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Studies on the Stability of Amides. III.[1] Hydrolysis of Amides in Aqueous Perchloric Acid Solution[2]

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Attempt was made to determine the number of water molecules needed from ground state to transition state in acid-catalyzed hydrolysis of amide. Using relative first-order rate constants and ionization ratios for derivative and standard amide could lead to the medium independence of activity coefficient term in the rate expression of amide acidic hydrolysis. Good linear relationship in the derivation of the relative hydration number ($r'-r$) between derivative (r') and standard amide (r) was obtained for the various amide hydrolyses in perchloric acid solutions. The observed ($r'-r$)-values were consistent with the mechanism change and with change in reactivity.

In the earlier paper[4] dealing with the hydrolysis mechanism of N-alkyl amides, it was reported that introduction of bulkyl groups in the nitrogen atom of acetamide could result the mechanism change from bimolecular reaction, in which water molecules assist in the rate-determining step, to unimolecular one, in which water molecules are not involved in this step, and postulated that the difference in the reactivity between N-mono and N,N-disubstituted amides was attributed to the amide-solvent interaction. Moreover, water molecules have been reported to play a particular role in the rate-determining step of another amide hydrolysis, *e.g.*, water molecules assist as the proton-transfer reagent,[5] and no participation[6] or opposite assist[7] of water molecules as the nucleophile can be caused by increasing acid concentration. These mechanism changes and differences of the reactivity which were observed in the hydrolyses of amide derivatives seem likely to correlate with change in the number of water molecules which assist between ground state and transition state of the reaction.

Bunnett[8] has related the first-order rate constant of many reactions in moderately concentrated acid to the acidity function H_0 and water activity, and defined its correlation coefficient as the hydration parameter, ω value, which can be used to classify the reactions according to mechanism. It has been pointed out, however, that the theory has a disadvantageous points because unexpectedly large values[8b,8d,9,10] of ω have often been obtained and plots according to Bunnett's prediction[8] have been reported to give curvature[11] especial-

1) Part II: T. Yamana, A. Tsuji, and Y. Mizukami, *Chem. Pharm. Bull.* (Tokyo), **20**, 922 (1972).
2) This work was presented at 91st Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April 1971.
3) Location: *Takara-machi, Kanazawa.*
4) T. Yamana, Y. Mizukami, A. Tsuji, Y. Yasuda, and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 881 (1972).
5) R.B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964).
6) *a*) M.I. Vinnik, I.M. Medvetskaya, L.R. Andreeva, and A.E. Tiger, *Russ. J. Phys. Chem. English Transl.*, **41**, 128 (1967); *b*) M.I. Vinnik and I.M. Medvetskaya, *ibid.*, **41**, 947 (1967); *c*) *idem, ibid.*, **43**, 345 (1969); *d*) J.A. Duffy and T.A. Leisten, *J. Chem. Soc.*, **1960**, 853.
7) M.L. Bender, Y. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).
8) *a*) J.F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961); *b*) *idem. ibid.*, **83**, 4968 (1961); *c*) *idem. ibid.*, **83**, 4973 (1961); *d*) *idem. ibid.*, **83**, 4978 (1961).
9) R.B. Martin, *J. Am. Chem. Soc.*, **84**, 4130 (1962).
10) H. Takaya, N. Todo, and T. Hosoya, *Bull. Chem. Soc. Japan*, **42**, 2748 (1969).
11) J.F. Bunnett and F.P. Olsen, *Can. J. Chem.*, **44**, 1899 (1966); *idem, ibid.*, **44**, 1917 (1966).

ly in amide hydrolysis.[12] Attempts[13,14] have been made recently to determine in a more exact way the number of water molecules needed from ground-state to transition-state in acid catalyzed hydrolysis of amide, by improving Bunnett's theory. But, a serious criticism[15] was passed on the treatment for the activity-coefficients in reaction medium.

Present paper describes the improvement of above theory and the correlation between mechanism or reactivity and change in the number of water molecules which assist in the rate-determining step of amide hydrolysis.

