Structure, Medium, and Temperature Dependence of Acid-Catalyzed Amide Hydrolysis

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Abstract: The kinetics of hydrolysis of benzamide, *N*-methylbenzamide, and *N*,*N*-dimethylbenzamide have been extensively studied in 5–60% aqueous sulfuric acids over the temperature range 25–85°. The order of reactivity with *N*-methyl substitution is unusual, namely primary > tertiary > secondary, and is due solely to variations in $\Delta H^{\ddagger}$ with structure. Water activity data for the above concentration and temperature range have been calculated from available emf data and a_{H_2O} is shown to be a strongly temperature-dependent reaction variable. The kinetic acidity dependence and medium dependence of the activation parameters have been analyzed using protonation and a_{H_2O} data appropriate to each kinetic temperature. It is found that appropriately calculated $\Delta H^{\ddagger}$ values for each amide are essentially medium independent, and that curvature of hydration parameter plots is due to medium variation of $\Delta S^{\ddagger}$. The possibility of dual competitive mechanisms for acid-catalyzed amide hydrolysis is considered and ruled out.

The technique of expressing rate constants as some function of the water activity has been used in investigations of organic reactions in strong acids for a variety of purposes: to categorize a large body of kinetic data,[1] to demonstrate mechanistic changes,[2,3] to express rate as a convenient function of changing acidity,[1–6] and to draw conclusions about the detailed nature of transition states.[1,3,6,7] This latter use has, however, recently been criticized.[5] Where it has not been convenient to follow kinetics at 25°, rates have frequently been determined at elevated temperatures, above 100° in some cases, and the data have been analyzed[1] using activity and acidity data measured at or near 25°. This practice has been justified[6] for the case where E_a (or $\Delta H^{\ddagger}$) is effectively constant over the range of acid studied. However from available data in the literature we have noted that this condition is not generally fulfilled for amide hydrolysis.[8] This apparent medium variation in E_a could be due to the temperature dependence of the protonation preequilibrium, variation of the mechanism with the medium, or temperature dependence of the water activity. We have investigated these possibilities for the acid-catalyzed hydrolysis of three amides (benzamide, *N*-methyl-, and *N*,*N*-dimethylbenzamide).

Although amide hydrolysis has been extensively studied,[2,5,6 8,9,10] the general mechanism is not yet unambiguously established. Because of structural similarities to esters, it has been tempting to suggest, as many investigators have[2,6,10] and as standard mechanistic reference works do,[11,12] that the mechanism is analogous to the $A_{Ac}2$ mechanism. However, unlike in ester hydrolysis, no ^{18}O exchange concurrent with hydrolysis has been observed.[9,13] Also, curvature is found consistently for amide hydrolysis in hydration parameter treatments[14] whereas linear plots are obtained for ester hydrolysis in the extensive $A_{Ac}2$ region.[3] Bunton and coworkers[9] have suggested a competitive dual mechanistic scheme that would be consistent with this curvature, but their model fails to give reasonable or consistent results when tested on all available data.[15] At present the similar approaches of Lane,[4] Yates[3,14] and Moodie[2,5] seem more appropriate. Also, Moodie[2] has made some serious criticisms of the two-mechanism model.

Thus the mechanism for amide hydrolysis will be discussed in terms of a protonation equilibrium, followed by rate-determining attack of water on one conjugate acid form only. It is assumed that the kinetically significant conjugate acid is the predominant[16] O-protonated form, although this has not been established. The consequences of reaction proceeding through the less predominant N-protonated conjugate acid are also considered.

Results

The kinetic results are given in Table I. These rate constants are considered to be accurate to ±1%, which is twice the standard deviation of the least-squares slope of the rate plots. Determinations in each acid were reproducible to ±0.5% and correlation coefficients were better than 0.999. The rates were found to be wavelength independent, and independent of varying amide concentrations over a factor of ten. The rate constants at 25° for benzamide are somewhat higher than the values reported by Edward and Meacock,[10]

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Table I. Rates of Hydrolysis in Sulfuric Acid

	k_{obsd}, min^{-1}				
% H_2SO_4	25.1° ($10^5 \times k$)	40.05° ($10^4 \times k$)	60.1° ($10^3 \times k$)	74.8° ($10^3 \times k$)	85.0° ($10^2 \times k$)
			Benzamide		
5.88	0.940				0.409
9.61	1.53		0.752	2.65	0.678
12.3	2.14				0.889
16.0	2.92	1.68	1.24	4.74	1.13
18.95	3.24				1.35
23.7	4.09	2.33	1.76	6.84	1.59
27.3	4.24	2.45	1.92		1.80
30.3	4.20	2.45	1.92	7.58	1.81
33.0	4.10	2.35	1.89	7.46	1.81
37.2	3.52	2.00	1.70	6.77	1.64
40.3	2.90				1.43
43.25	2.30	1.37	1.21	4.99	1.20
45.75	1.78				0.991
48.05	1.37	0.842	0.772	3.29	0.789
50.1	1.10				0.668
51.6	0.927	0.557	0.528	2.25	0.563
53.6	0.728				0.456
55.1	0.599	0.368	0.356	1.51	0.380
56.5	0.500				0.319
58.0	0.409	0.243	0.237	1.02	0.255
59.0	0.345				0.224

