18] For the *p*-nitro substituent, the σ value of +1.0, proposed by Bruice and Benkovic,[19] was found to give an excellent correlation.

The effect of temperature on rate of lactonization was determined for five compounds in the range 20–50°. Second-order rate constants are presented in Table V and the resultant activation parameters in Table VI.

(15) The values of k_0 given in Table III were obtained from rate data in buffer media (see below).
(16) K. B. Wiberg, *Chem. Rev.*, **55**, 719 (1955).
(17) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).
(18) The influence of the *t*-alkyl side chain on the pK_a of the phenolic group in **2** would probably vary slightly with the nature of the *para* substituent and the resultant requirements for phenoxide ion solvation (see L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963)). However, deviations from strict additivity may be unimportant in the nucleophilic properties of partially hindered phenols.
(19) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).

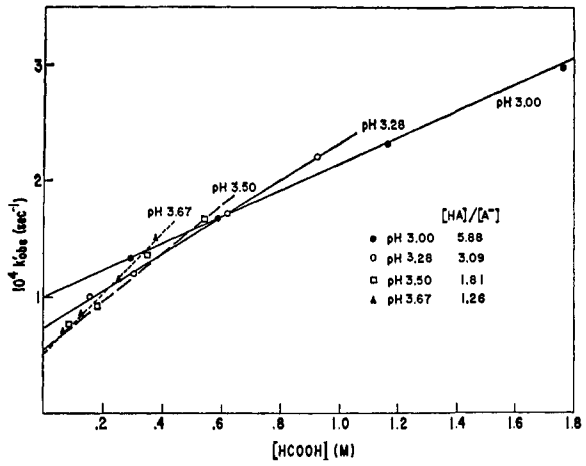


Figure 3. Observed rates of lactonization (k') of **2** (X = OCH_3) in formate buffer, as a function of pH and concentration of buffer acid.

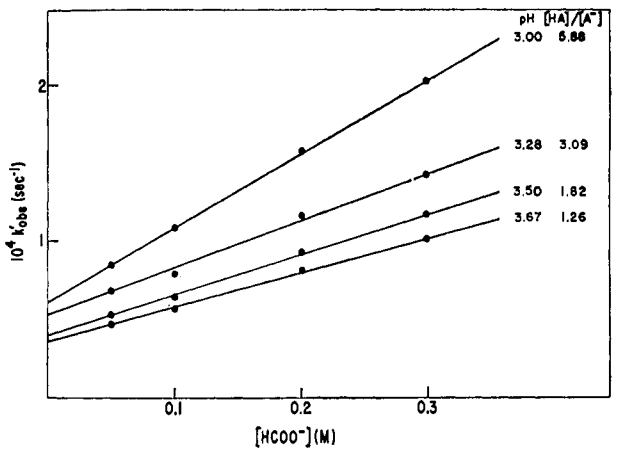


Figure 4. Observed rates of lactonization (k') of **2** (X = OCH_3) in formate buffer, as a function of pH and concentration of buffer anion.

Table IV. σ Constants Derived from Phenol Ionization Data

X	pK_a (25°)	σ^a
OH	10.30[b]	−0.17
OCH_3	10.21[c]	−0.13
C_2H_5	10.21[d]	−0.13
F	9.81[e]	+0.05
Cl	9.42[c]	0.22
$N(CH_3)_3^+$	8.35[f]	0.70
NO_2		1.00[g]

[a] Calculated from the regression line of ref 17. [b] Estimated from a value of 10.35 at 20° (R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, **11**, 1 (1928)). [c] Reference 17. [d] E. L. Wehry and L. B. Rogers, *J. Amer. Chem. Soc.*, **87**, 4234 (1965). [e] C. M. Judson and M. Kilpatrick, *ibid.*, **71**, 3110 (1949). [f] H. C. Ko, W. F. O'Hara, T. Hu, and L. G. Hepler, *ibid.*, **86**, 1003 (1964). [g] Reference 19.