Experimental

Materials——Phthalamic acid,[16] N-*tert*-butylacetamide,[17] N-methylbenzamide[18] and N,N-dimethylbenzamide[19] were prepared and purified by the method in the literature. N-Substituted acetamides used were recrystallized commercial materials. Perchloric acid solutions were prepared by diluting reagent grade concentrated acid (70%) and their concentrations were determined by titrating with standardized sodium hydroxide solution. The corresponding values of water activity were obtained by interpolation from a graph of the data of Bunnett.[8a])

Kinetics——Hydrolyses were carried out with 5.0×10^{-3}M of amides at desired temperatures (±0.05°). At appropriate intervals, some portions of the reaction mixture were withdrawn, rapidly cooled, and neutralized with sodium hydroxide solution of suitable concentration. The rates of hydrolyses were determined as follows:

a) For the hydrolyses of primary amides, the ammonia liberated during the reactions was estimated by the indophenol method.[20] The absorbance of the resulted indophenol blue was measured at 640 mμ on a Hitachi 101 spectrophotometer. Ammonia concentrations were read from a curve prepared from standard ammonium sulfate solutions.

Table I. Pseudo First-Order Rate Constants of Aliphatic Amide Hydrolysis at 80.0° in Perchloric Acid Solution of Various Concentrations

Acid concentration (M) $HClO_4$	Rate constant $10^3\ k_{obs}$ (min^{-1}) Acetamide	Acid concentration (M) $HClO_4$	Rate constant $10^3\ k_{obs}$ (min^{-1})		Acid concentration (M) $HClO_4$	Rate constant $10^3\ k_{obs}$ (min^{-1})	
			Propionamide	N-*tert*-Butylacetamide		N-Methylacetamide	N,N-Dimethyl acetamide
3.75	40.8	4.03	49.2	—	4.17	8.43	5.32
4.20	36.5	5.21	27.7	—	4.73	6.98	4.47
4.59	27.7	5.68	—	—	5.21	5.68	3.78
5.11	20.1	6.01	14.8	6.30	5.68	4.95	3.32
5.43	16.9	6.50	—	8.56	6.47	3.20	2.42
5.68	15.0	7.00	—	13.6	6.90	2.93	2.12
5.82	13.1	7.50	—	20.4			
6.19	10.2	7.63	4.44	—			
6.34	8.79	8.03	2.92	32.2			
6.62	7.28	8.55	1.98	46.2			
7.17	4.95						
7.40	4.83						
7.63	3.75						
8.07	2.60						
8.55	1.76						

12) C.A. Bunton, C. O'Connor, and T.A. Turney, *Chem. and Ind.*, **1967**, 1835.
13) R.B. Moodie, P.D. Wale, and T.J. Whaite, *J. Chem. Soc.*, **1963**, 4273.
14) *a*) K. Yates and J.B. Stevens, *Can. J. Chem.*, **43**, 529 (1965); *b*) K. Yates and J.C. Riordan, *ibid.*, **43**, 2328 (1965).
15) V.C. Armstrong, D.W. Farlow, and R.B. Moodie, *J. Chem. Soc.* (*B*), **1968**, 1099.
16) E. Chapman and H. Stephan, *J. Chem. Soc.*, **127**, 1791 (1925).
17) A.C. Cope, N.A. Lebel, H. Lee, and W.R. Moore, *J. Am. Chem. Soc.*, **79**, 4720 (1957).
18) F.L. Dunlap, *J. Am. Chem. Soc.*, **24**, 758 (1902); O.L. Brady and F.P. Dunn, *J. Chem, Soc.*, **1926**, 2414.
19) A. Hallman, *Chem. Ber.*, **9**, 846 (1876).
20) K. Yagi and J. Okada, *Protein, Nucleic Acid and Enzyme*, **4**, 139 (1959).