	10^4k_{obsd}, min^{-1}		
% H_2SO_4	50.3°	65.8°	85.0°
		N-Methylbenzamide	
5.89	0.091	0.453	2.72
9.61			4.90
12.3	0.193	0.965	6.02
16.0			7.32
18.9	0.282	1.42	8.50
23.8	0.340	1.72	10.0
27.5	0.372	1.82	11.1
30.4	0.378	1.83	11.3
32.8	0.373	1.85	11.2
37.2			10.9
40.3	0.310	1.55	9.37
43.25			8.17
45.75	0.227	1.18	7.12
48.05			6.18
50.1	0.166	0.858	5.43
53.6	0.127	0.675	4.17
55.1			3.72
56.5	0.099	0.507	3.35
58.0			2.92
59.2	0.076	0.395	2.73
		N,N-Dimethylbenzamide	
5.89	0.838	3.20	15.1
12.3	1.65	6.40	29.7
18.9	2.15	8.57	38.3
23.8	2.25	8.87	40.2
27.5	2.18	8.71	38.8
30.4	2.00	8.27	36.2
32.8	1.83	7.47	33.5
40.3	1.19	4.97	25.3
45.75	0.808	3.55	18.3
50.1	0.573	2.57	13.7
53.6	0.425	1.91	1.04
56.5	0.325	1.49	8.18
59.2	0.243	1.13	6.32

Table II. Protonation Correction for Observed Rate Constant Determined at 25 ± 1°

% H_2SO_4	*N*-Methyl-benzamide K^a	± σ	*N,N*-Dimethyl-benzamide K^a	± σ	Benzamide K^a	± σ
5.00	1.54	0.15	1.10	0.035	1.50	0.040
7.50	1.38	0.10	0.93	0.035	1.36	0.030
10.00	1.24	0.07	0.80	0.035	1.25	0.030
12.50	1.11	0.06	0.67	0.032	1.15	0.030
15.00	0.98	0.05	0.59	0.03	1.03	0.035
17.50	0.87	0.05	0.51	0.03	0.91	0.03
20.00	0.78	0.04	0.42	0.03	0.81	0.03
22.50	0.68	0.04	0.34	0.03	0.73	0.03
25.00	0.59	0.04	0.28	0.03	0.65	0.03
27.50	0.51	0.04	0.22	0.03	0.56	0.03
30.00	0.43	0.03	0.17	0.03	0.49	0.03
32.50	0.36	0.03	0.13	0.03	0.41	0.03
35.00	0.29	0.03	0.105	0.025	0.34	0.025
40.00	0.19	0.02	0.07	0.02	0.21	0.025
45.00	0.11	0.02	0.045	0.02	0.13	0.02
50.00	0.06	0.01	0.025	0.01	0.09	0.015
55.00	0.035	0.01	0.015	0.01	0.045	0.01
60.00	0.02	0.01	0.005	0.01	0.010	0.01

Calculated p*K* Values

λ, mμ	$-pK_a$	λ, mμ	$-pK_a$	λ, mμ	$-pK_a$
240	1.65	233	1.12	244	1.74
241	1.73	234	1.20	245	1.78
242	1.80	235	1.28	246	1.88

[a] $K = -\log [SH^+]/([SH^+] + [S]$.

Table III. Temperature Dependence of Protonation Correction for *N*-Methylbenzamide

	$K = -\log [SH^+]/([SH^+] + [S])$		
% H_2SO_4	25 ± 1°	48 ± 1°	67 ± 1°
18.9	0.85		0.80
27.5	0.50	0.52	0.50
37.2	0.25		0.24
43.3	0.15	0.14	0.14
51.6	0.05		0.06

but their substrate concentrations were about 10^{-1} *M* as compared with 10^{-4} *M* in the present work. The difference is probably due to a small medium or concentration effect.

