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Studies on the Stability of Amides. I. Hydrolysis Mechanism of N-Substituted Aliphatic Amides[1]

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The kinetics of hydrolyses of N-substituted aliphatic amides was studied spectrophotometrically in aqueous solution at 30—95°. In concentrated hydrochloric acid solution up to 2.0M, the observed rate constants were found to increase to a constant value. Activation entropies for acidic hydrolyses of N-alkyl acetamides were largely negative, ranging -18—-32 *e.u.* The results can be explained by a bimolecular reaction mechanism in which a nucleophilic attack by water molecules on a protonated amide molecule is the rate-determining step. In alkaline hydrolyses of N-alkyl amides, the observed first-order rate constants k_1 were found to follow a kinetic equation: $k_1=k_2[\mathrm{OH}^-]+k_3[\mathrm{OH}^-]^2$. The activation entropies were largely negative in the range from -29 to -38 *e.u.* and their activation enthalpies were approximately 4 to 7 kcal/mole smaller than in acidic hydrolysis. The results suggest that the rate-determining step is the nucleophilic attack on amide molecule by hydroxide ions, and that hydrolyses of N-substituted acetamides, acyl-substituted amides and esters have the same reaction mechanism.

Using Taft's method, polar and steric substituent effects on the rates of hydrolyses of N-substituted acetamides are also studied.

Although amide group of R-CO-NHR′ type has been recognized to be a fundamental significance in many drugs and in proteins, kinetic study about the stability of this linkage under acidic or alkaline hydrolysis seems to be sparse compared with that of ester linkage.

Amide hydrolysis is generally supposed to be similar to ester hydrolysis.[3,4] In comparison with the hydrolysis of ester, however, some different reactivities of amide have been reported as follows: Hydrolyses of some amide derivatives in concentrated alkaline medium follow a rate-law which has a second-order term for hydroxide ion concentration,[4b,5] and in acidic medium, the hydrolysis rate increases to a maximum and then decreases as the concentration of acid is increased.[6] These results make hard to understand the mechanism of amide hydrolysis. Recently, Bolton and co-workers[7] have found that the acidic hydrolyses of primary aliphatic amides were affected by a combination of steric and conjugative substituent effects. On the other hand, studies about the correlation between reactivities and structures of N-substituted aliphatic[7a,8a] or aromatic amides[8b] have not been carried out quantitatively.

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2) Location: *Takara-machi, Kanazawa.*

3) *a)* A.R. Osborn and E. Walley, *Can. J. Chem.*, **39**, 1094 (1961); *b)* M.L. Bender, *Chem. Rev.*, **60**, 53 (1960); *c)* E.S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehalt and Winston, Inc., New York, 1959, p. 314.

4) *a)* E.E. Reid, *Am. Chem. J.*, **21**, 284 (1899); *idem, ibid.*, **24**, 397 (1900); *b)* A. Bruylants and F. Kézdy, *Record Chem. Progr.*, **21**, 213 (1960).

5) S.S. Biechler and R.W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957).

6) V.K. Krieble and K.A. Holst, *J. Am. Chem. Soc.*, **60**, 2976 (1938).

7) *a)* P.D. Bolton, *Aust. J. Chem.*, **19**, 1013 (1966); *b)* P.D. Bolton and G.L. Jackson, *ibid.*, **22**, 527 (1969); *c) Idem, ibid.*, **24**, 471 (1971).

8) *a)* U. Mazzucato, A. Foffani and G. Cauzzo, *Ann. Chim.* (Rome), **50**, 521 (1960); *b)* C.A. Bunton, B. Nyak and C.J. O'Connor, *J. Org. Chem.*, **33**, 572 (1968).

The present paper is reported to study on mechanism of hydrolysis of N-substituted aliphatic amide in acidic and alkaline media, and to find out the correlation between reactivity and structure of the compound with the similar method of Taft.[9]

Experimental

Materials——N,N-Dimethylacetamide (AcN(Me)$_2$), N,N-diethylacetamide (AcN(Et)$_2$) and 2-chloroacetamide (ClAcNH$_2$) were of reagent grade and were further purified by distillation. The prepartaions of other amides were carried out by the methods respectively described in literatures: Acetamide (AcNH$_2$),[10] N-methylacetamide (AcNHMe),[11] N-ethylacetamide (AcNHEt),[11] N-*n*-propylacetamide (AcNH*n*Pr),[12] N-iso-propylacetamide (AcNHisoPr),[12] N-methyl-N-ethylacetamide (AcNMeEt),[12] N-*n*-butylacetamide (AcNH*n*Bu),[13] N-iso-butylacetamide (AcNHisoBu),[13] N,N-di-*n*-propylacetamide (AcN(*n*Pr)$_2$),[13] N,N-di-iso-propylacetamide (AcN(isoPr)$_2$)[13] and 2-chloro-N-methylacetamide (ClAcNHMe).[14]

In all the amides, a good agreement was found between the observed melting points or boiling points and the values given in the literature; Identifications of the compounds were made by either elemental analysis or nuclear magnetic resonance (NMR), mass and infrared (IR) spectral analyses. Other chemicals were of reagent grade, and redistilled water was used throughout the experiments.