Table II. Pseudo First-Order Rate Constants of Aromatic Amide Hydrolysis at 50.0° in Perchloric Acid Solution of Various Concentrations

Acid concentration (M) $HClO_4$	Rate constant $10^4\ k_{obs}$ (min^{-1})		
	Benzamide	*p*-Nitrobenzamide	Phthalamic acid
2.97	4.05	7.10	555
3.90	3.73	—	582
4.46	3.15	—	619
4.94	2.65	—	640
5.98	1.40	5.58	608
6.44	1.04	4.58	532
7.03	0.655	3.50	461
8.03	0.237	1.67	235
8.53	0.140	0.917	194

Table III. Pseudo First-Order Rate Constants of Aromatic Amide Hydrolysis at 95.0° in Perchloric Acid Solution of Various Concentrations

Acid concentration (M) $HClO_4$	Rate constant $10^3\ k_{obs}$ (min^{-1})		
	Benzamide	N-Methylbenzamide	N,N-Dimethylbenzamide
4.11	23.5	1.40	2.13
4.59	18.5	1.03	1.79
5.11	15.3	0.875	1.40
5.43	13.2	0.772	1.28
5.82	11.0	0.613	0.978
6.19	8.53	0.457	0.835
6.62	6.94	0.380	0.653
7.17	4.75	0.273	0.548

b) For the hydrolyses of N-substituted amides, the same procedure in the proceeding paper[4] was employed.

c) In the hydrolysis of N-*tert*-butylacetamide, acetamide and *tert*-butanol were reported[21] to be the reaction products. Since acetamide produced was further hydrolyzed during kinetic runs, the residual amide concentration $[amide]_t$ was calculated from the following equation.

$$[amide]_t = \{E_t - \varepsilon_b C_o - (\varepsilon_b - \varepsilon_c) C_{NH_3}\}/(\varepsilon_a - \varepsilon_b) \quad (1)$$

where C_0 is the initial concentration, C_{NH_3} is the concentration of liberated ammonia determined by indophenol method, E_t is the absorbance at 210 mμ at time t, and ε_a, ε_b and ε_c are molar extinction coefficients of acetamide, acetic acid and starting material respectively. In this case, the molar extinction coefficient at 210 mμ of *tert*-butanol was neglected owing to the extremely small value compared with other ones. The rate constant thus obtained at 80.0° in 8.03 M $HClO_4$ was in good agreement with that obtained under the same condition by the determination of *tert*-butanol using gas-chromatographic method.[21]

The resultant pseudo first-order rate constants for various amides and the perchloric acid concentrations used in their determination are given in Table I, II and III.

Measurement of Ionization Ratio——Since all the amides gave clearly spectral absorption changes in acid solutions strong enough to convert them essentially to their ionized forms, the ionization ratios were determined photometrically at suitable wavelengths (Table IV) and were calculated from the following equation.

$$[SH^+]/[S] = (\varepsilon_S - \varepsilon)/(\varepsilon - \varepsilon_{SH^+}) \quad (2)$$

where ε_S,ε_{SH^+} and ε are the molar extinction coefficients of the unprotonated acid(S) obtained in water, of the protonated acid(SH^+) obtained from the average value in 10 M and 11 M $HClO_4$ and of the mixture of

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

the protonated and unprotonated forms in a tested solution, respectively. All spectra were measured on a Shimadzu QV-50 spectrophotometer using 1 cm quartz cell. The experimental H_0 values[22] at half protonation were consistent with those reported as seen in Table IV.

TABLE IV. Wavelength used in Measurement of Ionization Ratio and H_0 Value at Half Protonation of Amide

Amide	Experimental wavelength λ_{exp} (mμ)	H_0 at half protonation	
		Observed	Reported
Acetamide	198	−0.85	−0.90[a]
Propionamide	198	−1.00	−1.00[a]
N-Methylacetamide	208	−0.70	−0.70[a]
N,N-Dimethylacetamide	205	>−0.7	−0.38[a]
N-*tert*-Butylacetamide	208	>−0.7	—
Benzamide	242	−1.95	−2.01[b]
p-Nitrobenzamide	200	−3.75	−3.23[c]
Phthalamic acid	275	−4.40	—
N-Methylbenzamide	241	−2.05	−2.00[b]
			−2.13[c]
N,N-Dimethylbenzamide	236	−1.45	−1.62[c]

a) M. Liler, *J. Chem. Soc.* (B), **1969**, 385.
b) A.R. Katritzky, A.J. Waring and K. Yates, *Tetrahedron*, **19**, 465 (1963).
c) J.T. Edward, H.S. Chang, K. Yates, and R. Stevart, *Can. J. Chem.*, **38**, 1518 (1960).