The protonation and p*K* data for the three amides are given in Table II and the latter agree well with literature values.[14] However, as noted previously,[17] benzamides exhibit solvent shifts on the absorption maximum of the protonated form, which can lead to variations in p*K* with wavelength, as illustrated in Table II. There are methods available[17,18] which attempt to correct for solvent shifts, but all of these involve some basic assumption and none are really satisfactory. To test whether these solvent shifts were large enough to affect interpretation of results the term used to correct the observed rate constants for protonation, $[SH^+]/([S] + [SH^+])$, was calculated directly from log *I* (log $[SH^+]/[S]$) values, rather than from plots of log *I* *vs.* some acidity function which has been used previously.[9,14] The errors given in Table II are calculated from standard deviations for the *I* values by the propagation of errors formula.[19] It was found that errors only became significant around values of $\log [SH^+]/([S] + [SH^+]) = -1.5$ which corresponds to about 3% protonation, where experimental errors are large.[20] However, the larger deviations in *I* above 50% ionization do not seriously affect the accuracy

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Table IV. Water Activity Data ($-\log a_w$) in Aqueous Sulfuric Acids[a]

%	0°	25°	40°	50.25°	60°	65.85°	75°	85°
0.49	0.0008	0.0008	0.0008	0.0008	0.0008	0.0008	0.0008	0.0008
1.00	0.0016	0.0015	0.0015	0.0015	0.0015	0.0015	0.0015	0.0015
1.92	0.0032	0.0031	0.0030	0.0030	0.0030	0.0030	0.0029	0.0029
4.67	0.0079	0.0078	0.0077	0.0077	0.0076	0.0076	0.0075	0.0075
8.94	0.0170	0.0167	0.0164	0.0163	0.0161	0.0161	0.0159	0.0157
12.82	0.0278	0.0271	0.0267	0.0265	0.0262	0.0261	0.0258	0.0256
16.40	0.0403	0.0391	0.0384	0.0379	0.0375	0.0373	0.0369	0.0365
22.73	0.0738	0.0700	0.0680	0.0667	0.0655	0.0648	0.0638	0.0627
28.17	0.1165	0.1091	0.1051	0.103	0.100	0.0991	0.0971	0.0950
32.90	0.168	0.156	0.149	0.145	0.141	0.139	0.136	0.133
37.04	0.224	0.207	0.198	0.193	0.187	0.185	0.180	0.175
40.71	0.285	0.263	0.251	0.243	0.236	0.233	0.227	0.220
43.96	0.349	0.320	0.305	0.296	0.287	0.282	0.274	0.267
46.88	0.414	0.379	0.361	0.349	0.338	0.332	0.322	0.312
49.51	0.478	0.437	0.415	0.401	0.389	0.382	0.370	0.359
51.89	0.546	0.499	0.473	0.457	0.442	0.434	0.421	0.407
54.06	0.614	0.561	0.532	0.513	0.497	0.487	0.472	0.457
56.04	0.684	0.624	0.592	0.571	0.553	0.542	0.526	0.510
57.86	0.757	0.688	0.652	0.629	0.609	0.597	0.579	0.560
59.53	0.830	0.754	0.713	0.688	0.665	0.652	0.631	0.612
61.08	0.905	0.821	0.777	0.750	0.726	0.721	0.691	0.670
62.51	0.984	0.890	0.841	0.810	0.783	0.768	0.745	0.721
63.18	1.022	0.925	0.875	0.844	0.816	0.800	0.777	0.752

[a] Calculated from the emf data of Hamer and Harned.[22]

Table V. Activation Parameters in Different Acid Solutions at Constant Water Activity[a,b]

	Benzamide[c]		*N*-Methylbenzamide[d]		*N*,*N*-Dimethylbenzamide[d]	
$-\log a_w$	$\Delta H_p^{\ddagger}$, kcal/mol	$-\Delta S_p^{\ddagger}$, eu	$\Delta H_p^{\ddagger}$, kcal/mol	$-\Delta S_p^{\ddagger}$, eu	$\Delta H_p^{\ddagger}$, kcal/mol	$-\Delta S_p^{\ddagger}$, eu
0.025	20.3 ± 0.55	14.4 ± 1.6	21.3 ± 0.32	17.5 ± 0.94	18.4 ± 0.14	24.2 ± 0.42
0.05	20.4 ± 0.23	14.8 ± 0.71	21.7 ± 0.05	16.8 ± 0.05	18.2 ± 0.10	25.1 ± 0.30
0.10	20.2 ± 0.04	16.2 ± 0.13	21.2 ± 0.25	19.2 ± 0.80	17.7 ± 0.04	27.7 ± 0.13
0.15	20.2 ± 0.05	17.2 ± 0.17	21.3 ± 0.28	19.6 ± 0.80	18.2 ± 0.17	27.0 ± 0.50
0.20	20.2 ± 0.06	17.8 ± 0.17	21.2 ± 0.12	20.6 ± 0.36	18.6 ± 0.10	26.5 ± 0.30
0.25	20.3 ± 0.12	18.2 ± 0.36	20.9 ± 0.14	22.2 ± 0.20	18.8 ± 0.03	26.4 ± 0.10
0.30	20.4 ± 0.20	18.8 ± 0.60	20.9 ± 0.09	22.7 ± 0.24	18.9 ± 0.12	26.6 ± 0.36
0.35	20.5 ± 0.20	19.0 ± 0.60	21.0 ± 0.12	22.8 ± 0.34	19.1 ± 0.02	26.4 ± 0.06
0.40	20.6 ± 0.20	19.5 ± 0.60	21.1 ± 0.14	23.1 ± 0.40	19.1 ± 0.04	26.9 ± 0.12
0.45	20.5 ± 0.15	20.1 ± 0.46	21.3 ± 0.05	22.9 ± 0.16	19.2 ± 0.08	27.2 ± 0.22
0.50	20.4 ± 0.12	21.2 ± 0.36	21.3 ± 0.10	23.3 ± 0.10	19.2 ± 0.15	27.3 ± 0.46
0.55	20.2 ± 0.12	22.2 ± 0.36	21.3 ± 0.28	23.6 ± 0.81	19.0 ± 0.20	28.3 ± 0.60
0.60	20.3 ± 0.12	22.5 ± 0.40	21.3 ± 0.47	23.8 ± 1.4	19.1 ± 0.04	28.4 ± 0.12