Kinetic Procedure——All the reactions were carried out with 5.0×10^{-3}M of amides (1.0×10^{-3}M of acetamide) and an excess hydrochloric acid or an excess alkali at a definite temperature. At appropriate intervals, some portions of the reaction mixture were taken out and the rates of the hydrolysis were measured spectrophotometrically by following the disappearence of amide absorption with a Shimadzu QV-50 spectrophotometer. The analytical wave length was as follows: AcNH$_2$, 206 mμ; AcNHMe, 211 mμ; AcNHEt, 213 mμ; AcNH*n*Pr, 213 mμ; AcNHisoPr, 214.5 mμ; AcNH*n*Bu; 214 mμ; AcNHisoBu, 215 mμ; AcN(Me)$_2$, 225 mμ; AcNMeEt, 227 mμ; AcN(Et)$_2$, 227 mμ; AcN(*n*-Pr)$_2$, 228 mμ; AcN(iso-Pr)$_2$, 226 mμ; ClAcNH$_2$, 209 mμ; ClAcNHMe, 218 mμ.

The effect of general base on the reaction rate in alkaline solutions was studied in the following mixture solutions which were adjusted to an ionic strength of 1.0 with potassium chloride; sodium hydroxide (0.01—0.20 M)-sodium phosphate (0.1 M) and sodium hydroxide (0.01—0.20 M)-sodium glycinate.

The pK_a values of phosphate and glycine were obtained from pH determination of the equimolar solutions of those conjugated acids and bases.

Result and Discussion

Mechanism of Acidic Hydrolysis

It is well known that a rate maximum has been found to occure in the hydrolysis of a number of aliphatic and aromatic amides in strong acid.[6,15] This fact has been understood by a mechanism of bimolecular reaction[3b,16] in which the rate-determining step is the reaction of water molecules with the conjugated acid of an amide (Chart 1). Gould[17] proposed that a cleavage between acyl-nitrogen rather than alkyl-nitrogen bond occured in hydrolyses of N-substituted amides. On the other hand, Itsuki, *et al.*[18] reported that an acidic hydrolysis of N-*tert*-butylacetamide proceeds as shown in Chart 2, *i.e.* as a unimolecular reaction, and that consequently *tert*-butyl alcohol is the product of the hydrolysis. These proposed mechanisms on the acidic hydrolyses of amides have made hard to interpret the

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[9] R.W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. by M.S. Newman, John Wiley and Sons, Inc., New York, 1956, p. 586.

[10] C.H. Caleman and A.M. Alvarado, *Org. Synth.*, Coll., **1**, 3 (1951).

[11] A. Galat and G. Elion, *J. Am. Chem. Soc.*, **65**, 1566 (1943).

[12] S. Wawzonek, W. McKillip and C.J. Peterson, *Org. Synth.*, **44**, 75 (1964).

[13] J.L.E. Erickson, *Chem. Ber.*, **59**, 2665 (1926).

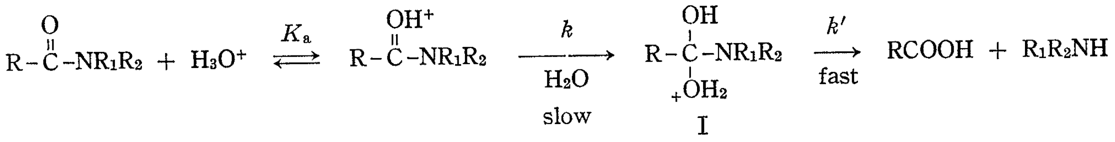
[14] W.A. Jacobs and M. Heidelberger, *Org. Synth.*, **7**, 16 (1927).

[15] J.T. Edward and S.C.R. Meacock, *J. Chem. Soc.*, **1957**, 2000.

[16] M.L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953); M.L. Bender, R.D. Ginger and K.C. Kemp, *ibid.*, **76**, 3350 (1954); M.L. Bender and R.D. Ginger, *ibid.*, **77**, 348 (1955).

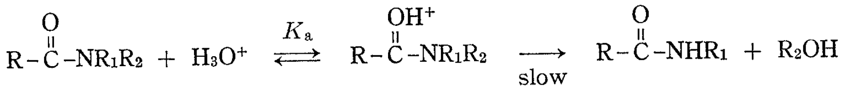
[17] Ref. 3*c*), p. 328.

[18] H. Itsuki and S. Terasawa, *Nippon Kagaku Zasshi*, **90**, 1012 (1969).



$$\text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-NR}_1\text{R}_2 + \text{H}_3\text{O}^+ \overset{K_a}{\rightleftarrows} \text{R-}\overset{\overset{\text{OH}^+}{\|}}{\text{C}}\text{-NR}_1\text{R}_2 \xrightarrow[\substack{\text{H}_2\text{O}\\ \text{slow}}]{k} \underset{\text{I}}{\text{R-}\overset{\overset{\text{OH}}{|}}{\underset{\underset{+\text{OH}_2}{|}}{\text{C}}}\text{-NR}_1\text{R}_2} \xrightarrow[\text{fast}]{k'} \text{RCOOH} + \text{R}_1\text{R}_2\text{NH}$$

Chart 1



$$\text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-NR}_1\text{R}_2 + \text{H}_3\text{O}^+ \overset{K_a}{\rightleftarrows} \text{R-}\overset{\overset{\text{OH}^+}{\|}}{\text{C}}\text{-NR}_1\text{R}_2 \xrightarrow[\text{slow}]{} \text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-NHR}_1 + \text{R}_2\text{OH}$$

Chart 2

mechanism of the reaction. Then, we attempted to clarify the mechanism of acidic hydrolyses of N-substituted amides in various conditions.

