

d -0.0018 M isobutyric acid (all at 35°) were added to each of eight 25-ml volumetric flasks in a 35° constant-temperature bath. The solutions had all been prepared and stored under nitrogen, the volumetric flasks had been flushed with nitrogen, and the addition was carried out under nitrogen. At recorded times 1 ml of 5 M acetic acid was added to stop the reaction and the solution was extracted immediately with 1 ml of spectral grade chloroform. The deuterium content of the isobutyraldehyde in the chloroform extract was determined by measuring the nmr spectra and comparing them with those of known mixtures of isobutyraldehyde and isobutyraldehyde-2- d .²³ For each point the deuterium content of the imine was taken as equal to the deuterium content of the aldehyde extracted, and the first-order rate constant was calculated from the slope of a plot of $\log ([\text{ImD}]_0/[\text{ImD}]_t)$ vs. time as shown in Figure 2. The deuterium content of aldehyde obtained from points taken

(23) A plot of the fraction of deuterated aldehyde vs. $d/(d + h)$, where d and h have the meanings used previously,^{1b} was found to be a straight line.

within a few seconds after the reaction began was found to be essentially the same as that of the aldehyde used in preparing the reaction solutions. Independent measurements show that the addition of excess acetic acid slows the reaction to a rate that may be neglected in the present case. Nmr measurements show that in acidic solution the aldehyde-imine equilibrium is shifted almost entirely to the side of the aldehyde.

pK Measurements. Titration of solutions of hydrochloric acid with standard methylamine (with and without added sodium chloride) was carried out using a Beckman research pH meter, Model 101900 and a constant-temperature bath that kept the solution at $35 \pm 0.5^\circ$. The pK values were calculated from the pH at the point where the concentrations of methylamine and methylammonium chloride were equal.

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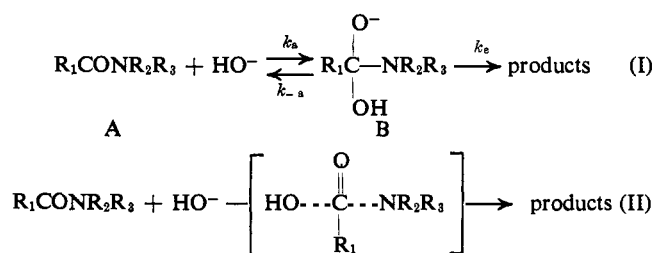
Catalytic Efficiencies in Amide Hydrolysis. The Two-Step Mechanism^{1,2}

Richard L. Schowen, H. Jayaraman,³ and Larry Kershner⁴

Contribution from the Department of Chemistry, University of Kansas, Lawrence, Kansas. Received February 14, 1966

Abstract: The kinetics of hydrolysis of 2,2,2-trifluoro- N -methylacetanilide (I) has been determined in aqueous solution from pH 11.2 to 12.6 at temperatures from 20 to 35° . The kinetic law, shown in eq 1, is consistent with intermediate formation of an adduct of I and hydroxide ion and general base catalyzed conversion of this species to products. The results are not consistent with a single-step conversion of I to hydrolysis products. The activation parameters for the processes corresponding to each rate constant are: $(k_a) \Delta H^* = 5.5$ kcal/mole, $\Delta S^* = -36$ eu; $(k_1) \Delta H^* = 5.9$ kcal/mole, $\Delta S^* = -37$ eu; $(k_2) \Delta H^* = 6.6$ kcal/mole, $\Delta S^* = -21$ eu, for standard states of 1 M aqueous solution for solutes and pure liquid for water. The catalytic efficiency of hydroxide ion relative to water in decomposition of the adduct is thus a purely entropic effect.

Previously available evidence⁵ on the mechanism of base-catalyzed amide hydrolysis is consistent with either of two mechanisms: (I) the reversible addition of hydroxide ion to the carbonyl function followed by expulsion of amide ion, and (II) a concerted displacement of amide ion by hydroxide ion in an $\text{S}_{\text{N}}2$ -like reaction at the carbonyl center. Our observation² that



(1) This research was supported by the National Institutes of Health under Research Grant No. GM-12477-02 and was carried out in part at the Computation Center of the University of Kansas.