Table V. Variation of $k_{H_3O^+}$ with Temperature (μ = 0.3 *M*)

	$10^2 k_{H_3O^+}$, M^{-1} sec^{-1}				
X	20°	30°	35°	40°	50°
OH	2.43	5.33	8.02	12.30	
OCH_3	1.95	4.36	6.37	8.86	
H		2.72	4.13	5.79	12.10
Cl		1.07	1.57	2.36	5.01
NO_2		0.05	0.09	0.13	0.36

Table VI. Activation Parameters and Isotope Effects for H_3O^+ Catalysis

X	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[a] eu	$k_{H_3O^+}/k_{D_3O^+}$
OH	14.6	14.0 ± 0.2[b]	−17.8 ± 0.7	0.88
OCH_3	13.8	13.2 ± 0.1	−20.9 ± 0.4	0.90
H	14.6	14.0 ± 0.2	−19.5 ± 0.6	0.87
Cl	15.0	14.4 ± 0.1	−19.8 ± 0.3	0.94
NO_2	18.3	17.7 ± 0.3	−14.8 ± 1.1	0.81

[a] Calculated at 30°. [b] Errors are standard deviations; all correlation coefficients were greater than 0.995.

Buffer Catalysis. Preliminary studies with various buffers and buffer dilutions revealed a dependence of lactonization rate on the concentration of buffer components at constant pH. Initially, catalysis by buffer acid alone was anticipated on the basis of mechanistic reasoning and the suggestions of buffer-acid catalysis in earlier studies of bimolecular[20a] and intramolecular esterification.[20b] However, plots of k_{obsd} (corrected for the degree of carboxyl ionization in **2**) *vs.* concentration of buffer acid, although linear, failed to give a constant slope (k_{HA}) at various pH values (Figure 3; **2**, X = OCH_3), as required for a reaction obeying eq 2,

$$k'_{obsd} = (k_0 + k_{H_3O^+}[H_3O^+]) + k_{HA}[HA] \quad (2)$$

where

$$k'_{obsd} = k_{obsd}K_a/(K_a + [H_3O^+])$$

The unanticipated result suggested the possibility that buffer anion was also active as a catalyst, *i.e.*, that the reaction followed the rate law of eq 3

$$k'_{obsd} = (k_0 + k_{H_3O^+}[H_3O^+]) + k_{HA}[HA] + k_{A^-}[A^-] \quad (3)$$

By setting $[HA]/[A^-] = R$

$$k'_{obsd} = (k_0 + k_{H_3O^+}[H_3O^+]) + (Rk_{HA} + k_{A^-})[A^-] \quad (4)$$

or

$$k'_{obsd} = (k_0 + k_{H_3O^+}[H_3O^+]) + S[A^-] \quad (5)$$

where

$$S = Rk_{HA} + k_{A^-} \quad (6)$$

It follows from eq 5 that a plot of k'_{obsd} *vs.* $[A^-]$, at fixed pH, should be linear, with slope = S and intercept = $(k_0 + k_{H_3O^+}[H_3O^+])$.[21] The results are shown in Figure 4 for **2**, X = OCH_3, a series of pH values providing a set of corresponding S values. By plotting S *vs.* the buffer ratio, R, for each pH value, k_{HA} and k_{A^-} can be evaluated as the slope and intercept, respectively, of eq 6. The results of such an analysis are shown in Figure 5 for formate buffers at 30°. The slopes and inter-

(20) (a) A. C. Rolfe and C. N. Hinshelwood, *Trans. Faraday Soc.*, **30**, 935 (1934); (b) D. P. Weeks, as cited in J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, **87**, 2214 (1965); D. P. Weeks and X. Creary, Abstracts of the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, ORGN-64.

(21) Reference 5, p 11; Y. Pocker and J. E. Meany, *J. Phys. Chem.*, 71, 3113 (1967).