AcNHMe, AcNHEt, AcNH*n*-Pr, AcNH*n*-Bu, and AcN(Me)$_2$ were hydrolyzed in hydrochloric acid of various concentrations and the pseudo first-order rate constants of their reactions were determined. Figure 1 shows the dependence of the observed first-order rate constant, k_{obs}, on hydrochloric acid concentration. With the increasing of acid concentration, the value k_{obs} of N-substituted acetamides was found to increase to a constant value.

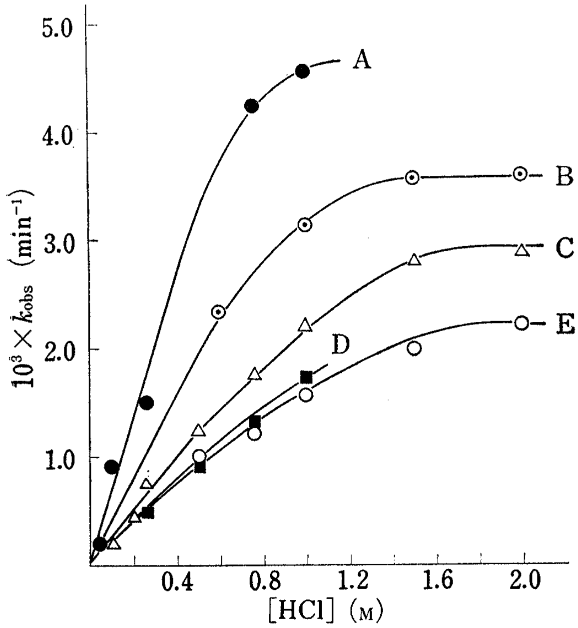


Fig. 1. Effect of Concentration of Hydrochloric Acid on the Pseudo First-Order Rate Constant of Acidic Hydrolysis of Amide

A: AcNHMe (at 85°); B: AcN(Me)$_2$(at 80°); C: AcNHEt (at 80°); D: AcNH*n*-Pr (at 80°); E: AcNH*n*-Bu (at 80°)

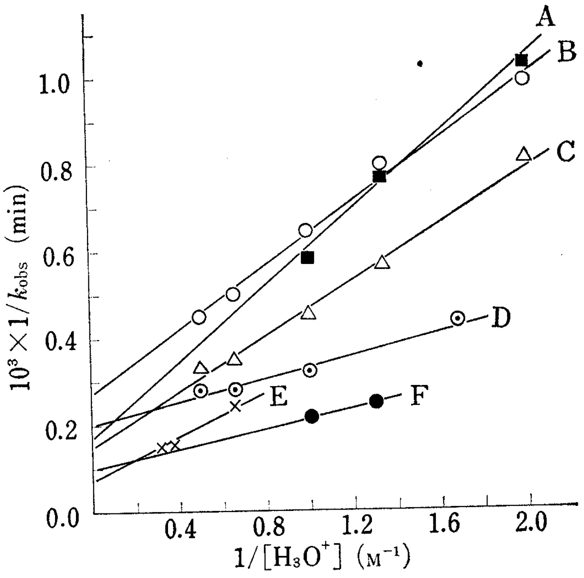


Fig. 2. Double Reciprocal Plot of the Data in Fig. 1 for Acidic Hydrolysis of Amide

A: AcNH*n*-Pr (at 80); B: AcNH*n*-Bu (at 80°); C; AcNH*n*-Et (at 80°); D: AcN(Me)$_2$(at 80°); E: AcNH$_2$ (at 50°); F: AcNHMe (at 85°)

If the acidic hydrolyses of these compounds proceed by way of the bimolecular reaction mechanism shown in Chart 1, the following equation is derived.

$$k_{obs} = \frac{k[H_2O][H_3O^+]}{K_a + [H_3O^+]} \tag{1}$$

When $K_a \ll [H_3O^+]$, Eq. (1) is simplified to Eq. (2).

$$k_{obs} = k[H_2O] \tag{2}$$

Under these conditions, Eq. (2) indicates that the observed first-order rate constant is independent of acid concentration,[19] and the results seen in Fig. 1 fit this relationship.