(2) Amide Hydrolysis. II. Part I: R. L. Schowen and G. W. Zuorick, *J. Am. Chem. Soc.*, **88**, 1223 (1966). A preliminary account of part of the present work has appeared: R. L. Schowen, H. Jayaraman, and L. Kershner, *Tetrahedron Letters*, 497 (1966).

(3) Fellow of the Institute of International Education.

(4) National Defense Education Act Predoctoral Fellow.

(5) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) A. Bruylants and F. Kézdy, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **21**, 213 (1960); (c) S. S. Biechler and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957).

the hydrolysis of 2,2,2-trifluoro- N -methylacetanilide exhibits general base catalysis superimposed upon hydroxide ion catalysis is consistent with mechanism I if formation or decomposition of the adduct B is general base catalyzed or with II if attack by hydroxide ion is general base catalyzed.

The finding of Bender and Ginger⁶ that the base-catalyzed hydrolysis of benzamide proceeds concurrently with exchange of O^{18} from the substrate carbonyl group is consistent with a scheme in which exchange occurs by the reversible formation of B, which almost always (a fraction $k_a/(k_a + k_e)$ of times) decomposes to reactants, rather than to products, by expulsion of the weaker base hydroxide in preference to the stronger base amide ion ($k_{-a} \gg k_e$). Hydrolysis could then result from (II) if its rate constant greatly exceeded $k_e/(k_a + k_e)$. Bender^{5a} has pointed out, as an argument against mechanisms such as (II), that no analogous displacement of such a poor leaving group by hydroxide ion is known in saturated carbon systems. However, saturated carbon substrates have no means for stabilization of the concerted-displacement transition state by electron acceptance from the very basic entering and leaving groups because high-energy σ^* orbitals are the

(6) M. L. Bender and R. D. Ginger, *ibid.*, **77**, 58 (1955).

Table I.^{a,b} Hydrolysis of 2,2,2-Trifluoro-N-methylacetanilide

$10^3[\text{HO}^-], M$	Temp, °C							
	20.9°		25.0°		29.8°		33.9°	
	$10^3k_{\text{obsd}}, \text{sec}^{-1}$	$10^3k_{\text{calcd}}, \text{sec}^{-1}$	$10^3k_{\text{obsd}}, \text{sec}^{-1}$	$10^3k_{\text{calcd}}, \text{sec}^{-1}$	$10^3k_{\text{obsd}}, \text{sec}^{-1}$	$10^3k_{\text{calcd}}, \text{sec}^{-1}$	$10^3k_{\text{obsd}}, \text{sec}^{-1}$	$10^3k_{\text{calcd}}, \text{sec}^{-1}$
1.5	4.9	4.9	5.7	5.9	6.9	6.3	7.4	7.2
3.0	12.7	12.9	15.3	15.7	17.1	16.7	18.6	19.0
4.5	23.8	21.2	27.5	27.8	31.4	29.3	33.7	33.3
6.0	34.5	31.3	40.2	41.1	45.2	43.2	47.7	49.0
8.0	48.9	45.7	58.3	60.2	64.4	63.1	66.7	71.3
10.5	67	65	92	85	99	89	105	101
12.0	84	77	98	101	108	105	112	119
13.5	102	89	126	117	127	122	140	137
15.0	124	101	135	133	145	138	173	155
20.0	145	142	176	188	201	194	207	218
25.0	208	183	228	224	258	251	301	281
30.0	241	225	268	299	282	308	343	345
35.0	254	267	345	355	354	365	410	409

^a Ionic strength 0.01 *M* (added KCl) below 0.008 *M* hydroxide, 0.05 *M* (added KCl) at higher base; S. S. Biechler and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957), found no salt effects in these reactions. ^b k_{obsd} values are averages of duplicate determinations, reproducible to $\pm 3\%$; k_{calcd} values are calculated from eq 1 with k_a , k_1 , and k_2 of Table II.

