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Studies on the Stability of Amides. V.[1] A Comparison of Intramolecular Catalysis by Phenolic and Alcoholic Hydroxyl Groups in Amide Hydrolysis[2]

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pH-Rate profiles for the hydrolyses of *o*-hydroxyphenylacetamide (I) and *o*-hydroxyphenylpropionamide (II) have been determined at 90.0° (μ=0.6). At pH region between 4 and 8, I and II were found to have their pH-independent reactions to form the corresponding lactones. The kinetic evidence indicates that the rate-determining step for the lactonizations of these amides is the breakdown of the tetrahedral intermediate. The mechanisms of intramolecular alcoholyses of amides were compared with alcoholic- and phenolic-hydroxyl amides, and the relative reactivities of these hydroxyamides were discussed.

Several intramolecular hydrolyses of amides by functional groups such as hydroxyl[1,4–9] and carboxyl[10] occur much more rapidly than their analogeous intermolecular hydrolysis. These intramolecular processes have recently been studied with a great attention as models for enzyme action,[11,12] and as the basic concepts to understand the reaction mechanism and structure-reactivity of the stability of drugs.[13]

The importance of the neighboring group participation has prompted to study the effect of hydroxyl substituents in a systematic study of stability of amide linkage.[14–16] The preceding paper[1] clarified that two different reactions controlled by activation entropy and by activation enthalpy occur simultaneously in the acidic hydrolyses of alcoholic-hydroxyl amides, one proceeding intramolecularly through lactone formation and the other proceeding intermolecularly with the nucleophilic attack by water molecules. The present investigation was undertaken to elucidate more general relationship between the mechanism and structure in the intramolecular hydrolyses of amides. For this purpose, the hydrolyses of *o*-hydroxyphenylacetamide (I) and *o*-hydroxyphenylpropionamide (II) were compared with those of some alcoholic-hydroxyl amides over a wide pH region.

1) Part IV: T. Yamana, A. Tsuji, and Y. Mizukami, *Chem. Pharm. Bull.* (Tokyo), **20**, 1217 (1972).
2) This work was presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1972.
3) Location: *Takara-machi, Kanazawa.*
4) M.F. Wolfrom, R.B. Bennett, and J.D. Crum, *J. Am. Chem. Soc.*, **80**, 944 (1958).
5) *a*) H. Zahn and L. Zürn, *Ann.*, **613**, 76 (1958); *b*) L. Zürn, *ibid.*, **631**, 56 (1960).
6) *a*) T.C. Bruice and F-Hans Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962); *b*) T.C. Bruice and D.W. Tanner, *J. Org. Chem.*, **30**, 1668 (1965).
7) R.B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964).
8) B.A. Cunningham and G.L. Schmir, *J. Am. Chem. Soc.*, **89**, 917 (1967).
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10) The pertinent references are cited in Part IV.
11) T.C. Bruice and S. Benkovic, "Bio-organic Mechanisms," Vol. 1, W.A. Benjamin, Inc., New York, 1966.
12) W.P. Jencks, "Chemistry and Enzymology," McGraw-Hill Book Co., New York, 1969.
13) H.J. Smith, *J. Pharm. Pharmacol.*, **17**, 529 (1965).
14) T. Yamana, Y. Mizukami, A. Tsuji, Y. Yasuda, and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 881 (1972).
15) T. Yamana, A. Tsuji, and Y. Mizukami, *Chem. Pharm. Bull.* (Tokyo), **20**, 922 (1972).
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We now report the first example of intramolecular hydrolysis of amide by phenolic hydroxyl group, and discuss the mechanism and relative reactivity of the intramolecular alcoholysis of the amides.

Experimental

Materials——*o*-Hydroxyphenylpropionic acid,[17] *o*-hydroxyphenylacetic acid-γ-lactone,[18] *o*-hydroxyphenylpropionic acid-δ-lactone,[19] *o*-hydroxyphenylacetamide (I),[18] *o*-hydroxyphenylpropionamide (II)[19] and phenylpropionamide[20] were prepared and purified by distillation or by recrystallization according to the method of the previous reports. β-Hydroxypropionamide, γ-hydroxybutyramide, γ-hydroxyvaleramide and δ-hydroxycapronamide were materials used in the earlier study.[1] The commercial *o*-hydroxyphenylacetic acid and phenylacetamide were used after recrystallization from water. Other reagents were of the purest grade.

Buffer Solutions——Buffer solutions were made up to a total concentration of 0.1 M or 0.12M and were adjusted to an ionic strength of 0.6 with potassium chloride. The pH regions covered by each buffer system at 90.0° were HCl–KCl, 0.24—1.20; H_3PO_4–NaH_2PO_4, 2.22—3.16; CH_3COOH–CH_3COONa, 3.84—5.71; NaH_2PO_4–Na_2HPO_4, 4.68—6.52; H_3BO_3–NaB_2O_7, 8.08—9.27; Na_2HPO_4–Na_3PO_4, 9.55—10.81; NaOH–KCl, 11.00—11.80. The pH values of the buffer solutions were measured at the experimental temperatures on a Hitachi-Horiba pH meter, Model F-5, equipped with high-temperature electrodes. pH of hydrochloric or sodium hydroxide solution at 90.0° and $\mu=0.6$ were calculated from:

$$\mathrm{pH} = -\log[\mathrm{HCl}]+0.26 \quad (1)$$

$$\mathrm{pH} = \log[\mathrm{NaOH}]+11.80 \quad (2)$$

These equations were obtained in the similar manner described by Finholt and Higuchi.[21]

pK_a Determination——The pK_a of phenolic group of I and II at 90° and at $\mu=0.6$ were determined spectrophotometrically. Two milliliters of 5.00×10^{-3}M aqueous solution of I or II were added to 50 ml of appropriate buffer solutions adjusted to $\mu=0.6$ and 90°. Within 5 min after mixing, the absorbances at 290 mμ were measured by Shimadzu QV-50 spectrophotometer. The pK_a was calculated from the following equation:

$$\mathrm{p}K_a = \mathrm{pH} + \log\frac{E_b-E}{E-E_a} \quad (3)$$

where E is the absorbance at the pH, E_a is the absorbance in acidic media and E_b is the absorbance in strong alkaline media. The pK_a values of I and II were found to be 9.53 and 9.79 respectively, and were in good agreement with those determined kinetically from the pH-rate profiles (see Table II).

Kinetics and Analysis——The experimental methods and analytical procedure used were as same as reported previously.[1] The theoretical concentration of lactone produced by first-order consecutive reaction were generated by a Hitachi analog computer, Model ALS-250, or calculated by the rate-expression (see equation (4)).