Equation (3) is obtained in rearranging Eq. (1), and plotting $1/k_{obs}$ against $1/[H_3O^+]$ give a straight line with a slope of $K_a/k[H_2O]$ and an intercept of $1/k[H_2O]$ in dilute acid.

$$\frac{1}{k_{obs}} = \frac{K_a}{k[H_2O]} \frac{1}{[H_3O]} + \frac{1}{k[H_2O]} \tag{3}$$

These plottings of k_{obs} for acidic hydrolyses of six amides are shown in Fig. 2, and K_a obtained from the slope of each line is listed in Table I. The values thus obtained were in good agreement with those determined directly from spectrophotometric method.[20]

Table I. Dissociation Constant K_a Obtained in Acid-Catalyzed Hydrolysis of Amide

Amide	Reaction Temp.	Dissociation constant calculated[a] K_a	Dissociation constant reference K_a
$AcNH_2$	50°	3.0	2.4[b], 2.7[c]
AcNHMe	85°	0.79	0.35[b]
AcNHEt	80°	2.0	
AcNH*n*-Pr	80°	2.2	
AcNH*n*-Bu	80°	1.6	1.4[b]
$AcN(Me)_2$	80°	0.68	0.63[b]

a) K_a was obtained from the rate constant of acid-catalyzed hydrolysis of amide using equation (3).
b) Ref. 20*a*) *c*) Ref. 20*b*)

Table II shows the second-order rate constants of the hydrolyses of N-substituted acetamides at various temperatures and their activation enthalpies $\Delta H^{\ast}$ and entropies $\Delta S^{\ast}$ calculated by Eyring's equation.[21] Activation entropies of all the N-substituted acetamides studied were between −18 and −32 *e.u.* On the other hand, N-*tert*-butylacetamide was reported to have largely positive activation entropy for its hydrolysis,[18] +18.1 *e.u.* It is generally well known that there is an empirical correlation between entropy of activation and reaction order for a number of acid catalyzed reaction; bimolecular reactions of acyl-compounds have $\Delta S^{\ast}$ values which are usually more negative than −15 *e.u.*, and unimolecular reactions have $\Delta S^{\ast}$ values which are near zero or positive.[22] The reactions studied and the other one cited are well in these categories each other.

From these results, the mechanism of the acidic hydrolyses of the N-substituted acetamides examined in this work seems to be a bimolecular reaction type.

Mechanism of Alkaline Hydrolysis

The mechanism generally accepted for basic amide hydrolysis involves the rate-determining step which is the nucleophilic attack by hydroxide ion on the amide to form intermediate II, as shown in Chart 3.[3b,c] This intermediate II has been confirmed by a convincing evidence obtained from the study of oxygen-isotope exchange and hydrolytic reaction of

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[19] In higher acid concentration, as the activity of water is lowered, k_{obs} must decrease under the condition. In the present study, limitted dilute acid solutions (2.0 M of hydrochloric acid is the highest concentration) were chosen to avoid more complicated rate-laws.

[20] *a*) A.R. Goldfarb, A. Mele and N. Gutstein, *J. Am. Chem. Soc.*, **77**, 6194 (1955); *b*) F. Kézdy and A. Bruylants, *Bull. Soc. Chim. Frans*, **1959**, 947.

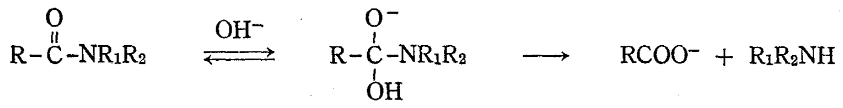
[21] K.J. Laidler, "Chemical Kinetics," 2nd ed., McGraw-Hill, Inc., New York, 1956, p. 90.

[22] L.I. Schaleger and F.A. Long, "Advances in Physical Organic Chemistry," Vol. 1, ed. by V. Gold, Acad. Press, London, 1963, p. 1.

Table II. Rate Constant, Enthalpy and Entropy of Activation for Acidic Hydrolysis of N-Substituted Acetamide

Amide	Reaction Temp. (°C)	$10^4 \times kH^{+a)}$ ($M^{-1} \cdot min^{-1}$)	$\Delta H^{\neq}$ (kcal·mole^{-1})	$\Delta S^{\neq}$ (75°) (cal·mole^{-1}·degree^{-1})
$AcNH_2$	60	137	22.0	−18.4
	65	190	(19.6)[b]	(−18.2)[b]
	70	310		
	75	511		
AcNHMe	75	25.5	20.6	−21.6
	85	59.0	(21.5)[c]	(−18.6)[c]
AcNHEt	70	8.85	22.1	−18.6
	75	14.0		
	80	22.2		
	85	32.7		
AcNH*n*-Pr	75	11.9	17.6	−31.8
	80	17.2		
	85	23.2		
AcNHiso-Pr	75	5.40		
AcNH*n*-Bu	75	10.1	22.0	−22.0
	80	15.6		
	85	24.1		
AcNHiso-Bu	75	8.09	21.1	−22.6
	80	11.3		
	85	17.5		
$AcN(Me)_2$	75	22.6	20.5	−22.2
	80	31.4	(20.2)[c]	(−22.0)[c]
AcNMeEt	75	6.10		
$AcN(Et)_2$	75	1.36		
ScN(*n*-Pr)$_2$	75	0.68		

a) All the experiments were carried out in aqueous 1.0N HCl solution.
b) P. D. Bolton, *Tetrahedron Letters*, **1963**, 843
c) Ref. 7)



$$R-\overset{\overset{O}{\|}}{C}-NR_1R_2 \xrightleftharpoons{OH^-} R-\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}-NR_1R_2 \longrightarrow RCOO^- + R_1R_2NH$$