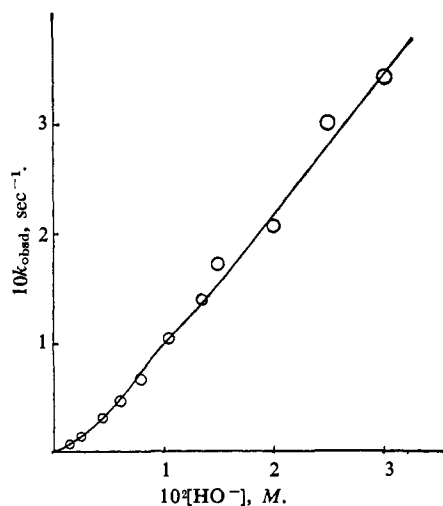


Figure 1. Dependence of the observed rate constant for hydrolysis of 2,2,2-trifluoro-N-methylacetanilide at 33.9° on hydroxide ion concentration. The line is calculated from eq 1 with the parameters of Table II, while the circles represent experimental measurements.

only available unoccupied orbitals. With a carbonyl central group, however, the hydroxide and amide lone pair electrons could conceivably "back bond" into the relatively low-energy π^* orbital of the carbonyl group, leading to a stabilization of the transition state analogous to that observed for transition metal carbonyl derivatives.⁷ Thus it is possible that $\text{S}_{\text{N}}2$ displacement of amide ion could occur from carbonyl substrates but not from saturated carbon substrates. In the present paper we report an unambiguous distinction of (I) and (II) and some evidence on the origins of catalytic efficiencies in amide hydrolysis.

Results

Table I shows observed rate constants for the hydrolysis of 2,2,2-trifluoro-N-methylacetanilide (I; structure A with $\text{R}_1 = \text{CF}_3$, $\text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{C}_6\text{H}_5$) as a function of hydroxide concentration at four tempera-

(7) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y. 1962, p 616.

tures. In alternate columns are shown values of the rate constant calculated from eq 1 with the parameters

$$-d[\text{I}]/dt = k_{\text{obsd}}[\text{I}] = [\text{I}] \left\{ k_0 + [\text{HO}^-] \frac{k_a(k_1 + k_2[\text{HO}^-])}{k_a + k_1 + k_2[\text{HO}^-]} \right\} \quad (1)$$

k_a , k_1 , and k_2 shown for each temperature in Table II. Figure 1 shows a plot of some of the data. The agreement of calculated and observed rate constants is very good. Table II also shows values of free energies (ΔF^\ddagger), enthalpies (ΔH^\ddagger), and entropies (ΔS^\ddagger) of activation for each of the rate processes (those corresponding to k_a , k_1 , and k_2), standard states being taken as 1 *M* aqueous solution for solutes and pure liquid for water.

Table II. Rate Constants^a and Activation Parameters^b for the Hydrolysis of 2,2,2-Trifluoro-N-methylacetanilide

Temp, °C	$k_a, M^{-1} \text{sec}^{-1}$	$k_1, M^{-1} \text{sec}^{-1}$	$k_2, M^{-2} \text{sec}^{-1}$
20.9 \pm 0.1	8.6	1.8	1900
25.0 \pm 0.1	11.0	2.0	2200
29.8 \pm 0.1	11.7	2.5	2700
33.9 \pm 0.1	13.0	2.7	3200
$\Delta F^\ddagger_{298}, \text{kcal/mole}$	16 \pm 1	17 \pm 1	13 \pm 1
$\Delta H^\ddagger, \text{kcal/mole}$	6 \pm 1	6 \pm 1	7 \pm 1
$\Delta S^\ddagger_{298}, \text{eu}$	-36 \pm 3	-37 \pm 3	-21 \pm 3

^a See eq 1. Uncertainties in rate constants are about 5%. ^b Standard states 1 *M* in aqueous solution for solutes and pure liquid for water.

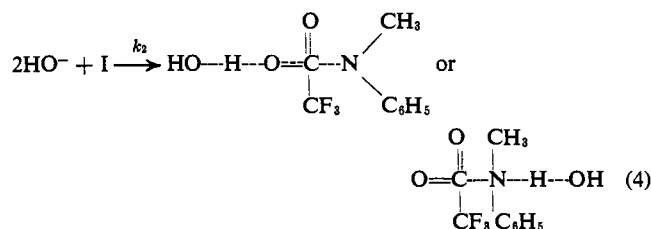
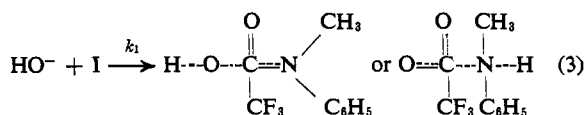
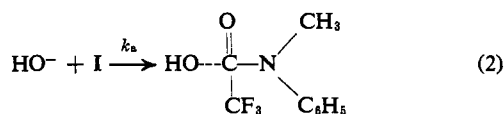
Discussion