[a] Activation parameters based on values of k_p at constant water activity. [b] Errors are one standard deviation. [c] Correlation coefficient, based on five points for linear $\log (k_p/T)$ *vs.* $1/T$ plots >0.9999 except at $\log a_w = 0.025$ where it equals 0.9990. [d] All correlation coefficients, although only based on three temperatures, were ≥ 0.9999.

of the protonation correction terms, as can be seen from the values listed in Table II.

The data in Table III show that temperature effects on the ionization equilibria for *N*-methylbenzamide are not large over the range 25–67°. Hydrolysis was not significant over the time of measurement even at the higher temperature, since spectra before and after heating were virtually identical. Similar small changes were found in the protonation correction terms for benzamide over the 25–50° range. Higher temperatures could not be studied since hydrolysis becomes significant over the time period required for spectral measurement. Significant deviations in the protonation correction terms were, however, found for *N*,*N*-dimethylbenzamide, below 20% acid. Since these occur in dilute acid, where $-\log a_{H_2O} \leq 0.05$, they should not materially affect any conclusions drawn from the rate–water activity dependence.

Water activity data for the temperature range 25–85° were calculated by the method of Stokes[21] from the emf data of Harned and Hamer[22] for the cell $H_2|H_2SO_4|HgSO_4|Hg$ and are given in Table IV. These data have been criticized by Stokes[21] since at 25° they give different values of a_{H_2O} than those obtained by other methods. However, at 63% H_2SO_4, for example, these differences amount of only 0.5% in $\log a_{H_2O}$. Also a plot of accepted values of $\log a_{H_2O}{}^{25°}$ [23] plotted against $\log a_{H_2O}{}^{25°}$ calculated as above gives a least-squares slope of 0.99, which is not significantly different from unity for the purpose of the present work.

Activation parameters for the hydrolysis of all three amides were calculated from the standard transition state theory equation and are given in Table V. The errors given are derived from the standard deviations of the slopes of the $\log (k/T)$ *vs.* $1/T$ plots for $\Delta H^{\ddagger}$ and derived from the standard deviations of the intercepts for $\Delta S^{\ddagger}$.

Discussion

Medium Dependence of Activation Parameters. The kinetics and mechanism of amide hydrolysis will be

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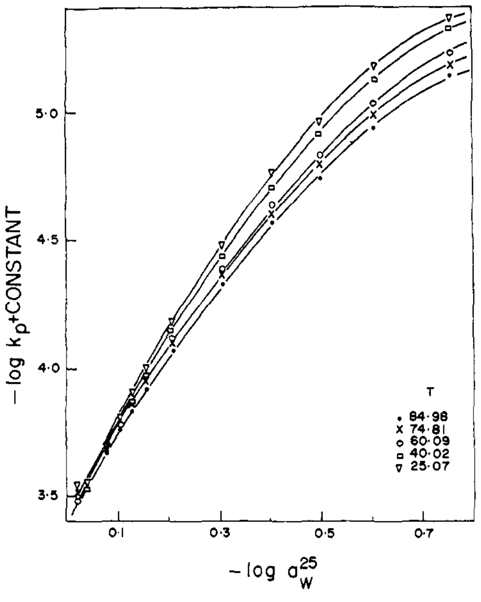

Figure 1. Rate of reaction of protonated benzamide at temperature T as a function of water activity measured at 25°.