II

Chart 3

amide.[16] Recently, Biechler and Taft[5] have found that the alkaline hydrolysis rate constants of anilide derivatives followed kinetic Eq. (4) and proposed the formation of two reactive intermediates II and III in their mechanism (Chart 4).

$$k_1 = k_2[OH^-] + k_3[OH^-]^2 \qquad (4)$$

Schowen, *et al.*,[23] however, reported that the intermediate II could be directly decomposed to its products by general base catalysis, and that the hydrolyses of all the amides, having second-order term for hydroxide ions in the equation of their reaction kinetics, do not necessarily proceed through an intermediate III. Studies on the alkaline hydrolysis of a series of aliphatic N-substituted amides, therefore, were carried out to elucidate the more general mechanism of this reaction.

The pseudo first-order rate constants k_1 of the reactions were determined under a constant ionic strength (μ=1.0). Plots of k_1 against hydroxide ion concentration [OH$^-$] gave upward curvatures and plots of k_1/[OH$^-$] against [OH$^-$] were reasonably linear for all studies.

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[23] R.L. Schowen and G.W. Zourick, *J. Am. Chem. Soc.*, **88**, 1223 (1966).

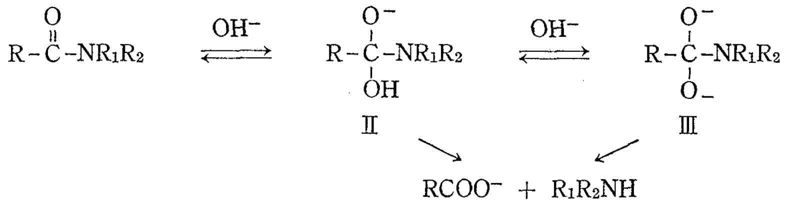

Chart 4

The typical plots for the hydrolyses of AcNHMe and $AcN(Me)_2$ are illustrated in Fig. 3. In this case, the straight line for each compound gives the third-order rate constant, k_3, from the slope and the second-order one, k_2, from the intercept. The rate constants k_2 and k_3 of a series of aliphatic amides are summarized in Table III. These results indicate that the hydrolytic reactions of these compounds in alkaline hydroxide solutions seem to follow the kinetic Eq. (4).

Table III. Rate Constants, k_2 and k_3 for the Alkaline Hydrolysis of Amide[a)]

Amide	Reaction Temp. (°C)	$10^3 \times k_2$ (M^{-1} min^{-1})	$10^3 \times k_3$ (M^{-2} min^{-1})
$AcNH_2$	50	22.5	3.8
AcNHMe	75	19.3	2.1
AcNHEt	75	8.9	1.9
AcNH*n*-Pr	75	6.1	0.55
AcNHiso-Pr	90	4.8	0.55
AcNH*n*-Bu	75	5.5	0.68
AcNHiso-Bu	80	4.8	0.55
$AcN(Me)_2$	75	27.3	3.8
$AcN(Et)_2$	90	1.7	0.38
Ac(*n*-Pr)$_2$	75	0.25	0.15
$ClAcNH_2$	50	1500	7000
ClAcNHMe	50	260	400

a) All the experiments were carried out at ionic strength $\mu=1.0$. The definition of k_2 and k_3 is seen in equation (4).

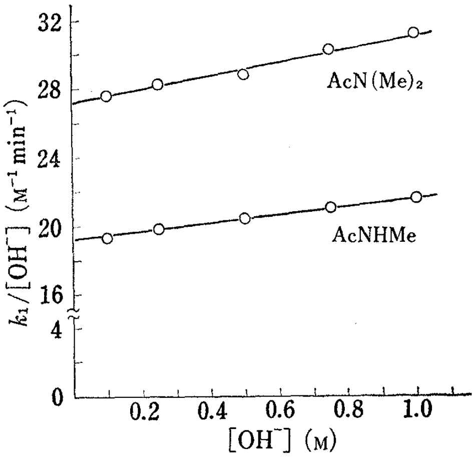

Fig. 3. Effect of Concentration of Hydroxide Ion on the Observed First-Order Rate Constant of Base-Catalyzed Hydrolysis of Amide

a) The reaction was carried out at $\mu=1.0$ and at 75°.

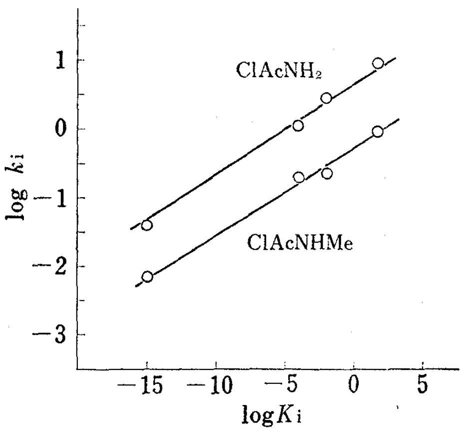

Fig. 4. Brönsted Plot of Hydrolysis Rate Constants of $ClAcNH_2$ and ClAcNHMe for General Base Catalysts at Ionic Strength $\mu=1.0$ and at 50°