Result

Reaction Route of Lactone Formation in the Hydrolysis of Phenolic-Hydroxyl Amides

The kinetic parameters for the hydrolyses of the phenolic-hydroxyl amides (I and II) and related compounds were determined by following the concentration of ammonia liberated and/or of lactone formed, as previously described.[1] In aqueous solutions, the hydrolyses of I and II were first-order with respect to the compounds over whole pH and temperature range. These several typical first-order plots are shown in Fig. 1.

In Fig. 2 and 3, plots of the concentrations of the relevant species *vs.* time are shown for the hydrolysis of I in acidic and neutral media. The resultant assay data indicated that

17) C.W. Bauer and E.F. Lasala, *J. Am. Pharm. Assoc.*, **49**, 48 (1960).
18) R. Stoermer, *Ann.*, **313**, 79 (1900).
19) E. Marui, *Sci. Pep. Tohoku Univ.*, **17**, 695 (1928).
20) D.W. Ingles and J.R. Knowles, *Biochem. J.*, **108**, 561 (1968).
21) P. Finholt and T. Higuchi, *J. Pharm. Sci.*, **51**, 655 (1962).

the kinetic pathway at each media could be interpreted as consecutive first-order reaction (Chart 1).

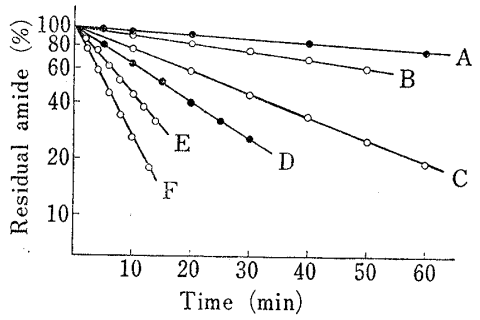

Fig. 1. Typical Appearent First-Order Plots for the Hydrolyses of *o*-Hydroxyphenylacetamide (○) and *o*-Hydroxyphenylpropionamide (●) under Various Conditions

experimental condition: A, in 0.104N HCl at 50.0°; B, in phosphate buffer of pH 9.55 at 90.0°; C, in acetate buffer of pH 3.84 at 90.0°; D, in 0.102N NaOH at 80.0°; E, in phosphate buffer of pH 2.22 at 90.0°; G, in 0.1044N HCl at 80.0°

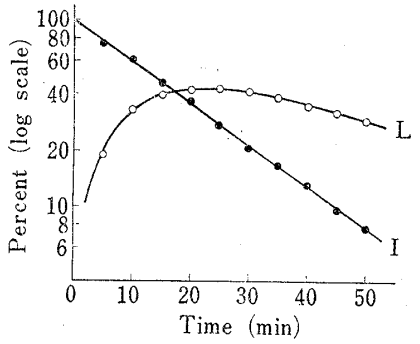

Fig. 2. Disappearance of *o*-Hydroxyphenylacetamide (I) and Formation of *o*-Hydroxyphenylacetic Acid-γ-lactone (L) in 0.104N HCl at 70.0° and at $\mu=0.6$

The curves are the amounts of I and L calculated on the reaction route:

$$\mathrm{I} \xrightarrow{k_a} \mathrm{L} \xrightarrow{k_l} \text{Acid.}$$

The kinetic parameters on the basis for the calculation are: $k_a=5.10\times10^{-2}$ min^{-1} and $k_l=3.77\times10^{-2}$ min^{-1}

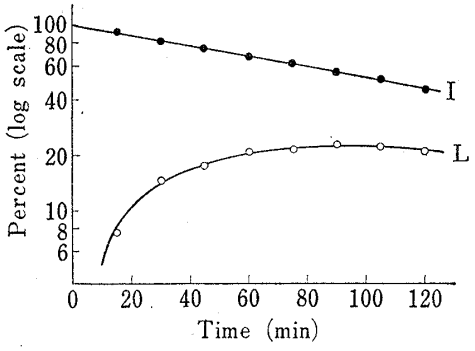

Fig. 3. Disappearance of *o*-Hydroxyphenylacetamide (I) and Formation of *o*-Hydroxyphenylacetic Acid-γ-lactone (L) in Phosphate Buffer of pH 5.56 at 70.0° and at $\mu=0.6$

The curves are the amounts of I and L calculated on the reaction route:

$$\mathrm{I} \xrightarrow{k_a} \mathrm{L} \xrightarrow{k_l} \text{Acid.}$$

The kinetic parameters on the basis for the calculation are: $k_a=6.65\times10^{-3}$ min^{-1} and $k_l=1.61\times10^{-2}$ min^{-1}

$$\text{hydroxyamide} \xrightarrow{k_a} \text{lactone} \xrightarrow{k_l} \text{hydroxy acid}$$

Chart 1

In this case the concentration of lactone formed can be calculated from the expression[22]

$$[\mathrm{L}] = [\mathrm{A}]_0 \frac{k_a}{k_l - k_a}(e^{-k_a t} - e^{-k_l t}) \qquad (4)$$

where [L] and $[A]_0$ are the concentration of lactone at time t and the initial concentration of hydroxyamide, respectively. The amounts of lactone as a function of time calculated on the basis of equation (4), using k_a and k_l determined separately from the hydrolysis of hydroxyamide and the corresponding lactone, are in fair agreement with the experimental values. In the hydrolysis of II, similar results were obtained under acidic and neutral conditions.

Effect of Buffer Concentration on the Rate Constants of the Hydrolyses of I and II

The hydrolyses of I and II are subject to catalysis by buffer species. Typical plots showing the effects of the phosphate, acetate and borate buffer concentrations are represented in Figs. 4, 5, and 6. It is evident from the plots that only general acids have a significant catalytic effect on the rate constants of hydrolysis of I. The observed rate constants, k_{obs}, in these buffers can be expressed by the following equations.