These results show clearly that hydrolysis of this amide proceeds by way of the two-step mechanism (I); eq 1 can be derived from this mechanism by application of the steady-state approximation for the intermediate B, with $k_e = k_1' + k_2'[\text{HO}^-]$ (where $k_i' = k_{-i}k_i/k_a$, $i = 1, 2$) corresponding to the general base catalyzed decomposition of B to products.² At low base concentrations (pH 9.5–10), superimposed general base catalysis is observed² because the decomposition of B is rate determining. At higher base concentrations

(pH 12), the reaction kinetics reverts to simple first order in hydroxide ion (*cf.* Table I and Figure 1) because the hydroxide ion catalyzed decomposition of B to products now exceeds in rate the unimolecular reversion of B to reactants. The addition step has become rate determining. These observations demonstrate that elimination, rather than addition, is subject to general catalysis since, in order for the reaction to go over from second order in base at *lower* base concentrations to first order in base at *higher* concentrations, it must be the second of the two steps, not the first, which involves two hydroxide ions. This observation of a change in rate-determining step with pH requires a multistep reaction pathway⁸ and excludes single-step routes such as (II).

It may be noted that eq 1 is also consistent with simple inhibition by hydroxide ion through formation of an unreactive complex with the amide. The difficulty of formulating such a species has led us to prefer the explanation above.

Catalytic Efficiencies. The activation parameters of Table II can be associated with the following activation processes.



Here the water catalyst of the k_1 process is not shown explicitly, since it is not clearly differentiable from a solvating water molecule in either of the other activated complexes. It is reasonable that the activation parameters for eq 2 and 3 are approximately equal. The negative values of the entropies of activation are consistent with the multimolecular character of both processes. If the carbon–nitrogen bond is breaking² in the k_1 process (eq 3), then the only structural changes

(8) As W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86**, 5616 (1964), have likewise shown for the hydroxylaminolysis of amides.

on going from the activated complex of eq 2 to that of eq 3 are a shift of charge among oxygen and nitrogen atoms and a reorganization of solvating molecules, to which the enthalpy might conceivably not be sensitive. If this bond is not breaking,^{5c} the rate-determining process is an O to O or O to N proton transfer for which ΔH^* should be small. The enthalpy change for eq 2 might be correspondingly small because of activation of the carbonyl group toward addition by the trifluoromethyl substituent. The small values of ΔH^* for eq 3 and 4 make a simple proton transfer seem a more likely rate-determining step than we previously believed.²

The efficiency of hydroxide ion relative to water as a base catalyst in this reaction results *entirely* from a more positive entropy of activation for the stronger base. Schmid⁹ pointed out that the catalytic advantages of both hydrogen and hydroxide ions over water in the mutarotation of glucose, in which the transition state resembles the one under discussion here, arise from entropic contributions alone. Presumably the important factors⁹ are the greater degree of solvation of the ions and their consequently greater desolvation upon activation, resulting in a more positive entropy of activation. If this is correct, the hydroxide ion must be bound into the activated complex more strongly than is water, presumably by formation of a stronger hydrogen bond, with liberation of sufficient enthalpy to “pay off” the greater enthalpy of desolvation required for the stronger base.¹⁰ The result is a greater entropy of activation for the stronger base while the enthalpy remains the same. It is true that stronger binding of the hydroxide ion may slightly reduce the entropy of the transition state but this effect should be very small compared to the increase in entropy associated with the liberation of the initial-state solvation shell. This kind of detailed interaction of entropy and enthalpy terms is likely to be an important determinant of catalytic efficiencies in a variety of solution reactions.

Experimental Section

Materials and kinetic methods were identical with those reported previously.² Kinetic runs were carried out in part with a Beckman DB recording spectrophotometer, the temperature being controlled to within 0.1° by use of a thermostated cell compartment.

(9) H. Schmid and co-workers, *Monatsh.*, **96**, 1503 (1965); **95**, 454 (1964); **94**, 1206 (1963).

(10) This condition is apparently not met in nucleophilic displacements at carbon, as opposed to those at hydrogen. As a result, heavy solvation of the nucleophile exerts an inhibitory, rather than a catalytic, effect; see C. A. Bunton, “Nucleophilic Substitution at a Saturated Carbon Atom,” Elsevier Publishing Co., New York, N. Y., 1963, p 75 ff, and references cited therein.