Since temperature effects on the protonation equilibria of amide derivatives have been reported[15,23] to be small and, in fact, ionization ratios of benzamide measured in various acid concentrations at 25° agreed with those obtained at 50° at which the hydrolysis was carried out, this study employed ionizations ratios examined at 25° for all the amides.

Result and Discussion

Theoretical Relationship

The generalized mechanism for acid catalyzed hydrolyses of amides, in terms of fully hydrated species, can be presented in Chart 1.[14] In Eqs (3) and (4) s, p, t, and n are the

$$S(H_2O)_s + H(H_2O)_n^+ \overset{K_a}{\rightleftharpoons} SH(H_2O)_p^+ + (s+n-p)H_2O \quad (3)$$

$$SH(H_2O)_p^+ + (t-p)H_2O \overset{K}{\rightleftharpoons} [SH(H_2O)_t^*]^+ \overset{k}{\longrightarrow} \text{products} \quad (4)$$

Chart 1

hydration numbers of neutral amide, protonated amide, activated complex (SH^*) and proton, respectively, K_a is the dissociation constant of amide conjugated acid, K is the equilibrium constant and k is the first-order rate constant. For reactions in which the protonation step (Eq. (3)) is rapidly reversible, this reaction scheme leads to the rate Eq. (5) from the absolute-rate theory.[24]

$$\begin{aligned} v &= k_{obs}\{[S(H_2O)_s]+[SH(H_2O)_p^+]\} \\ &= kK[SH(H_2O)_p^+]a_{H_2O}^{(t-p)} \cdot f_{SH^+}/f_{SH^*} \end{aligned} \quad (5)$$

Where k_{obs} is the observed pseudo first-order rate constant, a_{H_2O} is the activity of water, and f_{SH^+} and f_{SH^*} are activity coefficients of SH^+ and SH^* respectively. Taking logarithm and rearranging, Eq. (5) gives

22) J.E. Lefler and E. Grunwald, "Rate and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, 1963, p. 272.
23) V.C. Armstrong and R.B. Moodie, *J. Chem. Soc.* (*B*), **1969**, 934.
24) K.J. Laidler, "Chemical Kinetics," 2nd ed., McGraw-Hill, Inc., New York, 1965, p. 72.

$$\log k_{obs} + \log(m+1) = r \log a_{H_2O} + \log kK + \log f_{SH^+}/f_{SH^*} \quad (6)$$

where

$$r = t - p \quad (7)$$

$$m = [S(H_2O)_s]/[SH(H_2O)_p^+] \quad (8)$$

In Eq. (6), m is the reciprocal of the amide ionization ratio and r is a hydration number which gives a direct measure of the number of water molecules needed to convert a protonated substrate molecule to the transition state.

In order to calculate $(m+1)^{-1}$, Yates, *et al*[14] used H_A which is a specific acidity function, and Moodie, *et al.*[13] applied spectrophotometrical method without using any acidity functions. Both investigators[13,14] concluded that r value could be easily obtained from the slope of plotting log k_{obs} $(m+1)$ against log a_{H_2O}. In the derivation of hydration number (r), however, these treatments involved the universal assumption that the ratio of the activity coefficient for the protonated amide to that of the transition state (f_{SH^+}/f_{SH^*}) is independent of medium. Plots according to Moodie, *et al.*'s[13] and Yates, *et al.*'s[14] theories have often given curvatures,[11] and log k_{obs} $(m+1)$ of butyramide hydrolysis in perchloric and sulphuric acid for the same water activity differed by an appreciable factor.[15] These facts may be attributed to this assumption about the activity coefficient (*i.e.* cancellation of f_{SH^+} with f_{SH^*}). In order to remove this defect, therefore, the modification of the theories of Moodie[13] and Yates[14] was made in the following way.