22) A.A. Frost and R.G. Pearson, "Kinetics and Mechanisms," 2nd ed., John Wiley and Sons, Inc., New York, 1961, p. 166.

$$k_{obs-phos} = k_{pH} + k_{H_3PO_4}[H_3PO_4] + k_{H_2PO_4^-}[H_2PO_4^-] + k_{HPO_4^=}[HPO_4^=] \quad (5)$$

$$k_{obs-acet} = k_{pH} + k_{CH_3COOH}[CH_3COOH] \quad (6)$$

and

$$k_{obs-borate} = k_{pH} + k_{H_3BO_3}[H_3BO_3] \quad (7)$$

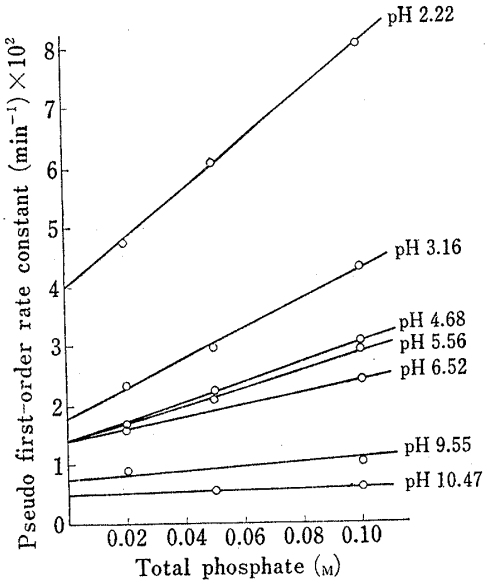

Fig. 4. Plots of Pseudo First-Order Rate Constants against Phosphate Buffer Concentration in the Hydrolysis of *o*-Hydroxyphenylacetamide at Constant Ionic Strength (μ=0.6) and at 90.0°

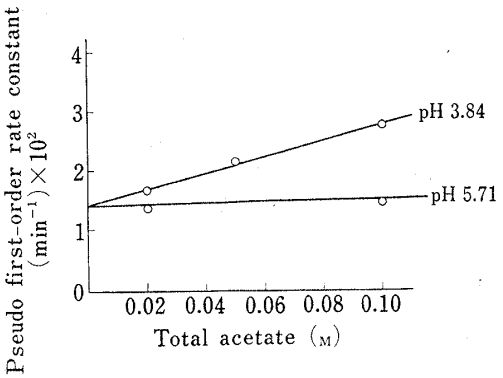

Fig. 5. Plots of Pseudo First-Order Rate Constants against Acetate Buffer Concentration in the Hydrolysis of *o*-Hydroxyphenylacetamide at Constant Ionic Strength (μ=0.6) and at 90.0°

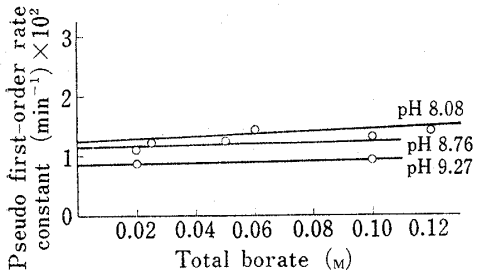

Fig. 6. Plots of Pseudo First-Order Rate Constants against Borate Buffer Concentration in the Hydrolysis of *o*-Hydroxyphenylacetamide at Constant Ionic Strength (μ=0.6) and at 90.0°

where k_{pH} is the rate constant extraporated to zero buffer concentration, $k_{obs-phos}$, $k_{obs-acet}$, and $k_{obs-borate}$ are the observed first-order rate constants, and $k_{H_3PO_4^-}$, $k_{H_2PO_4^-}$, $k_{HPO_4^=}$, k_{CH_3COOH}, and $k_{H_3BO_3}$ are the second-order catalytic rate constants. The concentration of these buffer acid-components can be calculated from the total buffer concentration at any pH using the dissociation constants at 90.0° and at μ=0.6 (Table I). On this basis, these catalytic rate constants calculated in the same way described previously[23] are listed in Table I, and a Brönsted plot for acidic species provides a slope, α, of 0.15 as seen in Fig. 7.

pH-Rate Profile of Hydrolysis of I and II

The observed first-order rate constants at 90.0° extraporated to zero buffer concentration are plotted as a function of pH in Fig. 8. The shape of the pH-rate profile suggests that the over-all hy-

23) P. Finholt, G. Jürgensen, and H. Kristiansen, *J. Pharm. Sci.*, **54**, 387 (1965).

Table I. Second-Order Rate Constants (k_{cat}) for the General Acid Catalyzed Hydrolysis of *o*-Hydroxyphenylacetamide at 90.0° and at $\mu=0.6$

General acid	pK_a[a]	Rate constant, $k_{cat}\times 10$ (M^{-1} min^{-1})
H_3O^+	−1.74	46
H_3PO_4	2.22	8.0
CH_3COOH	4.75	1.5
$H_2PO_4^-$	6.52	1.7
H_3BO_3	8.76	0.40
$HPO_4^=$	10.47	0.30

a) The pK_a of the conjugated acid was determined from measurements of the pH of half neutralized solutions under the conditions of the kinetic experiments ($\mu=0.6$ and 90°).

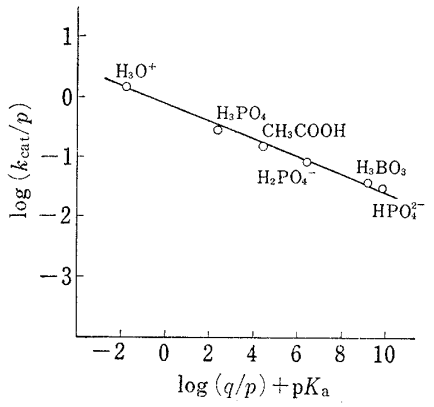

Fig. 7. Brönsted Plot for the General Acid Catalyzed Lactonization of *o*-Hydroxyphenylacetamide at 90.0° and at $\mu=0.6$

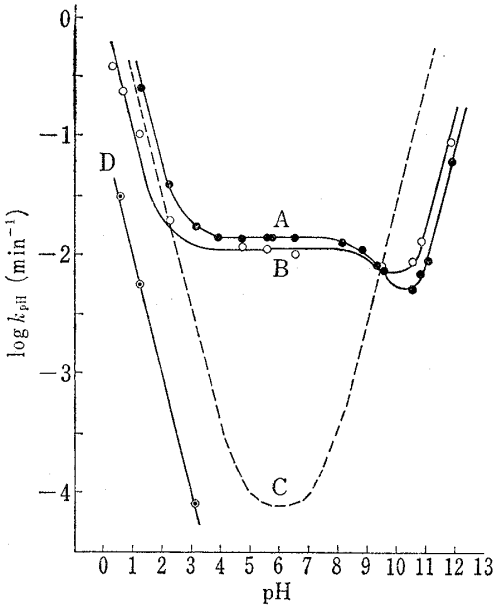

Fig. 8. Log *k*-pH Rate Profiles at 90° for Hydrolyses of Amides

The lines represent the theoretical curves drawn from Eq. 12 or 13 and 14. The points are the experimental values.
curve: *A*, *o*-hydroxyphenylacetamide; B, *o*-hydroxyphenylpropionamide; C, *γ*-hydroxybutyramide; D, phenylpropionamide

drolytic rate of I and II represents a summation of the following separate reactions:

$$\text{S-OH} + \text{H}^+ \xrightarrow{k_{H^+}} \text{products} \quad \text{Reaction 1}$$

$$\text{S-OH} \xrightarrow{k_{na}} \text{products} \quad \text{Reaction 2a}$$

or

$$\text{S-O}^- + \text{H}^+ \xrightarrow{k_{nb}} \text{products} \quad \text{Reaction 2b}$$

$$\text{S-O}^- \xrightarrow{k_s} \text{products} \quad \text{Reaction 3}$$

and

$$\text{S-O}^- + \text{OH}^- \xrightarrow{k_{OH^-}} \text{products} \quad \text{Reaction 4}$$

Chart 2

Reactions 2a and 2b are kinetically equivalent. In these reactions, S-OH and S-O$^-$ are the free and anionic forms of the phenolic-hydroxyl amides, respectively.

