The Mechanism of Acid Hydrolysis of Lysidine[1,2] and *N*-(2-Aminoethyl)acetamide and Related Amides

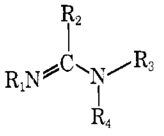
P. HAAKE AND JOSEPH W. WATSON[3]

Contribution No. 2180 from the Department of Chemistry, University of California, Los Angeles, California 90024

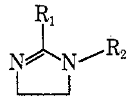
Received February 17, 1970

The kinetics of the acid-catalyzed hydrolysis of lysidine (2-methyl-2-imidazoline) in HCl and H_2SO_4 at 100° were investigated. The nmr chemical shifts of the methyl and methylene signals of lysidinium ion undergo large downfield shifts above 102% sulfuric acid (dimethylammonium ion internal standard) which are accompanied by broadening of the signals. Above 105% H_2SO_4, the methyl signal resharpens but the methylene signal remains broad. The rate of acid hydrolysis of lysidine is linearly dependent on the acid concentration and shows a maximum at 10–12 *M* H_2SO_4. In LiCl–HCl solutions, the rate is dependent on the acidity (H_0) and the activity of water. The nmr and rate data are consistent with significant protonation of lysidinium ion to a dication (6) above 102% H_2SO_4 and acid hydrolysis of lysidine *via* a transition state composed of lysidinium ion, a proton, and water. Rate-determining nucleophilic attack by water on the dication (6) is tentatively proposed as the mechanism. The same mechanism may hold for the acid hydrolysis of guanidines. The rates of acid hydrolysis of *N*-(2-aminoethyl)-, *N*-(2-dimethylaminoethyl)-, *N*-(2-trimethylaminoethyl)-, and *N*-propylacetamides are reported.

To our knowledge, no kinetic studies of the acid-catalyzed hydrolysis of alkyl substituted amidines (**1**) or imidazolines (**2**) have been reported. In connection with some studies of acyl derivatives of ethylenediamine,[2] it was important to know the stability in acid of



1



2

lysidine (**3**), 2-methyl-2-imidazoline (**2**, R_1 = Me; R_2 = H), and its initial hydrolysis product, *N*-(2-aminoethyl)acetamide. Qualitative observations have indicated slow hydrolysis of alkyl substituted imidazolines in acid.[4,5] Concentrated HCl at 175° for 12 hr has been reported to hydrolyze 2-imidazolines.[6] The kinetics of the hydrolysis of *N,N'*-diarylamidines in acid have been interpreted in terms of rate-determining decomposition of a protonated amidine hydrate.[7]

The kinetics of the hydrolysis of lysidine in alkaline solution have been interpreted in terms of rate-determining decomposition of the intermediate resulting from the addition of hydroxide ion to lysidine[4a] and rate-determining addition of hydroxide ion to lysidinium cation.[5] The hydrolysis of 1,3-diphenyl-2-imidazolinium ion in alkaline solutions has been shown to occur by general acid catalyzed decomposition of the anionic tetrahedral addition intermediate.[4b]

We report here a study of the protonation and hydrolysis of lysidine (**3**) including evidence for a dication which undergoes nucleophilic attack by water in the hydrolysis reaction.

Experimental Section

All melting points are corrected; all boiling points are uncorrected. Nuclear magnetic resonance spectra were determine on a Varian A-60 spectrometer. Electronic absorption spectra were determined on a Cary Model 14M recording spectrophotometer. Absorbances for kinetic purposes were determined on an Hitachi Perkin-Elmer No. 139 spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Infracord or a Perkin-Elmer No. 137. Elemental analyses were performed at the University of California at Los Angeles by Miss Heather King.

Sodium hydroxide was prepared carbonate free from a 50% stock solution and protected against CO_2 absorption. Sodium hydroxide was standardized against potassium biphthalate with phenolphthalein as indicator. Reagent grade HCl and H_2SO_4 were standardized by titration with standardized sodium hydroxide using phenolphthalein as indicator or with Borax[8] using methyl red as indicator. Solutions of H_2SO_4 between 90 and 108% were obtained by addition of the proper weight of water to 20 or 30% fuming H_2SO_4 which had been standardized by titration with distilled water.[9]

Rate Measurements.—A stock solution of acid of the proper concentration was added to the appropriate amount of substrate and aliquots were sealed in glass tubes. The tubes were placed in the constant temperature bath and removed at appropriate intervals; the reaction was quenched by cooling in ice. The solutions were placed in the spectrophotometer and the absorbance reading was noted when the solution reached room temperature. Completely hydrolyzed solutions were obtained from tubes kept at 100° for ten half-lives or by allowing a tube to stand in refluxing *p*-xylene (bp 138°) for at least two 100° half-lives. Plots of log ($A_t - A_\infty$) against time gave a slope = $k/2.3$; A_t and A_∞, respectively, are absorbances at time, *t*, and after complete hydrolysis. Good straight lines were obtained for seven to nine points over two to three half-lives for these first-order plots. For the acidic hydrolyses, the initial lysidine concentration was 3×10^{-4} *M* and the 230–236-mμ region was observed. For the amide hydrolyses disappearance of the absorption in the 208–215-mμ region was followed. The overall absorbance change in all the rate determinations was between 0.9 and 1.4 absorbance units.