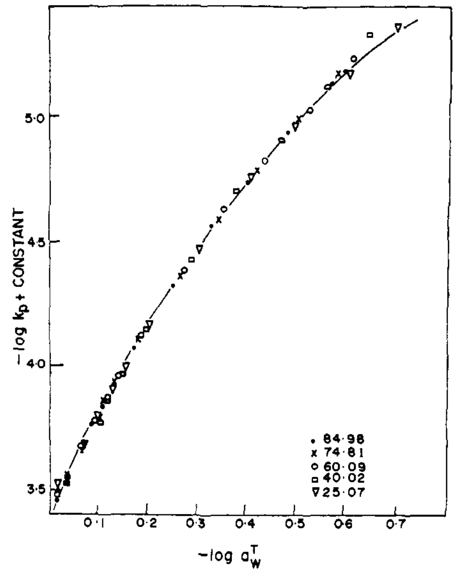

Figure 2. Rate of reaction of protonated benzamide at temperature T as a function of water activity at temperature T.

discussed in terms of the following hydration model, similar to that developed previously[6,14]

$$\mathrm{S}_s + \mathrm{H}_n^+ \underset{K_{\mathrm{SH}^+}}{\rightleftharpoons} \mathrm{SH}_p^+ + (s + n - p)\mathrm{H_2O} \quad \text{Fast}$$

$$\mathrm{SH}_p^+ + r\mathrm{H_2O} \underset{K_a}{\rightleftharpoons} [\mathrm{TS}]^\ddagger \xrightarrow{k} \text{products} \quad \text{Slow}$$

where s, n, and p are the hydration numbers of the substrate, proton, and protonated substrate, respectively. All activity coefficients refer to fully hydrated species.[1]

Since

$$K_a = \frac{a_{\mathrm{SH}_p^+} a_w^r}{a_\ddagger}$$

and

$$K_{\mathrm{SH}^+} = \frac{a_{\mathrm{S}_s} a_{\mathrm{H}_n^+}}{a_{\mathrm{SH}_p^+} a_w^{s+n-p}}$$

where a_w is the water activity, and rate $= k_\psi[\mathrm{S_{stoich}}] = k_\psi([\mathrm{S}_s] + [\mathrm{SH}_p^+]) = k_p[\mathrm{SH}_p^+]$ where k_ψ is the observed pseudo-first-order rate constant, and k_p is similarly defined for the rate-determining step only; then

$$\text{rate} = \frac{k}{K_a}[\mathrm{SH}_p^+]a_w^r \frac{f_{\mathrm{SH}^+_p}}{f_\ddagger}$$

Thus in the r-parameter treatment, r is obtained from the slope of a plot of $\log k_p$[24] *vs.* $\log a_w$, since from the above equations

$$\log k_p = r \log a_w + \log k/K_a + \log f_{\mathrm{SH}^+_p} f_\ddagger \quad (1)$$

If the r plot is approximately linear, then $kf_{\mathrm{SH}_p^+}/K_a f_\ddagger = k'$ is a constant essentially independent of medium. However, regardless of the linearity of the plots, k_p is never medium independent since $k_p = k' a_w^r$. Thus temperature dependence of a_w could affect both $\Delta H_p^\ddagger$ and $\Delta S_p^\ddagger$. To illustrate this possible temperature dependence of r plots, expansion of the rate constants using the Arrhenius equation gives

$$\log k_p^{T_1} - \log k_p^{T_2} = \frac{E_a}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

Thus if r plots at different temperatures are parallel,[25] E_a (or $\Delta H_p^\ddagger$) would have to be constant over the acid range studied. If they are not parallel E_a must vary with medium. In Figure 1, $\log k_p^T$ is plotted against $\log a_w^{25}$ for benzamide. The plots have been shifted by constant amounts so that they coincide at low water activity. The plots are clearly not even approximately superimposable, and therefore are not parallel. Similar results are obtained for both *N*-methyl- and *N*,*N*-dimethylbenzamide. This implies that E_a (or $\Delta H_p^\ddagger$) is medium dependent. However, plotting $\log k_p^T$ *vs.* $\log a_w^{25}$ corresponds to considering activation parameters at the same per cent acid (defined by a_w^{25}) at different temperatures. It can be seen from Table IV that $\log a_w$ varies significantly with temperature; therefore, as calculated above, the variation of a_w^r with temperature is incorporated into $\Delta H_p^\ddagger$. If r plots are constructed as in Figure 2 with a_w values appropriate to the kinetic temperatures, then when displaced as in Figure 1, these are almost exactly superimposable and therefore parallel. This procedure corresponds to calculating activation parameters for acids having the same a_w at different temperatures.