Two rate equations can be derived to describe the above proposed reactions:

$$-\frac{d[S]_T}{dt} = k_{H^+}[\text{S-OH}][H^+] + k_{na}[\text{S-OH}] + k_s[\text{S-O}^-] + k_{OH^-}[\text{S-O}^-][OH^-] \quad (8)$$

or

$$-\frac{d[S]_T}{dt} = k_{H^+}[\text{S-OH}][H^+] + k_{nb}[\text{S-O}^-][H^+] + k_s[\text{S-O}^-] + k_{OH^-}[\text{S-O}^-][OH^-] \quad (9)$$

where $[S]_T$ is the total hydroxyamide concentration, and k_{H^+}, k_{na}, k_{nb}, k_s, and k_{OH^-} are the specific catalytic constants. By introducing the dissociation constant, K_a, to equations (8) and (9), the apparent first-order rate constant (k_{pH}) for hydroxyamide hydrolysis can be expressed by equations (10) and (11), respectively.

$$k_{pH} = \frac{[H^+]}{K_a+[H^+]}\{k_{H^+}[H^+]+k_{na}\} + \frac{K_a}{K_a+[H^+]}\{k_s+k_{OH^-}[OH^-]\} \quad (10)$$

or

$$k_{pH} = \frac{[H^+]}{K_a+[H^+]}k_{H^+}[H^+] + \frac{K_a}{K_a+[H^+]}\{k_{nb}[H^+]+k_s+k_{OH^-}[OH^-]\} \quad (11)$$

The specific catalytic rate constants and the K_a values determined kinetically from the observed pH-rate profiles are listed in Table II.

Table II. Catalytic Rate Constants and Kinetic K_a from the Hydrolysis of *o*-Hydroxyphenylacetamide(I) and *o*-Hydroxyphenylpropionamide (II) at 90.0° and at $\mu=0.6$

Kinetic value	I	II
k_{H^+}	4.60 M^{-1} min^{-1}	1.10 M^{-1} min^{-1}
k_{na}	1.40×10^{-2} min^{-1}	1.10×10^{-2} min^{-1}
k_{nb}	4.43×10^{7} M^{-1} min^{-1}	6.92×10^{7} M^{-1} min^{-1}
k_s	1.60×10^{-3} min^{-1}	2.00×10^{-3} min^{-1}
k_{OH^-}[a]	6.20×10^{-2} M^{-1} min^{-1}	0.135 M^{-1} min^{-1}
K_a	3.16×10^{-10} ($pK_a=9.50$)	1.59×10^{-10} ($pK_a=9.80$)

a) Calculated from the equation; $\log k_{pH}=\log k_{OH^-}+11.80+pH$ at high pH region.

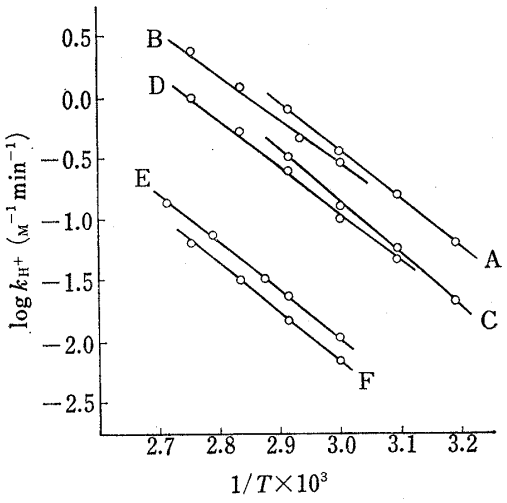

Fig. 9. Typical Arrhenius Plots for Acidic Hydrolyses of Amides

curve: A: δ-hydroxycapronamide
B: *o*-hydroxyphenylacetamide
C: γ-hydroxybutyramide
D: *o*-hydroxyphenylpropionamide
E: phenylacetamide
F: phenylpropionamide

In Fig. 8 is also presented pH-rate profile for the hydrolysis of γ-hydroxybutyramide. The curve at 90.0° was derived from the equation (12) using the apparent activation energies[1] (see also Table IV and V).

$$k_{pH}' = k_{H^+}'[H^+] + k_0' + k_{OH^-}'[OH^-] = 1.60[H^+] + 8.09\times10^{-5} + 2.13[OH^-] \quad (12)$$

Rate Constants and Activation Parameters of Acidic, Neutral and Basic Hydrolyses

The effects of temperature on the rate constants of hydrolyses of I and II, and the related amides were determined in acidic, neutral and basic media. Typical Arrhenius plots are shown in Fig. 9. The enthalpy, $\Delta H^{\ddagger}$, and entropy, $\Delta S^{\ddagger}$, of activation were calculated on the basis of absolute rate theory:[24]

$$\Delta H^{\ddagger} = \Delta E_a^{\ddagger} - RT \quad (13)$$

and

$$\Delta S^{\ddagger} = 4.574\log k - 49.18 - 4.574\log T + \Delta H^{\ddagger}/T \quad (14)$$

where R is gas constant, k is the second-order rate constant in M^{-1}sec^{-1} and $\Delta E_a^{\ddagger}$ is the activation energy which was obtained from the slope of Arrhenius plot. The k, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ values for the hydrolyses of hydroxyamides and the related compounds under acidic, neutral and basic conditions are given in Tables III, IV, and V.

24) K.J. Laidler, "Chemical Kinetics," 2nd ed., McGraw-Hill, Inc., New York, 1965, p. 90.

Table III. Rate Constants and Activation Parameters for the Acidic Hydrolyses of Amides

Amide	Reaction Temp. (°C)	Rate constant $k_{H^+} \times 10^2$ (M^{-1} min^{-1})	Activation parameter $\Delta H^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$(at 60°) (*e.u.*)
o-Hydroxyphenylacetamide	60.0	27.7	16.7	−21.2
	69.0	49.0		
	80.0	129		
	90.0	244		
o-Hydroxyphenylpropionamide	50.0	4.49	17.5	−20.7
	60.0	9.90		
	70.0	24.5		
	80.0	52.1		
	90.0	101		
Phenylacetamide	60.0	1.18	18.5	−22.4
	70.0	2.14		
	75.0[a]	3.11		
	85.0[a]	7.74		
	95.0[a]	13.5		
Phenylpropionamide	60.0	0.675	18.1	−24.4
	70.0	1.50		
	80.0	3.09		
	90.0	6.19		

a) The data were those of Bolton, *et al.*: P.D. Bolton and G.L. Jackson, *Aust. J. Chem.*, **22**, 527 (1969).