The similar treatment for amide derivatives can lead to Eq. (9)

$$\log k_{obs}' + \log(m'+1) = r' \log a_{H_2O} + \log k'K' + \log f_{SH^+}/f_{SH^*}' \quad (9)$$

where symbols with prime refer to amide derivatives and have the same significance in Eq. (6). Equation (10) is deriven by substracting Eq. (6) from Eq. (9).

$$\log \frac{k_{obs}'(m'+1)}{k_{obs}(m+1)} = (r'-r) \log a_{H_2O} + \log \frac{k'K'}{kK} + \log \frac{f_{SH^*}f_{SH^+}'}{f_{SH^*}'f_{SH^+}} \quad (10)$$

There is empirical and qualitative rule that like substances react similarly and that similar change in structure produce similar change in reactivity, under the same condition.[25] This suggests that the term $f_{SH^*}f_{SH^+}'/f_{SH^*}'f_{SH^+}$ to the same type of species can be approximately equal in all solutions. Accordingly, it is reasonable to assume that the second and last terms on the right in Eq. (10) will be nearly medium independent. Thus the rate expression becomes

$$\log \frac{k_{obs}'(m'+1)}{k_{obs}(m+1)} = (r'-r) \log a_{H_2O} + \text{constant} \quad (11)$$

Equation (11) shows that a plot of log $[k_{obs}'(m'+1)/k_{obs}(m+1)]$ obtained under the same conditions against log a_{H_2O} gives a straight line. Then the slope indicates the difference in the number of water molecules assisted to convert the protonated amide to the transition state structure between a standard amide and a derivative.

We have tested Eq. (11) for some amide hydrolyses, which have been known to follow unimolecular or bimolecular mechanism, by determining the hydrolysis rate constants and by measuring the ionization ratios spectrophotometrically, in perchloric acid solutions. In this case, the hydrolyses of acetamide and benzamide were chosen as standard for those of aliphatic and aromatic series of amides, respectively.

Relationship between (r'—r)-Value and Reaction Mechanism

1) Unimolecular Reaction Mechanism——Figure 1 shows the plots according to Eq. (11) for the hydrolysis of N-*tert*-butylacetamide against that of acetamide in perchloric acid solu-

25) L.P. Hammett, "Physical Organic Chemistry," 2nd ed., McGraw-Hill, Inc., New York, 1970, p. 347.

tions at 80.0°. A good linear relationship was obtained as seen in Fig. 1 and the slope of this line gave $r'-r=-3.2$.

Since the average hydration number for acetamide has been reported to be $r=3.1$,[14b] value r' for N-*tert*-butylacetamide can be evaluated to be −0.1. This suggests that water molecules do not assist in the rate-determining step and is consistent with the reported result[21] that the acidic hydrolysis of N-*tert*-butylacetamide proceeds as a unimolecular reaction.

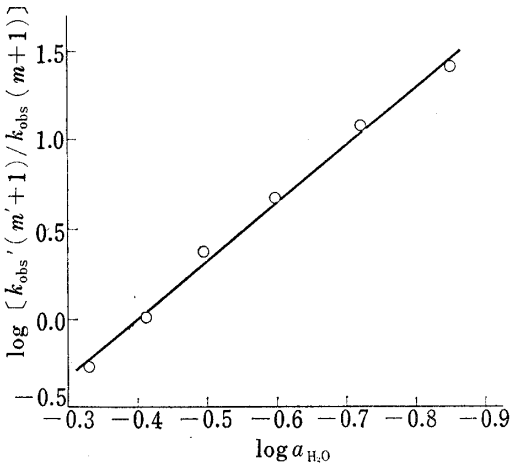

Fig. 1. Plot of log [k_{obs}' ($m'+1$)/k_{obs} ($m+1$)] against log a_{H_2O} for the Hydrolysis of N-*tert*-Butylacetamide in Perchloric Acid Solutions at 80.0°