Using plots of observed $\log k_p$ *vs.* $\log a_w$, rate constants at the same water activity at the different temperatures were obtained by interpolation. These were then used to calculate the activation parameters for each substrate and are listed in Table V. It can be seen that $\Delta H_p^\ddagger$ is effectively constant over the whole medium range for benzamide and *N*-methylbenzamide, and over most of the range for *N*,*N*-dimethylbenzamide.

Thus observed variations in $\Delta H^\ddagger$ with medium reported by other workers[8] were due primarily to ignoring a_w variation over the range from 25° to the temperatures where kinetics were measured. In the pres-

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[24] As presently defined, $\log k_p$ is equivalent to the term $\log k_\psi - \log(h_x/(h_x + K_{\mathrm{SH}^+}))$ used in previous treatments.[1,6,14]

[25] In the usual acidity function sense, parallel is taken to mean that the vertical distances between two curves are constant.

ent case, if the temperature dependence of a_w is ignored, calculated $\Delta H_p^{\ddagger}$ values increase steadily and significantly (by up to 2.5 kcal) over the acid range 5–60% for all three benzamides.

If the ideal conditions that the r plot is linear and r is temperature independent are assumed, then the nonlogarithmic form of eq 1 can be written as $k_p = a_w^r k'$, where k' is a constant with respect to the medium and has been defined previously. Activation parameters based on k', $\Delta H_{k'}^{\ddagger}$, and $\Delta S_{k'}^{\ddagger}$ will then be medium independent. By calculating activation parameters for k_p at constant a_w, k_p will show the same temperature dependence as k' and therefore $\Delta H_p^{\ddagger} = \Delta H_{k'}^{\ddagger}$. Then $\Delta H_p^{\ddagger}$ will also be medium independent. For benzamides, the r plots are curved but r is temperature independent since the shape of the curve is temperature invariant (Figure 2). Since the observed $\Delta H_p^{\ddagger}$ fits the ideal situation (it is medium independent), the curvature in the r plots must be due to the manner in which the entropy of the reaction varies with medium.

It should be pointed out that use of incorrect a_w data may not in general affect the *shape* of r plots or Bunnett w-type plots[1] since log a_w^T is remarkably linear in log a_w^{25} over the temperature range 25–85° up to log $a_w = -0.7$. However, the slopes of such plots do vary significantly with temperature; hence values of hydration parameters can be materially affected if a_w values and rate constants do not refer to the same temperature. For example, at 85° the slope of an r plot for amide hydrolysis could be changed by more than 0.5 unit if log a_w^{25} were used instead of log a_w^{85}. This represents an error of 20% for typical amide hydrolysis plots. It is also possible that the linearity of log a_w^T in log a_w^{25} breaks down below log $a_w = -0.7$ where many such plots could be seriously affected by ignoring the temperature variation of a_w.

The Dual-Mechanism Postulate. If amide hydrolysis occurs by two independent rate processes, k_1 and k_2, it can be shown that linear plots of log k_p/T *vs.* $1/T$ would only be obtained if $\Delta H^{\ddagger}_{\text{obsd}} \simeq \Delta H_1^{\ddagger} \simeq \Delta H_2^{\ddagger}$. Excellent linear plots were in fact obtained for benzamide over a 60° range, and for the other two amides over a 35° range. Hence if two competitive mechanisms were involved,[9] the two $\Delta H_s^{\ddagger}$ would have to be nearly equal for each substrate. This seems improbable since the three amides are subject to different steric and inductive effects. The idea of dual mechanisms is also inconsistent with the observed lack of medium dependence of $\Delta H_p^{\ddagger}$, since this would mean that the contribution from each mechanism would have to be virtually medium invariant over the range 5–60% H_2SO_4, which is also improbable.

Thus the problem of curvature of r-type plots for amide hydrolysis cannot easily be explained by postulating dual competitive mechanisms,[9] and is more likely to be due to medium variation of activity coefficient ratios $f_{SH^+}/f_{\ddagger}$ as suggested previously.[2] Because of the extensive linear r-type plots frequently obtained for esters[3] and other substrates,[1] such ratios must effectively cancel in a number of cases and it is not clear why amide hydrolysis differs in this respect.

A reasonable explanation can be obtained by use of the Hammond postulate, as follows. Esters (E) are significantly weaker as bases than amides (A), but ester conjugate acids (EH^+) react much more rapidly than amide conjugate acids (AH^+) in the hydrolysis step. Thus, it is clear that EH^+ is much closer in free energy to its transition state $E^{\ddagger}$ than is AH^+ to $A^{\ddagger}$. It can be estimated from available pK and rate data that this difference, $\Delta\Delta F^{\ddagger}$, is of the order of 8 kcal. Then according to the Hammond postulate, EH^+ and $E^{\ddagger}$ should resemble each other more closely in structure than do AH^+ and $A^{\ddagger}$. Therefore, it might be expected that cancellation of the ratio $f_{SH^+}/f_{\ddagger}$ would be more valid for ester hydrolysis than for amide hydrolysis.