Accordingly, from Schowen, *et al.*'s suggestion[23] it is expected that all the amides of this series are subject to catalysis by a general base. To study the effect of general base catalysts on the amide hydrolysis, ClAcNH$_2$ and ClAcNHMe are suitable compounds because of their relatively large rate constants of second-order term in hydroxide ion catalyzed hydrolysis (Table III). Equation (5), which was derived from Eq. (4) by changing hydroxide ion concentration to general base concentration [B$_i$], was used for the kinetic study of the reaction.

$$k_1 = (k_2 + \sum_i k_i[\mathrm{B}_i])[\mathrm{OH}^-] \qquad (5)$$

Where k_2 is the same significance with Eq. (4) and k_i is the third-order rate constant. Table IV shows the values k_i for ClAcNH$_2$ and ClAcNHMe obtained by Eq. (5) and the logarithm plots of the data in Table IV are shown in Fig. 4. It is clear from the result shown in Fig. 4 that the rate constants, k_i of the hydrolyses of these compounds have a good correlation with the Brönsted catalysis law.[24]

Table IV. Rate Constants of Hydrolyses of 2-Chloroacetamide (ClAcNH$_2$) and 2-Chloro-N-Methylacetamide (ClAcNHMe) with General Base Catalysts at Constant Ionic Strength μ=1.0 and at 50°

General base	Equilibrium constant[a] K_i (M)	Rate constant k_i (M^{-2} min^{-1}) ClAcNH$_2$	Rate constant k_i (M^{-2} min^{-1}) ClAcNHMe
H_2O	$10^{-15.0}$[b]	2.7×10^{-2}	4.7×10^{-3}
Gly$^-$	$10^{-4.60}$[c]	1.0	1.5×10^{-1}
$PO_4^{\equiv}$	$10^{-2.16}$[c]	6.0	5.0×10^{-1}
OH$^-$	$10^{1.74}$[d]	7.6	4.0×10^{-1}

a) These are equilibrium constants for the reaction: $B_i + H_2O \rightleftarrows B_iH^+ + OH^-$.
b) calculated from $K_W(=10^{-13.26})$ at 50° by H. Harned and W. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed., Reinhold Publishing Co., New York, 1963, p. 645
c) determined by the half-neutralization method at ionic strength μ=1.0 and at 50°
d) calculated by the equation: $K_{OH^-} = K_W/K_{H_2O}$ (at 50°)

The results of kinetic study of alkaline hydrolyses of ClAcNH$_2$ and ClAcNHMe suggest that intermediate II, which is formed in the initial step of their hydrolyses, is decomposed by general base catalysts. The alkaline hydrolyses of other N-substituted acetamides, whose first-order rate constants also fit Eq. (4), probably follow the same mechanism as ClAcNH$_2$ and ClAcNHMe.

The second-order rate constants of the hydrolyses of N-substituted derivatives at various temperatures and their activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, are summarized in Table V. The enthalpies of activation for alkaline hydrolyses of all the amides examined in Table V are approximately 4 to 7 kcal/mole smaller than the enthalpies for their acidic hydrolyses in Table II, and the entropies of activation are largely negative ranging from −29 to −38 *e.u.* The large negative values of $\Delta S^{\neq}$ probably reflect the bimolecular rate-determining step.[22] These activation parameters are closely similar to those reported for the hydrolysis of acyl-substituted aliphatic amide, for which the activation enthalpies are approximately 3.5 kcal/mole smaller for base- than those for acid-catalyzed hydrolyses,[25] and largely negative activation entropies are in the range from −26 to −39 *e.u.*[26] These data are con-

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[24] A.A. Frost and P.G. Pearson, "Kinetics and Mechanism," 2nd ed., John Willey & Sons, Inc., New York, 1961, p. 218.

[25] M. Roo and A. Bruylants, *Bull. Soc. Chim. Belges.*, **63**, 140 (1954).

[26] P.D. Bolton and G.L. Jackson, *Aust. J. Chem.*, **24**, 969 (1971).

TABLE V. Rate Constant, Enthalpy and Entropy of Activation for Alkaline Hydrolysis of N-Substituted Acetamide

Amide	Reaction Temp. (°C)	$10^3 \times k_{OH^-}$[a] ($M^{-1} \cdot min^{-1}$)	$\Delta H^{\ddagger}$ ($kcal \cdot mole^{-1}$)	$\Delta S^{\ddagger}$ ($cal \cdot mole^{-1} \cdot degree^{-1}$)
$AcNH_2$	30	7.99	13.3	−32.8
	40	12.1	(13.2)[b]	(−33.9)[b]
	45	19.5		
	50	26.9		
	75	112		
AcNHMe	55	5.08	16.6	−29.1
	60	6.78	(16.4)[c]	(−27.7)[c]
	65	10.1		
	75	21.5		
AcNHEt	60	3.83	16.1	−31.7
	65	5.42		
	70	7.72		
	75	10.8		
AcNH*n*-Pr	60	2.24	16.4	−32.7
	65	3.37		
	70	4.50		
	75	6.62		
AcNHiso-Pr	65	1.05	17.5	−29.4
	75	2.20		
	85	4.07		
	90	5.31		
AcNH*n*-Bu	65	2.83	15.4	−34.9
	70	3.58		
	75	6.17		
	80	8.33		
AcNHiso-Bu	75	3.85	16.8	−31.8
	80	5.58		
	85	7.58		
$AcN(Me)_2$	55	8.27	15.1	−31.4
	60	11.9	(15.4)[c]	(−30.8)[c]
	65	16.6		
	75	31.1		
AcNMeEt	70	4.25	16.2	−30.6
	75	5.90		
	80	7.99		
	85	11.2		
	90	15.0		
$AcN(Et)_2$	70	0.51	18.0	−31.1
	75	0.70		
	80	1.04		
	85	1.49		
	90	2.12		
$AcN(n\text{-}Pr)_2$	75	0.40	15.2	−37.6
	85	0.75		
	90	0.87		
	95	1.32		
$AcN(iso\text{-}Pr)_2$	85	0.15	17.5	−32.5
	95	0.31		