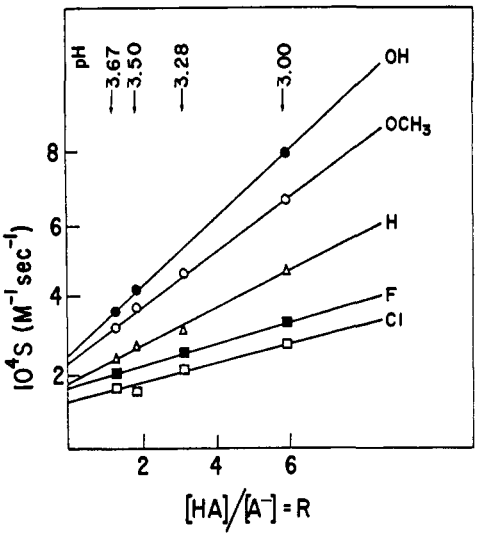


Figure 5. Plots of S (see text) *vs.* formate buffer ratio, as a function of the *para* substituent in **2**.

cepts are recorded in Table III as k_{HCOOH} and k_{HCOO^-}. A similar analysis for acetate buffers provides values of k_{CH_3COOH} and $k_{CH_3COO^-}$ (Table III). The linearities of the plots of Figures 4 and 5, over a wide range of buffer concentrations, indicate the absence of any significant catalysis by the concerted action of buffer acid and anion. Values of k_0 were obtained by subtracting $k_{H_3O^+}[H_3O^+]$ from the intercept values of eq 5 (Figure 4) and are recorded in Table III. Second-order rate constants for several compounds were obtained in formate buffers in D_2O (Table III). The solvent isotope effect (Table VII, av $k_{H_2O}/k_{D_2O} \sim 2$) suggests proton

Table VII. Activation Parameters and Solvent-Deuterium Effects for Buffer Catalysis

Catalyst	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$,[a] eu	k_H/k_D
H_3O^+ [b]	14	−20	0.9
HCOOH[c]	15	−28	1.9
$HCOO^-$ [c]	15	−27	2.2

[a] Calculated at 30°. [b] Averages of first four values in Table VI. [c] Based on data for X = OCH_3 and Cl, which gave essentially the same results.

transfer to be involved in the rate-determining step, both for general-acid and general-base catalysis.

In Table VII are listed the activation parameters for general-acid and general-base catalysis in the lactonization of **2** (X = OCH_3, Cl) in formate buffer. Although the enthalpies of activation are similar to those for hydronium ion catalysis, the entropies of activation are more negative by *ca.* 8 eu. As in the case of hydronium ion catalyzed lactonization, the rates of the general-acid and general-base catalyzed reactions are influenced by the electronic natureof the *para* substituent in **2**. Hammett plots of log k *vs.* σ for formate and acetate buffer species are shown in Figure 6, and the corresponding ρ values are listed in Table III. Exploratory runs demonstrated the existence of concurrent general-acid–general-base catalysis in other buffer media, including phosphate, glycine, imidazole, and Tris. A Brønsted

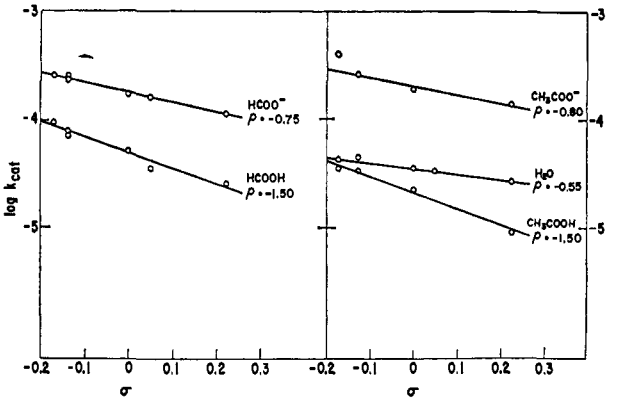


Figure 6. Hammett plots of catalytic rate constants for the lactonization of **2** in buffer media *vs.* σ for the *para* substituent.