Dual Conjugate Acid Approach. If amides hydrolyze through the predominant[16] O-protonated form (SH^+), it can be estimated from observed rate constants and pK values that this would have to react about 10^5 times more slowly than a corresponding esterium ion in the hydrolysis step. However, it is quite possible that amides hydrolyze *only* by way of the much less predominant N-protonated form[26] (HS^+). This would help to explain more easily why amide hydrolysis is so slow relative to ester hydrolysis, and why ^{18}O exchange concurrent with hydrolysis has not been observed for the former in acid solutions.

It can be shown that in such a case amide hydrolysis would not generally yield linear r plots, even if the ratio $f_{HS^+}/f_{\ddagger}$ were medium independent. This is independent of any assumptions about activity coefficient behavior; all that is required is that reaction proceed by way of a minor conjugate acid form which has a significantly different pK and acidity function dependence (h_2) from those of the predominant form (K_{SH^+} and h_1). The difficulty would arise from the fact that the correction term for substrate protonation

$$\frac{K_{SH^+}h_2}{K_{SH^+}h_2 + K_{HS^+}h_1 + K_{HS^+}K_{SH^+}}$$

would then follow a complex and changing function of acidity, which could not be estimated directly from any results presently available.

Structural Effects

The effects of methyl substitution on the rate of benzamide hydrolysis[9] are somewhat unusual and similar to those observed for acetamides by Bolton,[27] namely primary > tertiary > secondary. The activation parameters listed in Table VI also show a similar pattern to those observed for the acetamide series. The order for $\Delta S_p^{\ddagger}$ is primary > secondary > tertiary at all

Table VI. Effect of Methyl Substitution on Activation Parameters

Substrate	$\Delta H^{\ddagger}$,[a] kcal/mol	σ[b]	$-\Delta S_p^{\ddagger}$,[c] eu	$-\Delta S_p^{\ddagger}$,[d] eu
Benzamide	20.3	0.13	14.4	22.5
N-Methyl-	21.2	0.20	17.5	23.8
N,*N*-Dimethyl-	18.7	0.46	24.2	28.4

[a] Average $\Delta H_p^{\ddagger}$ from Table V. [b] Standard deviation of $\Delta H_p^{\ddagger}$. [c] Based on dilute acid, where log $a_w = -0.025$. [d] Based on concentrated acid, where log $a_w = -0.600$.

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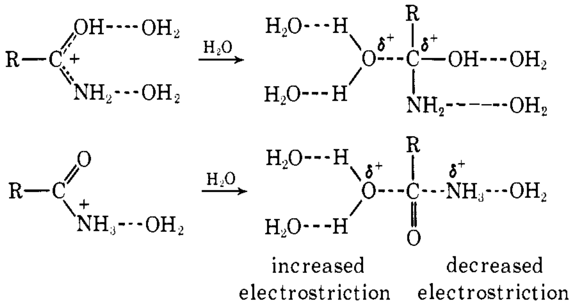
(26) A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem. Soc.*, 81, 62 (1959).

(27) P. D. Bolton, *Aust. J. Chem.*, 1013 (1966).

acid concentrations. This is not unexpected in terms of increased steric effects on methyl substitution, leading to an increased loss of vibrational and rotational freedom at the transition state. Also, since methyl substitution removes available hydrogen bonding sites on nitrogen, the increased electrostriction of solvent as charge is developed on the attacking oxygen cannot be partially offset to the same extent in the methyl derivatives by loss of hydrogen-bonded solvent from nitrogen, as charge is decreased on this atom in the rate-determining step. This would apply to both types of possible mechanisms for amide hydrolysis, as shown schematically. The changes in $\Delta H_p^{\ddagger}$ on methyl substitution are less easy to understand, and are mainly responsible for the observed order of reactivity. It would be expected from inductive effects that methyl substitution would make it progressively more difficult for a nucleophile such as water to attack by releasing negative charge to the amide group, thereby decreasing its electrophilicity. Thus $\Delta H_p^{\ddagger}$ would increase with methyl substitution. Increased steric repulsions in the transition state would also be expected to increase $\Delta H_p^{\ddagger}$. However, the steric requirements in the region of the carbonyl carbon would not be seriously affected by one methyl group and in fact $\Delta H_p^{\ddagger}$ does show an expected small increase of about 1 kcal in going from benzamide to *N*-methylbenzamide. However, adding a further methyl group decreases $\Delta H_p^{\ddagger}$ by 2.5 kcal in *N*,*N*-dimethylbenzamide.[28]



The observed small effects of *N*-methyl substitution on the basicity of amides[29] suggest that inductive effects are small, and it seems more likely that steric effects are responsible for the observed order primary > tertiary > secondary in both the benzamide and acetamide series. It is possible that the added strain of two methyl groups causes some mechanistic change, resulting in a significantly lower $\Delta H_p^{\ddagger}$. However, if the shape of the previously described *r*-parameter plots is indicative of mechanism, the implication from Figure 3 is that *N*-methyl- and *N*,*N*-dimethylbenzamides hydrolyze by similar mechanisms since their curves are nearly superimposable, whereas that for benzamide is quite different. Work is in progress to investigate the possibility of a change in mechanism with methyl substitution .