a) The experiments were carried out in aqueous 1.0 N NaOH solution.
b) Data taken from. ref. 26).
c) Recalculated value of the data of ref. 8*a*).

sistent with the previously reported kinetic evidence that the alkaline hydrolysis of $AcNHMe$[8a] as well as $AcNH_2$ and propionamide[27] was accelerated by increasing the dielectric constant of the solvent system such as ethanol–water or dioxane–water mixture.

From the evidence thus obtained in this study together with some previously published work, it may be said that the rate-determining step in the alkaline hydrolysis of N-substituted acetamide is the nucleophilic attack of hydroxide ions on neutral amide molecules to form intermediate II.

Substituent Effect

It is accepted that the polar effects of substituents on the rate constant of acid-catalyzed hydrolysis of amide are almost insignificant, but the steric effects of those are sensitive to the reaction rates,[3b] and that both effects play an important part on its base-catalyzed reaction.[26] In the above sections, we showed that the mechanism of acidic and alkaline hydrolyses of N-substituted amides is the same with that of the hydrolysis of ester. That is, in acidic hydrolysis of these amides pass through intermediate I and in alkaline hydrolysis they pass through intermediate II. These results suggest that the steric effects must be almost the same in two types of hydrolyses of N-substituted amides although there is the difference between the numbers of protons in the reaction intermediates. Accordingly, the difference $\log(k/k_o)_{\text{base}}$—$\log(k/k_o)_{\text{acid}}$ can be taken as a measure of the polar effect and the quantity $\log(k/k_o)_{\text{acid}}$ can be taken as a measure of the steric effect. The polar substituent constant, E_σ, and the steric substituent constant, E_s', for N-substituted components are defined in Eq. (6) and Eq. (7) by treatment similar to Taft.[9]

$$E_\sigma = \log(k/k_0)_{\text{base}} - \log(k/k_0)_{\text{acid}} \tag{6}$$

$$E_s' = \log(k/k_0)_{\text{acid}} \tag{7}$$

In these equations, base and acid refer respectively to the hydrolysis in basic and acidic media, and k_o and k mean respectively the rate constants of the hydrolysis of acetamide, which is the reference, and those of N-substituted acetamides. Chiang and Tai[28] reported that the inductive indexes (*I.I.*) calculated from Pauling's electronegativity[29] and the covalent radius[30] of each atom of various substituent groups had a good correlation with Taft's polar substituent constants,[9] E_σ^*.

Table VI shows the E_σ and E_s' values obtained from the hydrolysis rate constants of acetamide derivatives at 75° in aqueous 1.0N NaOH solution and in aqueous 1.0N HCl solution, and also contains *I.I.* difference, $\Delta I.I.$, of N-alkyl substituents of the amides and Taft's steric parameters, Es, for acyl substituent groups. These *I.I.* difference are obtained by subtraction of the value of inductive index of acetamide ($I.I.=1.59\times10^{-1}$) from those of Nalkyl substituents.

The values of E_σ of N-alkyl substituent groups in Table VI were plotted against the values of $\Delta I.I.$ in Fig. 5. All the points examined were devided into two groups according to the number of hydrogen atoms bound to nitrogen atom of amide and fall on two parallel lines corresponding to N-mono- and N,N-di-substituted derivatives respectively. The difference in intercept between two lines will suggest the occurrence of other effects on each series of the compounds. Plotting[31] the values E_s' of the amide against their steric parameter E_s in Table VI gives likewise two separated lines for N-substituted compounds in Fig.

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[27] K.J. Laidler and P.A. Landskroener, *Trans. Farady Soc.*, 52, 200 (1956).

[28] M.C. Chiang and T.C. Tai, *Scientia.*, 12, 785 (1963); *cf.* T. Yamamoto, *Kagaku* (Kyoto), 22, 226 (1967).

[29] W. Gordy and W. Thomas, *J. Chem. Phys.*, 24, 439 (1956).

[30] L. Pauling, "The Nature of Chemical Bond," Cornell University Press, Ithaca, 1948, p. 164.

[31] Because the covalent radius[30] of N(=0.70 Å) is nearly equal to that of C(=0.77 Å), an N-alkyl component of amide, NR_1R_2, and a corresponding acyl component of ester, CHR_1R_2, seem to have a proportional relationship in their substituent constants.