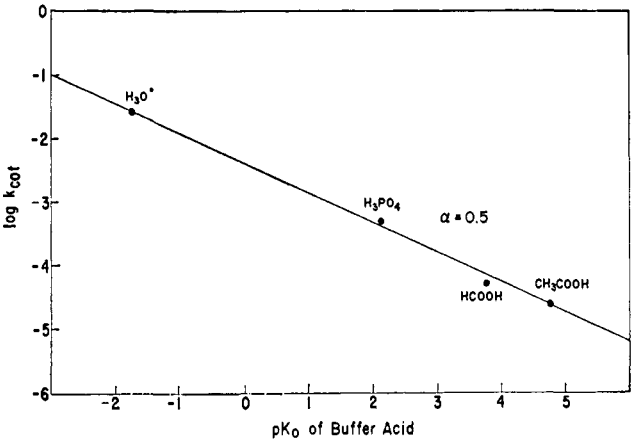


Figure 7. Brønsted plot of log $k_{cat.}$ *vs.* pK_a of the buffer acid for the lactonization of **2** (X = OCH_3).

plot for acidic species (Figure 7) provides a slope, α, of 0.5.

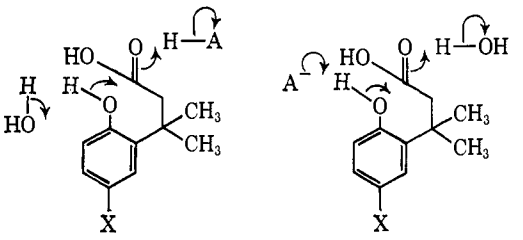
Discussion

Bimolecular esterification reactions are generally considered to involve a rate-determining attack of the hydroxyl component on the protonated carboxylic acid, with formation of a transient tetrahedral intermediate.[22] An alternative mechanism, in which collapse of the tetrahedral intermediate is rate limiting, is kinetically indistinguishable from the former. Furthermore, variations in the physical properties of either component, such as pK_a, would be predicted to have similar effects on rate by either mechanism. In the transformation from an intermolecular to an intramolecular reaction, a change in the rate-limiting step, or even in overall mechanism, is entirely conceivable. In the following discussion, we shall attempt to support the premise of a rate-limiting *collapse* of intermediate in the lactonization of **2**.

According to the first mechanism, lactonization in weakly acidic media may be visualized as depending on the rate-determining formation of a tetrahedral intermediate, the process being catalyzed by general acid and water (**3-ga**) or by general base and water (**3-gb**). Alternatively, the rate of lactone formation may be

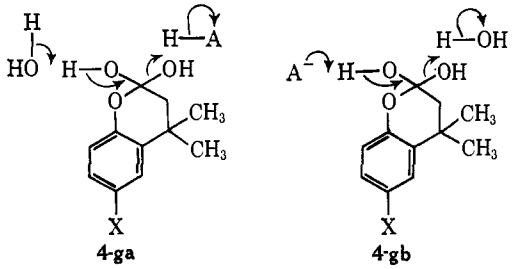
(22) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 1144.

determined by general-acid catalyzed (**4-ga**) or general-base catalyzed (**4-gb**) collapse of the tetrahedral inter-



3-ga.

3-gb



4-ga

4-gb

mediate (T), whose rapid formation from the hydroxy acid (M) is governed by the magnitude of K (eq 7 and 8).

$$M \underset{}{\overset{K}{\rightleftharpoons}} T \xrightarrow{k} \text{lactone} + H_2O \quad (7)$$

$$\text{rate} = k_{obsd}[T] = Kk_{obsd}[M] \quad (8)$$

An inspection of mechanism **3-gb** suggests that the rate of general-base catalyzed lactonization should show at least as great, if not a greater, dependence on the electron density on the phenolic oxygen than in **3-ga**. Such a prediction is, however, contradicted by the ρ values obtained (Table III and Figure 6).