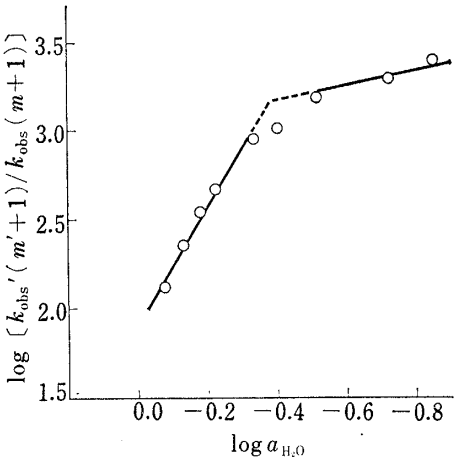

Fig. 2. Plot of log [k_{obs}' ($m'+1$)/k_{obs} ($m+1$)] against log a_{H_2O} for the Hydrolysis of Phthalamic Acid in Perchloric Acid Solutions at 50.0°

Plotting in the similar manner as above, for the hydrolysis (at 50.0°) of phthalamic acid against that (at 50.0°) of benzamide, were shown in Fig. 2. In the region of concentration lower than 6.44M (log $a_{H_2O}>-0.4$), the plot is reasonably linear giving a slope $r'-r=-3.3$. This result suggests that phthalamic acid hydrolysis in this region undergoes without participation of water molecules, because Yates and Stevents[14a] have already reported the average hydration number for benzamide to be $r=3.2$. Bender, *et al.*[7] gave a convincing evidence that phthalamic acid was hydrolyzed in dilute hydrochloric acid solution proceeding through a phthalic anhydride intermediate by a direct intramolecular process, and that the reaction assisted by water molecules did not proceed. The same authors[7] suggested that in concentrated acid solution phthalamic acid as well as benzamide is hydrolyzed *via* the direct attack of water molecules on the protonated amide group as represented in bimolecular reaction mechanism. As obviously in Fig. 2, it may be concluded that below 6.44M (log $a_{H_2O}>-0.4$) predominant reaction route of phthalamic acid is the reaction of no assist of water molecules, and on the contrary, in more concentrated acid solution (>6.44M) value-($r'-r$) gave −0.2 and this suggests that water molecules must play an important role as nucleophile

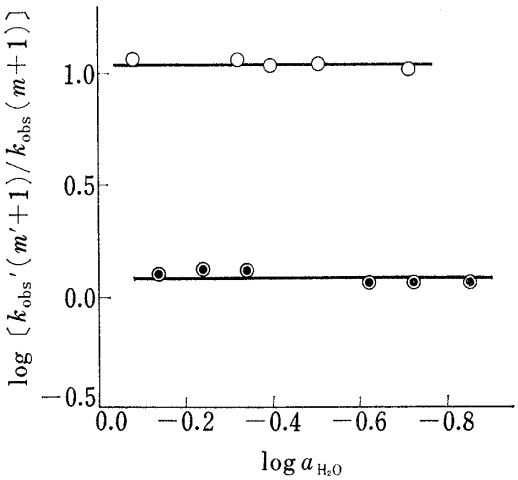

Fig. 3. Plot of log [k_{obs}' ($m'+1$)/k_{obs} ($m+1$)] against log a_{H_2O} for the Hydrolysis of *p*-Nitrobenzamide (○, at 50.0°) and Propionamide (◉, at 80.0°) in Perchloric Acid Solutions

in the rate-determining step. This relationship between change in mechanism and change in $(r'-r)$-value is consistent with Bender, *et al.*'s suggestion.[7]

2) Bimolecular Reaction Mechanism——a) Hydrolysis of Acyl Substituted Amide: Plots of log $[k_{obs}'(m'+1)/k_{obs}(m+1)]$ against log a_{H_2O} for the hydrolysis (at 80.0°) of propionamide and that (at 50.0°) of *p*-nitrobenzamide using reference hydrolysis of acetamide and benzamide examined under the same conditions gave both good straight lines with no slope (*i.e.* $r'-r=0.0$), as shown in Fig. 3. From these results, it may be said that in the rate-determining step of these amide hydrolyses water molecules as a nucleophilic reagent attack on the protonated amides, as well as acetamide and benzamide.

b) Hydrolysis of N-Substituted Amide: Valeues-$(r'-r)$ obtained for N-substituted-acetamide and -benzamide[26] whose hydrolyses in acidic media follow the bimolecular reaction,[4] were almost -1 and 0, respectively (Fig. 4 and 5). The effects of methyl substitution on the rate constants of benzamide hydrolysis are somewhat interesting. The order for rate constants is primary>tertiary>secondary at all acid concentrations (see Table III). A slightly negative slope in the plot of Eq. (11) for the N,N-dimethylbenzamide hydrolysis (Fig. 4) may be responsive to this rate anomaly. These differences in value-$(r'-r)$ between N-substituted and standard amide in both the aromatic and aliphatic series may be due to amide-solvent interaction as proposed earlier.