Table VI. Steric Substituent Constant[a], E_s', Taft's Steric Substituent Constant, E_s, Polar Substituent Constant[a], E_σ, and *I.I.* Difference, Δ *I.I.*, of Amide

No.	Amide	Substituent constant			
		E_s'	E_s[b]	E_σ	$10^2 \times \Delta I.I$
1	$AcNH_2$	0.00	0.00	0.00	0.00
2	AcNHMe	−1.29	−0.07	0.57	0.83
3	AcNHEt	−1.56	−0.36	0.54	0.78
4	AcNH*n*-Pr	−1.62	−0.39	0.36	0.73
5	AcNHiso-Pr	−1.98	−0.93	0.28	0.65
6	AcNH*n*-Bu	−1.70	−0.40	0.42	0.72
7	AcNHiso-Bu	−1.81	−0.35	0.35	0.69
8	$AcN(Me)_2$	−1.35	−0.47	0.76	1.81
9	$AcN(Et)_2$	−2.56	−1.98	0.49	1.56
10	AcNMeEt	−1.92	−1.13	0.62	1.69
11	AcN(*n*-Pr)$_2$	−2.87	−2.11	0.41	1.47

a) Definitions and calculations of E_s' and E_σ are based on equation (7) and equation (6).
b) Data taken from ref. 9.

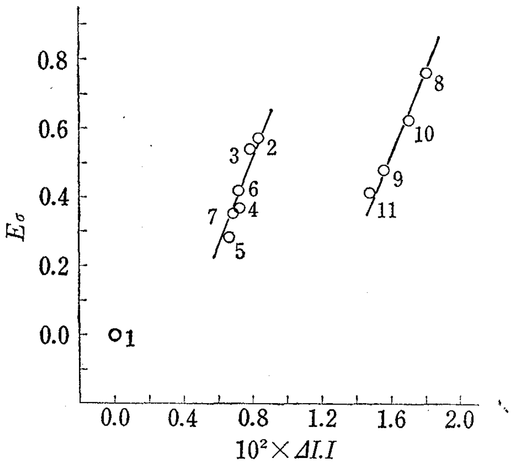

Fig. 5. Relationship between Polar Substituent Constant of N-Alkyl Substituted Acetamide and *I.I.* Difference[a]

a) The numbers in the figure are corresponded to the same number in Table VI.

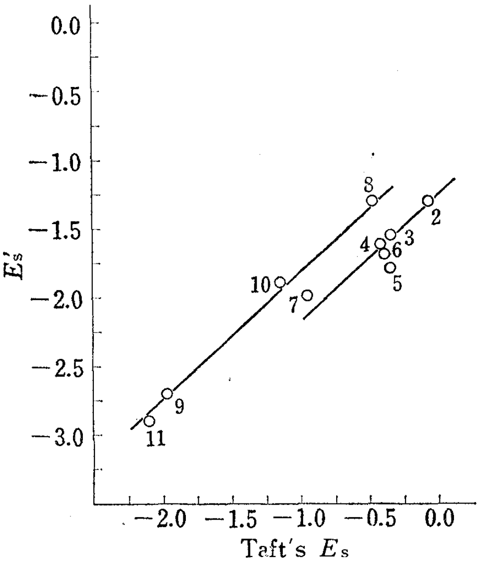

Fig. 6. Relationship between Steric Substituent Constant of N-Alkyl Substituted Acetamide and Taft's Steric Substituent Constant[a]

a) The number in the figure are corresponded to the same number in Table VI.

6. These facts attract the attention on the similarities of the properties of the substituent steric effect parameters of two series of amides and its properties of esters.

N—H bond effect was observed on the three parallel lines separated depending upon the number of hydrogen atoms bound to nitrogen atom by plotting pK_a against E_σ* of alkyl substituted ammonium ions.[32] Hall[32] explained this separation by the solvation mechanism susceptible to steric hindrance involving NH···O type hydrogen bonds. As regards the acidic hydrolyses of acetamides in the present study, introduction of methyl group in

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[32] H.K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

the nitrogen atom seems to decrease considerably the rate constant (Table II) and in alkaline hydrolyses, the introduction of the second methyl group in the nitrogen atom seems to increase the rate constant in a relatively large amount (Table V). Bolton7(a) has also observed similar results in the study of the hydrolyses of two N-substituted aliphatic amides and pointed out that these anomalies might be attributed to amide-solvent interaction between an acidic proton of the nitrogen atom and water molecules.

The results seen in Fig. 5 and Fig. 6 seem likely to be caused by an identical reason suggested by Bolton7(a) and Hall32) since the reactivity of the nitrogen atom in amides is similar to its reactivity in the corresponding amines.33) Present work shows that the substituent-effect parameters on the rate constants of the hydrolyses of N-alkyl acetamides are found to have closely a correlation to Taft's equation with mono- or di-substituted derivatives. Further studies are required for clarifying the reason of the different reactivity between N-mono- and N,N-di-substituted compounds.

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33) F.M. Arshid, C.H. Giles, S.K. Jain and A.S.A. Hassan, *J. Chem. Soc.*, **1956**, 72.