Experimental Section

The amides were commercially available. Benzamide was recrystallized (H_2O) to constant melting point (128–129°).

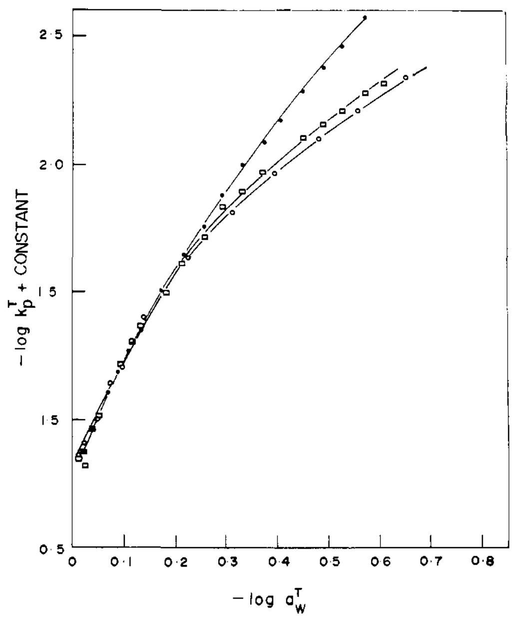


Figure 3. Rate of reaction of protonated benzamide (dots), *N*-methylbenzamide (squares), and *N*,*N*-dimethylbenzamide (circles) as a function of water activity.

N-Methylbenzamide was distilled under reduced pressure; bp 130.0–130.5° (1.5 mm); mp 81.5–82.5°. *N*,*N*-Dimethylbenzamide was also distilled before use; bp 116.0–116.2° (2.5 mm); mp 41.5–43°.

p*K* Determinations. The spectra of acid solutions containing identical concentrations of each amide were recorded on a Unicam SP800 spectrophotometer. Spectra were analyzed at a number of wavelengths around the absorption maxima of the protonated amides. Ionization rates ($I = [SH^+]/[S]$) were calculated from the expression

$$I = \frac{A_S - A}{A - A_{SH^+}}$$

The temperature dependence of the I values was determined by measuring the variation in A_S, A_{SH^+}, and A with temperature.

Kinetic Method. Sulfuric acid solutions were prepared by diluting CIL reagent grade acid to the desired concentration, followed by standardization with sodium hydroxide. The rates of hydrolysis were measured by recording spectral changes on a Cary 16 spectrophotometer, at the wavelengths given in Table VII. A stock solution of amide was prepared in the appropriate sulfuric acid and 14 samples were prepared for each kinetic run by sealing 3 ml of solution in glass ampoules. (*N*-Methyl- and *N*,*N*-dimethylbenzamide samples were sealed under nitrogen. This procedure was found to reduce experimental scatter in the rate plots.) The ampoules were allowed to equilibrate in a bath thermostatted to $T \pm 0.05°$, and were quenched in ice when withdrawn. Runs were followed for 1.5–2 half-lives. Infinity points A_∞ were obtained in all cases in triplicate and were reproducible to ±0.5%. Infinity values for runs at lower temperatures were carried out at 105° Rate constants were obtained from plots of log $(A - A_\infty)$ *vs.* time.

Table VII. Concentration Ranges and Wavelengths for Kinetic Measurements

Substrate	Molarity	% H_2SO_4	λ, mμ
Benzamide	$1.7\text{–}5.1 \times 10^{-4}$	5.9–30.2 27.4–59.0	210 252
N-Methyl-	$1.9\text{–}2.8 \times 10^{-4}$	5.9–32.0 37.5–60.0	211 248
N,*N*-Dimethyl-	$1.8\text{–}2.7 \times 10^{-4}$	5.9–60.0	210

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[28] Although the differences in $\Delta H_p^{\ddagger}$ for the three amides are not very large, the experimental accuracy of the rate data in Table I is such that these differences are significant. The standard deviations in Table VI are considerably smaller than the changes produced on successive methyl substitution.

[29] K. Yates, J. B. Stevens, and A. R. Katritzky, *Can. J. Chem.*, **42**, 1957 (1964).