Table IV. Rate Constants and Activation Parameters for the Neutral Hydrolyses of Amides

Amide	Reaction Temp. (°C)	Rate constant k_0 (min^{-1})	Activation parameter $\Delta H^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$(at 60°) (*e.u.*)
γ-Hydroxybutyramide	90.0	0.81×10^{-4}	18.5	−36.5
	98.0	1.30		
δ-Hydroxycapronamide	80.0	0.70×10^{-4}	20.8	−28.9
	90.0	1.62		
	98.0	2.92		
o-Hydroxyphenylacetamide	50.0	0.55×10^{-3}	18.3	−26.9
	70.0	3.21		
	90.0	14.4		
Acetamide[a]	100	2.0×10^{-6}		

a) The datum was taken from reference 6*a*) and cited rate constant is that at the minimum point (pH 6.16) in the pH-rate profile.

Salt and Solvent Effects

Tables VI and VII show that, in 0.1N hydrochloric acid or 0.1N sodium hydroxide and ethanol and/or dioxane mixtures, the second-order rate constants of both reactions (k_{H^+} and k_{OH^-}) decrease with the increase of the organic solvents.

Variations in the apparent first-order rate constants were observed with ionic strength changes for the hydrolysis of I at pH 11.00 at 90.0° where I would exist almost an anionic form (S-O$^-$). Plots of the logarithm of the second-order rate constant (k_{OH^-}) *vs.* $\sqrt{\mu}$ gave a straight line with a positive slope (Fig. 10).

Table V. Rate Constants and Activation Parameters for the Alkaline Hydrolyses of Amides

Amide	Reaction Temp. (°C)	Rate constant $k_{OH^-} \times 10^2$ (M^{-1} min^{-1})	Activation parameter $\Delta H^{\neq}$ (kcal/mole)	$\Delta S^{\neq}$(at 60°) (*e.u.*)
Alcoholic-hydroxyl amide				
β-Hydroxypropionamide	60.0	2.90	13.7	−34.8
	70.0	5.40		
	80.0	8.50		
	90.0	17.5		
γ-Hydroxybutyramide	30.0	2.74	15.7	−24.0
	40.0	7.00		
	50.0	16.0		
	60.0	28.0		
γ-Hydroxyvaleramide	30.0	1.20	14.3	−30.5
	40.0	2.80		
	50.0	5.38		
	60.0	9.74		
δ-Hydroxycapronamide	50.0	7.48	14.2	−30.1
	60.0	13.0		
	70.0	25.6		
	90.0	63.0		
Phenolic-hydroxyl amide				
o-Hydroxyphenylacetamide	70.0	1.67	15.2	−32.6
	80.0	3.33		
	90.0	6.06		
o-Hydroxyphenylpropionamide	70.0	2.68	14.5	−33.8
	80.0	4.43		
	90.0	6.51		
Other amide				
Propionamide[a)]	60.0	3.30	14.7	−29.7
Butyramide[a)]	60.0	1.67	14.1	−32.9
Valeramide[a)]	60.0	1.24	14.5	−32.1
Phenylacetamide[a)]	60.0	5.00	12.5	−37.3
Phenylpropionamide	70.0	2.76	11.7	−41.9
	80.0	4.37		
	90.0	7.20		

a) These Data were taken from the reference; P.D. Bolton and G.L. Jackson, *Aust. J. Chem.*, **24**, 969 (1971).

Table VI. Rate Constants for Acidic Hydrolysis of o-Hydroxyphenylacetamide in Ethanol- and Dioxane-Water Mixtures at 70.0° and at $\mu = 0.1$

Vol. % organic solvent[a)]	Dielectric constant[b)]	$k_{H^+} \times 10$ M^{-1} min^{-1}
0.0	63.5	4.89
20.0 EtOH	53.2	3.31
20.0 Dioxane	48.2	2.97
50.0 EtOH	38.7	1.60
50.0 Dioxane	26.5	0.722

a) The solutions were made by proper dilution from concentrated hydrochloric acid solution by adding organic solvents.
b) Data at 70° were taken from G. Akerlöf, *J. Am. Chem. Soc.*, **51**, 4125 (1932).; *ibid.*, **58**, 1242 (1936).

Table VII. Rate Constants for Alkaline Hydrolysis of *o*-Hydroxyphenylacetamide in Ethanol–Water at 90.0° and at $\mu=0.1$

Vol. % EtOH[a]	Dielectric constant[b]	$k_{OH^-} \times 10^2$ M^{-1} min^{-1}
0.0	57.0	8.53
20.0	46.5	7.20
40.0	35.0	3.97

a) The solutions were made by proper dilution from concentrated sodium hydroxide solution by adding ethanol
b) Data at 90° were taken from G. Akerlöf, *J. Am. Chem. Soc.*, **51**, 4125 (1932).

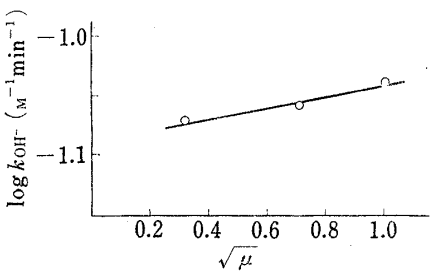

Fig. 10. Effect of Ionic Strength on the Rate Constants of *o*-Hydroxyphenylacetamide in 0.1N NaOH at 90.0°

Discussion

The plateaus between pH 4 and 8 in Fig. 8 for phenolic-hydroxyl amides are probably attributed to intramolecular facilitative mechanisms participated by neighboring phenolic-hydroxyl group. Further evidence for intramolecular catalysis of this reaction in acidic and neutral solution can be provided from the facts: (1) phenolic-hydroxyl amides were hydrolyzed approximately 10^2 times faster at pH 3 than the corresponding amides involving no hydroxyl groups (see Fig. 8), (2) these reactions lead to the direct formation of the corresponding lactones in acidic and neutral media, as seen in Figs. 2 and 3.

Although no direct evidence was obtained for the formation of tetrahedral intermediates in both reaction processes, it has recently been shown that a tetrahedral addition intermediate is formed in many nucleophilic reactions at the acyl carbon atom.[25] In the lactonization of γ-hydroxybutyranilide, Cuningham and Schmir[8] have provided kinetic evidence for the existence of an additional intermediate. This reaction mechanism is consistent with the rate-determining formation (or breakdown) of the intermediate. Another case has most recently been reported in the 2-hydroxymethylbenzamide hydrolysis,[9] in which tetrahedral intermediates were confirmed to be formed and the rate-determining step is the protonic interconversion of one intermediate to another. On the basis of these investigations, it seemed reasonable to assume that this type of intermediate is formed in the lactonization of alcoholic and phenolic hydroxylamides.