Turning to mechanism **4**, the magnitude of ρ for the overall reaction may be treated as the sum of two components, ρ_K and ρ_k, in which ρ_K represents the dependence of K, or the transient concentration of T, on the electron density at the phenolic hydroxyl group. The second component, ρ_k, reflects the ability of the *para* substituent to assist or retard the rate-limiting breakdown of the tetrahedral intermediate. According to the proposed scheme, the equilibrium concentration of T should be independent of external catalysts and should be favored by increased electron density on the phenolic oxygen;[23] accordingly, ρ_K should be negative for both **4-ga** and **4-gb**. For general-acid catalysis, the rate-limiting step involves the cleavage of a carbon–oxygen bond in the tetrahedral intermediate; clearly, increased electron density at the phenolic oxygen could facilitate such cleavage by stabilizing a partial positive charge on the tetrahedral carbon; a negative value of ρ_k would be anticipated. In the general-base catalyzed reaction, the rate-limiting step involves removal of a weakly acidic proton, a process which would be retarded by electron donation from the benzene ring, and would require a positive value for ρ_k. The fact that ρ for general base catalysis is less negative than for general acid catalysis is, therefore, in accord with these considerations.

General-acid and general-base catalysis show similar enthalpies and entropies of activation, the magnitude of the latter (*ca.* 28 eu) suggesting some degree of water involvement in the rate process, in addition to that of the acidic or basic species.[25] Partial proton transfer in the rate-limiting step is supported by a deuterium isotope effect of *ca.* 2.

Although the kinetic data, by itself, do not permit a choice of mechanism for the hydronium ion catalyzed reaction, the fact that the hydronium ion fits on the Brønsted slope for general acids (Figure 7) suggests the incurrence of similar mechanistic features in this case. The similarities in the values of ρ for hydronium ion and for general-acid catalysis may also be significant. The decreased activation entropy (20 eu) and deuterium isotope effects (0.9) suggest protonation of the tetrahedral intermediate to be fairly complete prior to its breakdown. It should be noted that, in the mechanism proposed for hydronium ion catalyzed lactonization, protonation of the carboxyl group, to form $-C(OH)=OH^+$, is not considered essential to induce formation of the tetrahedral intermediate.

Concurrent general-acid and general-base catalysis has often been observed in the breakdown of tetrahedral intermediates derived from aldehydes and ketones,[24] in which cases tetrahedral intermediate formation does not require a significant loss of resonance stabilization. In carboxylic acid systems, nonrate-limiting addition of nucleophiles may occur if the carbonyl group has been activated by strongly electronegative substituents. In such cases, general-acid or -base catalysis may be observed.[26] The rapid formation of a tetrahedral intermediate from **2** may be viewed as the result of the combined effects of the entropically favorable intramolecular process and of the conformational limitations imposed by the bulky side chain. Because of the latter factor, measurable rates of lactonization are attainable at pH values at which buffer catalysis becomes significant. These results suggest that rate-limiting breakdown may be a more common feature of intramolecular carboxyl-group reactions than heretofore supposed and, indeed, concurrent general-acid–general-base catalysis has also been observed in the intramolecular aminolysis of esters.[27]

It is clear that esterification of an unactivated carboxyl group is entirely feasible in an enzyme-promoted reaction, and would be sensitive to assistance by general-acid and general-base components of the protein matrix.

Acknowledgment. The authors are indebted to Professor W. P. Jencks for helpful discussion of the manuscript.

(23) This conclusion was drawn by use of the principles of hard and soft species (R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963)). Since an increase in electron density on the phenolic oxygen should increase its degree of softness, the stability of its bond to carbon should also increase at the expense of bonding to the harder acid, the proton. Supporting data on the relationship between equilibrium constant and pK in the addition of oxygen nucleophiles to carbonyls seems to be unavailable (ref 24). Nor can the magnitude of K be estimated; examination of the nmr spectra of the hydroxy acids (**2**) failed to reveal any peaks attributable to tetrahedral intermediates.

(24) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(25) Exploratory studies indicate decreased rates of lactonization in mixed-solvent systems. Although such data are suggestive of the involvement of water, alternative explanations cannot be excluded.

(26) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

(27) K. L. Kirk and L. A. Cohen, studies in progress.