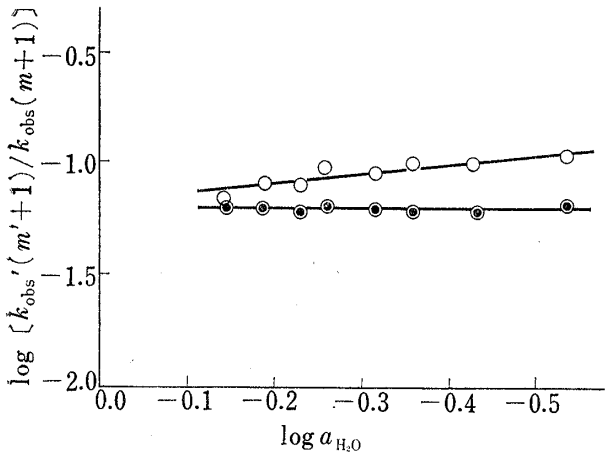

Fig. 4. Plot of log $[k_{obs}'(m'+1)/k_{obs}(m+1)]$ against log a_{H_2O} for the Hydrolysis of N-Methylbenzamide (◉) and N,N-Dimethylbenzamide (○) in Perchloric Acid Solutions at 95.0°

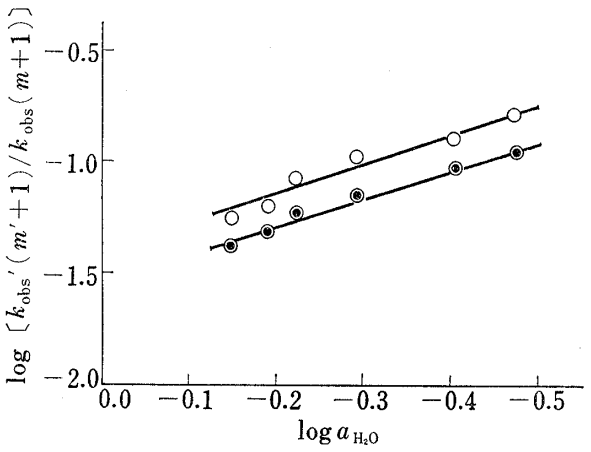

Fig. 5. Plot of log $[k_{obs}'(m'+1)/k_{obs}(m+1)]$ against log a_{H_2O} for the Hydrolysis of N-Methylacetamide (○) and N,N-Dimethylacetamide (◉) in Perchloric Acid Solutions at 80.0°

26) After this manuscript had been submitted for publication we recieved an extensive paper (C.R. Smith and K. Yates, *J. Am. Chem. Soc.*, 93, 6578 (1971)), in which the kinetic acidity dependence and medium dependence of the activation parameters for the hydrolyses of benzamide and N-substituted benzamides in 5—60% aqueous sulfuric acid have been analyzed using protonation and a_{H_2O} data appropriate to each kinetic temperature. They found that appropriately calculated activation enthalpies for each amide are essentially medium independent, and that plots for equation (6) give yet curvature. Smith and Yates concluded that the possibility of dual competitive mechanism, as suggested by Bunton *et al.*,[12] for acid-catalyzed amide hydrolysis can be ruled out and that this curvature may be due to medium variation of activity coefficient ratios $f_{SH^+}/f_{SH^\pm}$. The similar treatment of their data (all the data were referred to kinetic temperature) according to equation (11) gave good linear relationship for N-methylbenzamide and N,N-dimethylbenzamide hydrolyses in the region above 20% acid, respectively.