In strong basic media, on the other hand, distinguishing between intramolecular catalyzed reaction by phenolic or alcoholic hydroxyl group and other kinetically equivalent mechanism is difficult since absolute proof of lactone formation by analytical procedure is impossible owing to their rapid hydrolyses.

An argument to their possible mechanisms will be presented below.

Mechanism

1) Acidic Hydrolysis——In the acidic region below pH 2, the rate constants for I and II increase proportionately to $[H^+]$ and therefore their protonated amides must be the major reactants, which are known to be the most reactive species for amides.[25c] Their entropies of activation were largely negative ($\Delta S^{\neq}=ca.-21$ *e.u.*) and the decreased rate constant of lactonization of I in mixed-solvent systems was observed (Table VI). These kinetic data together with the small Brönsted exponent value, α, of 0.15 (will be discussed below) indicate that water molecules play an important role in the rate-determining step.[26,27] The

25) *a*) W.P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964); *b*) A. Kirby and W.P. Jencks, *J. Am. Chem. Soc.*, **87**, 3217 (1965); *c*) M.L. Bender, *Chem. Rev.*, **60**, 53 (1960); *d*) S.L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).
26) Ref. 12, p. 608.
27) *a*) S.V. Anantakrishan and P.S. Radhakrishnamurti, *India. J. Chem.*, **3**, 336 (1965); *b*) M.A. Paul, and F.A. Long, *Chem. Rev.*, **57**, 935 (1957).

quite different behavior was found previously[1] on the lactonization of alcoholic-hydroxyl amides, for which activation entropies were slightly negative (ΔS^{*}=*ca.* −5——12 *e.u.*) and the rate constant of the lactonization was almost independent of ethanol concentration up to 50%.

Accordingly, for the hydrolyses of phenolic-hydroxyl amides such as I and II, a mechanism of rate-determining cyclization by the attack of unionized hydroxyl group on the protonated amide, as concluded for the lactonization of alcoholic-hydroxyl amides, would not account for the predominant role of water molecules. The fact that Arrhenius plots for I and II did not pass through the same isokinetic temperature (500°K)[1] with plots for the hydronium ion catalyzed lactonization of alcoholic-hydroxyl amide series suggests that the rate-determining step for former reactions must be quite different from that for latter reactions. These observed kinetic evidences can be explained by the mechanism as shown in Chart 3.

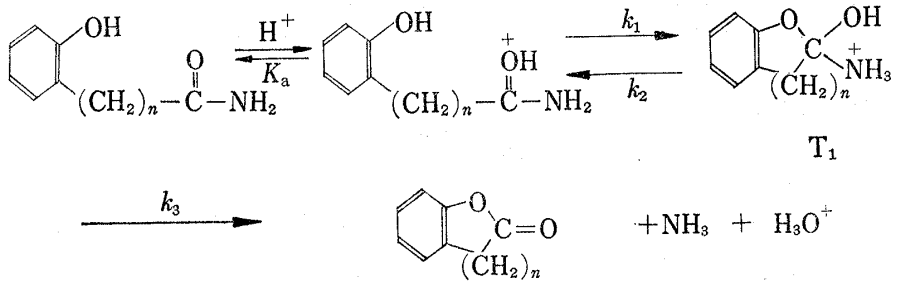

Chart 3

Protonated amide first forms the tetrahedral intermediate by rapid attack of the phenolic-hydroxyl group on the amide carbonyl carbon, the proton shifts to the amide nitrogen, and ammonia is lost slowly. In this mechanism water molecules would act to remove the proton from the carbonyl oxygen[1] and to assist rate-determining breakdown of the tetrahedral intermediate (T_1) to the lactone

2) Neutral Hydrolysis——The pH-independent reaction can be explained as the reaction of neutral amide (Reaction 2a) or kinetically equivalent reaction of anionic form with hydronium ion (Reaction 2b).

In this region, the neighboring phenolic-hydroxyl group participates in the general-acid catalyzed hydrolyses of I and II by the direct lactone formation (see Fig. 3). This general acid catalysis of the lactonization is characterized by a Brönsted α value of 0.15. The low value of α in the present case suggests that proton transfer is probably concerted with breaking of a covalent bond to carbon,[28] and that rate-determining breakdown of the tetrahedral intermediate is more reasonable than rate-determining cyclization to the intermediate.[9]

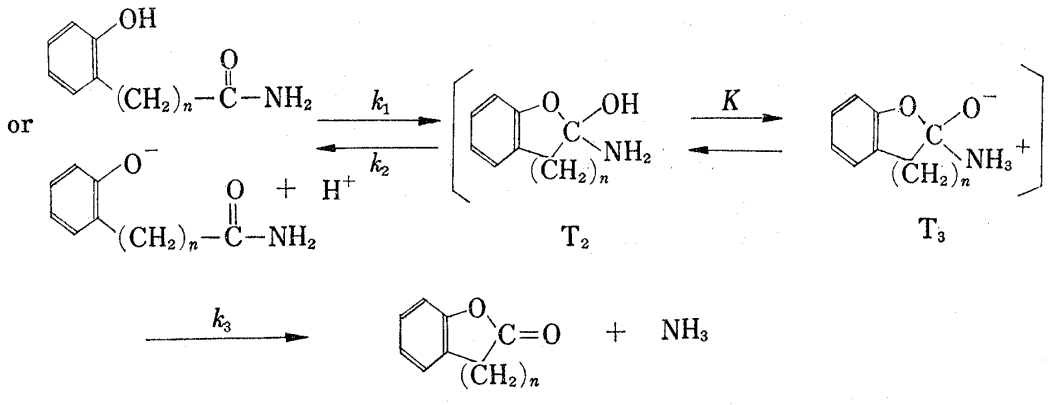

Chart 4

In this step water molecules, which are present in higher concentration than any added catalyst, must be predominantly operative[28] because of $\alpha=0.15$. The mechanism is represented in Chart 4.

Formation of the phenolic hydroxyl oxygen-amide carbonyl carbon bond and proton donation to the amide nitrogen or carbonyl oxygen occurs concertedly in this mechanism, and rate-determining step is the loss of ammonia with assistance of water molecules.[29] The activation entropy for the lactonization of phenolic-hydroxyl amides agrees with such a bimolecular interaction ($\Delta S^{\ddagger}=ca.$ -26 *e.u.*). The fact that the hydronium ion fits on the Brönsted slope for general-acid catalyzed lactonization of I (see Fig. 7) suggests that rate-determining breakdown may be a common feature to the lactonization of phenolic-hydroxyl amides.

The broad plateau in the pH-rate profile of γ-hydroxybutyramide is also attributed to the water-catalyzed reaction with the same mechanism as represented in Chart 4. This mechanism of the rate-determining breakdown of the tetrahedral intermediate in the lactonization of alcoholic-hydroxyl amides is consistent with the largely negative entropy of activation ($\Delta S^{\ddagger}=ca.$ -30 *e.u.*).

3) Basic Hydrolysis——The basic hydrolyses observed above pH 7 for γ-hydroxybutyramide and above pH 11 for I and II show a first-order dependence with respect to hydroxide ion concentration (see Fig. 8).

The larger rate enhancement by factor 10—20 in the hydrolyses of γ- and δ-alcoholic hydroxyl amides compared with those of β-hydroxypropionamide and other *n*-alkyl amides (see Table V) is probably due to the intramolecular participation by the neighboring hydroxyl group. There are three possible mechanisms which could explain the above rate-facilitation:[11] a) intramolecular nucleophilic catalysis, b) specific-base, general-base catalysis as reported in the hydrolysis of salicylamide,[6b] and c) intramolecular general-acid catalysis, as illustrated in Chart 5. The latter two mechanisms can be easily excluded since no rate-accelerated effect could be observed on the hydrolysis rate of β-hydroxypropionamide (see Table V) which must be favorable to those two mechanisms. Accordingly, the first mechanism (Mechanism a) is left as the possible one.

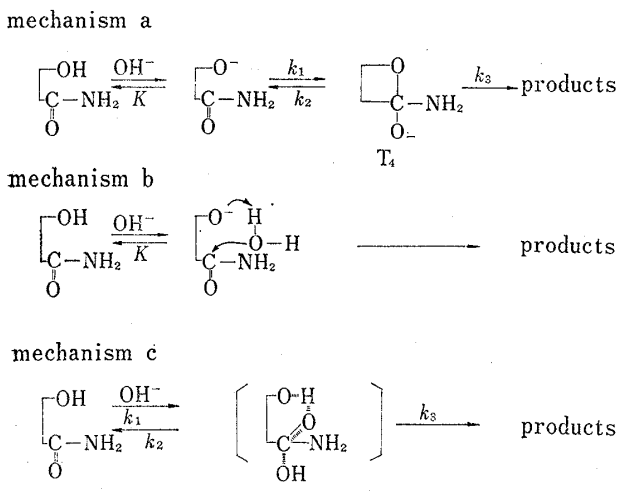

Chart 5

In this mechanism, rate-determining attack by the ionized hydroxyl group on the carbonyl carbon and formation of a tetrahedral intermediate (T_4) can be ruled out because of the largely negative entropy of activation ($\Delta S^{\ddagger}=-24$——-31 *e.u.*). Such values must be attributed to the necessity for the proper orientation of several water molecules in the transition state[30] and consistent with the rate-determining breakdown (k_3 step) of the tetrahedral intermediate.

On the other hand, the hydrolysis rates of phenolic-hydroxyl amides, I and II, are not facilitated (see Table V) compared with those of amides without *o*-hydroxyl group. The

28) Ref. 12, p. 174 and p. 241.
29) When the intermediate formation (T_2 or T_3) is not rate-determining step, even if the rate-determining step is the protonic interconversion of one intermediate to another (*e.g.* $T_2 \leftrightarrows T_3$), as illustrated in the hydrolysis of 2-hydroxymethylbenzamide,[9] we employed the rate-determining breakdown.
30) J.G. Tillett and D.E. Wiggins, *Tetrahedron Letters*, **14**, 911 (1971).

absence of the rate-facilitation and existence of minimum points[31] at about pH 10 in their pH-rate profiles can be accounted by the generally accepted intermolecular hydroxide ion attack mechanism, as shown in Chart 6. In the rate constants of the hydrolysis of I by

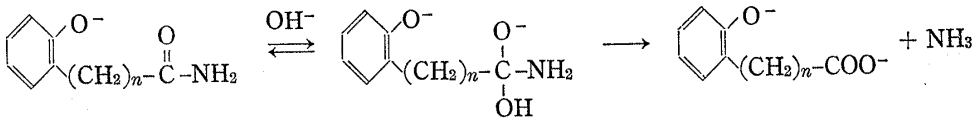

Chart 6

0.1N sodium hydroxide solution, there was no decrease with increasing the ionic strength (Fig. 10) and a large decrease with the dielectric constant of the solvent (Table VII). These results strongly support[32] the proposed mechanism shown in Chart 6. Smaller rate constant in the hydrolysis of I in comparison with that of phenylacetamide is probably attributed to the *o*-steric hindrance, as observed in the basic hydrolyses of *o*-substituted benzamide.[33]

A Comparison of Reactivity of Alcoholic and Phenolic Hydroxyl Groups

1) Rate-determining Step——There is a convincing evidence,[34] in the aminolyses of esters, for the existence of tetrahedral intermediate which has a sufficiently long lifetime to allow complete proton-transfer equilibrium to be attained among the various ionic forms of the intermediate. This is true for the reverse as well as the forward reaction, so that the same intermediate must be formed in the corresponding alcoholysis reaction of amide.[8,9,35] This application of the principle of microscopic reversibility[36] enables to discuss the intramolecular alcoholysis of amide, because the reverse reaction, *i.e.* ester aminolysis reaction, has been studied in some detail.[34,37]

Results obtained here on the conversion of phenolic-hydroxyl amide to lactone in aqueous solution, as well as those obtained previously[1] on alcoholic-hydroxyl amide, are consistent with the mechanism outlined in Chart 7.

$$\text{hydroxyamide} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{lactone} + NH_3$$

Chart 7

Since k_4[Lactone][NH_3] term can be negligible under the experimental condition of the hydroxyamide hydrolysis,[38] the observed first-order rate constant, k_{app}, for the hydrolysis of hydroxyamide according to this scheme is in a two-step reaction of this type, the rate-

$$k_{app} = k_1k_3/(k_2+k_3) \qquad (15)$$

31) Although k_s values have been provided in Table II, their contributions to the log k_{pH}-pH profiles of I and II, and actual magnitude of this term (k_s) are not reliably known. This intramolecular reaction by phenolate anion (Reaction 3) will be discussed in the following paper.

32) *a*) K.J. Laidler and P.A. Landskroener, *Trans. Faraday Soc.*, **52**, 200 (1956); *b*) E. Tommila and M.P.O. Ilomaki, *Acta Chem. Scand.*, **6**, 1249 (1952); *c*) S.A. Bernhard, A. Berger, J.H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962); *d*) E.S. Amis, "Solvent Effects on Reaction Rates and Mechanisms," Academic Press, New York, 1966; *e*) Ref. 24, Chapt. V; *f*) E.R. Garrett, *J. Pharm. Sci.*, **51**, 811 (1962).

33) I. Meloche and K.J. Laidler, *J. Am. Chem. Soc.*, **73**, 1712 (1951).

34) *a*) G.M. Blackburn and W.P. Jencks, *J. Am. Chem. Soc.*, **90**, 2638 (1968); *b*) T.C. Bruice, A.F. Hegarty, S.M. Felton, A. Donzel, and N.G. Kundu, *ibid.*, **92**, 1370 (1970).

35) A.R. Fersht, *J. Am. Chem. Soc.*, **93**, 3504 (1971).

36) R.C. Tolman, *Phys. Rev.*, **23**, 699 (1924); *cf.* see reference 24), p. 110.

37) *a*) W.P. Jencks and J. Carriuodo, *J. Am. Chem. Soc.*, **82**, 675 (1960); *b*) T.C. Bruice, A. Donzel, R.W. Huffman, and A.R. Butler, *ibid.*, **89**, 2106 (1967); *c*) W.P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

38) In the hydrolyses of hydroxyamides studied, the plots of logarithm of residual amide concentration calculated from the liberated ammonia concentration against time were found to be reasonably linear during the kinetic runs under any conditions, as seen in Fig. 3. These results suggest that the reverse reaction can be negligible.

determining step is determined by the relative magnitude of k_2 and k_3. If $k_3 \gg k_2$, equation (15) can be simplified to

$$k_{app} = k_1 \tag{16}$$

and the formation of tetrahedral intermediate will be rate-determining step. On the other hand, if $k_2 \gg k_3$, the first step will be a rapid preequilibrium, and the breakdown of a tetrahedral intermediate to lactone must be rate-determining step. This situation leads to

$$k_{app} = k_3 K \tag{17}$$

where $K = k_1/k_2$.

For the aminolysis of alkylester by aliphatic amines, Blackburn and Jencks[34a] interpreted that the changeover from the rate-determining formation to breakdown of the tetrahedral intermediates occur about 1—2 pH units below the pK_a of amine. Below this pH, rate-determining step is the breakdown of the tetrahedral intermediate (this suggests $k_3 \gg k_2$ in Chart 7), whereas above this pH rate-determining step is amine attack ($k_2 \gg k_3$). The situation is quite different with phenylester aminolysis,[34a,37c,39] in which rate-determining step is the formation of the tetrahedral intermediate over a wide pH range ($k_2 \gg k_3$).

The relative rate of k_2 and k_3 for the lactonization of hydroxyamide will have same relationship with that for the ester aminolysis. This can easily lead to the argument that rate-determining step of the alcoholysis of amide by phenolic-hydroxyl group, such as the intramolecular lactonization of *o*-hydroxyphenylacetamide, is the breakdown of the tetrahedral intermediate ($k_2 \gg k_3$) over a wide pH range. The argument can also be given for the intramolecular amide alcoholysis by alcoholic-hydroxyl group, such as γ-hydroxybutyramide, that below neutral pH the attack of hydroxyl oxygen is rate-determining step ($k_2 \gg k_3$), and at high pH slow expulsion of ammonia ($k_3 \gg k_2$). These arguments are consistent with the evidence obtained in the present study together with that obtained previously.[1]

This change in rate-determining step must be reflected to the relative leaving tendencies of attacking group and leaving group.[37c] Since phenol is a better leaving group, phenol expulsion must be favored over ammonia expulsion, so that the intermediate breakdown step must become rate-determining step as seen for the case of the lactonizations of I and II. The change in rate-determining step at high pH is probably a consequence of the fact that the intermediates of different charge (*e.g.*, T_2, T_3, and T_4) are favored for departure either of alcoxide or of ammonia. Alcoxide is a far better leaving group than amine anion ($pK_a = ca.$ 30) and is expelled through an anionic intermediate (*e.g.* T_4) at high pH, so that ammonia expulsion is rate-determining step, whereas ammonia expulsion ($pK_a = ca.$ 9) is preferred to alcohol expulsion ($pK_a = ca.$ 15) through a cationic intermediate, so that intermediate formation is rate-determining step.

2) Nucleophilicities of Alcoholic and Phenolic Hydroxyl Groups——We applied the emperical equation (20) shown by Fersht[35] to the intramolecular alcoholysis of amides on the basis of the equilibrium reactions (18) and (19). The application of the equilibrium theory is convenient to the argument of the reactivity, because equiliblium does not concern with the reaction route.

$$\text{HO–R–CON}\langle \overset{k_{ROH}}{\rightleftarrows} \text{lactone} + \text{NH}\langle \tag{18}$$

$$\text{O}^-\text{–R–CON}\langle \overset{k_{OR}}{\rightleftarrows} \text{lactone} + \text{NH}\langle + \text{OH}^- \tag{19}$$

$$\log \frac{k_{OR}}{k_{ROH}} = pK_{a_{ROH}} - pK_{a_{NH\langle}} - 0.4 \tag{20}$$

39) M. Kandel and E.H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

Equation (20) indicates that the relative nucleophilicities of the hydroxyl and hydroxyl anion to amide derivatives are controlled by the difference in pK_a of the alcohol and leaving group amine. When alcoholic hydroxyl group (pK_{aROH}=*ca.* 15—16) is operative as in the case of γ-hydroxybutyramide ($pK_{aNH<}$=*ca.* 9), the alcoxide ion is a stronger nucleophile. In the pH-rate profile for the hydrolysis of γ-hydroxybutyramide (Fig. 8), the observed first-order rate constant in the basic region must be apparently the same with that of alcoxide reaction (Reaction (19)). On the other hand, when intramolecular alcoholysis is carried out by the phenolic hydroxyl group (pK_{aROH}=*ca.* 9), such as I and II, the slightly larger reactivity of ROH than RO^- reactions is expected ($pK_{aNH<}$ is nearly equal with pK_{aROH}), then intermolecular reaction by more nucleophilic hydroxide ion must be operative predominantly in the phenolic-hydroxyl amide hydrolysis above pH 10. These arguments are consistent with the kinetic evidence.

Fersht[35] reported that as the nucleophilic alcohol becomes more basic, its reactivity toward amides decreases. The rate constants at the plateau region in the pH-rate profiles for phenolic and alcoholic hydroxyl amides (Fig. 8) are reasonably in this direction. That is, phenolic hydroxyl groups are more favorable for lactonization than alcoholic one.

Detailed discussion of relative nucleophilicities of ionized and un-ionized hydroxyl groups toward amides will be presented in the following paper.