Lysidine (**3**) was synthesized from *N*-(2-aminoethyl)acetamide[10] and recrystallized from benzene. After drying over P_2O_5 at room temperature under vacuum for 12 hr, the melting point was 102.0–103.5° (lit. 103°[10] and 105–106°[11]).

Lysidine hydrochloride was prepared by saturating a solution of lysidine in absolute ethanol with dry HCl gas and precipitating the hydrochloride by the addition of ether. The salt was recrystallized from absolute ethanol and dried at 100° under vacuum for 21 hr. The melting point was 172–173° (lit. 163–167°[12]

---

[1] This research was supported in part by Grant AM-6870 from the U. S. Public Health Service and by an Alfred P. Sloan Research Fellowship, 1964–1967, to P. H.

[2] J. W. Watson, Ph.D. Thesis, University of California, Los Angeles, Calif., 1966.

[3] Inquiries should be directed to J. W. W., Department of Chemistry, University of California, San Diego, La Jolla, Calif. 92037.

[4] (a) B. G. Harnsberger and J. L. Riebsomer, *J. Heterocycl. Chem.*, **1**, 188, 229 (1964). (b) D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 7088 (1967); D. R. Robinson, *Tetrahedron Lett.*, 5007 (1968).

[5] R. B. Martin and A. Parcell, *J. Amer. Chem. Soc.*, **83**, 4830, 4835 (1961).

[6] W. L. Hawkins and B. S. Biggs, *ibid.*, **71**, 2530 (1949).

[7] R. H. DeWolfe, *ibid.*, **86**, 864 (1964).

[8] A. Vogel, "Quantitative Inorganic Analysis," 3rd ed, Wiley, New York, N. Y., 1962, p 238.

[9] J. C. D. Brand, *J. Chem. Soc.*, 585 (1946).

[10] A. J. Hill and S. R. Aspinal, *J. Amer. Chem. Soc.*, **61**, 822 (1939).

[11] J. A. King and F. H. McMillan, *ibid.*, **68**, 1774 (1946).

[12] J. C. Mackenzie, G. S. Myers, G. N. R. Smart, and C. F. Wright, *Can. J. Res.*, **26**, 138 (1948).

and 171° [11]). The nmr spectrum of 0.6 *N* lysidine hydrochloride in D_2O (DSS standard[13]) had the following signals: singlet τ 5.30 (HOD), singlet 6.10, area 4.0 (CH_2CH_2), singlet 7.80, area 3.1 (CH_3).

***N*-Propylacetamide** (**8**) was prepared by adding 1.0 mol of sodium-dried *n*-propylamine to 1.1 mol of acetic anhydride over a period of 0.5 hr. The reaction mixture was then heated on a steam bath for 1 hr. Low boiling materials were removed at atmospheric pressure. The fraction distilling at 124–125° (23 mm) was collected and redistilled, bp 122.0–123.5° (19.2–20.5 mm).

Anal. Calcd for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.27; H, 10.87; N, 14.13.

***N*-(2-Aminoethyl)acetamide.**—This amide (**5**) was prepared from ethylene diamine and ethyl acetate as previously described.[10] The first product isolated in all vacuum distillations of **5** was a basic solid which melted at 85–90°. The properties of this solid were similar to those of 2-methyl-2-imidazoline, lysidine (**3**), a reported[14] impurity of amide (**5**), and did not agree with the properties of the other likely contaminant, *N*,*N′*-diacetylethylenediamine (mp 172–174° [10]). The collection of substantial amounts of lysidine as the first distillate in all redistillations of amide **5**, no matter how many times previously amide **5** had been distilled with care to collect the fractions least contaminated by lysidine, suggest that lysidine is formed from **5** on distillation and is not just a side product of the original synthesis. This cyclization, dehydration phenomenon has been noted to occur on vacuum distillation of *N*-aroylethylenediamines.[10]

Lysidine contamination of the amide **5** used in the rate determinations was minimized by twice distilling the amide, retaining only the middle 50%, and by adding an approximately equal weight of water to the amide **5** and heating the mixture for 2 hr, conditions which affect the complete hydration of lysidine to amide **5**.[15,16] The initial nmr spectrum of the amide **5** dissolved in an equal weight of water showed signals attributable to 3% contamination by lysidine. After heating at 75°, the signals attributable to lysidine were undetectable, indicatiug less than 1% contamination by lysidine.

In the distillations of amide **5**, lysidine sublimed over at 72° (2 mm) and the amide distilled at 114° (1 mm): nmr (in D_2O) τ 6.49 (singlet, area = 0.08, CH_2 of lysidinium ion), 6.75 [triplet area = 2.00 $-CH_2NHC(O)-$], 7.30 (triplet, area = 2.1, H_2NCH_2-), 8.00 (singlet, area = 3.5, CH_3).

***N*-(2-Dimethylaminoethyl)acetamide.**—*N*,*N*-dimethylglycinonitrile was prepared by two methods[17,18] giving identical infrared spectra and an nmr spectrum (neat liquid) with singlets at τ ~6.8 (area = 2.0) and ~8.0 (area ~6.3). This nitrile was reduced to 2-dimethylaminoethylamine by reduction with $LiAlH_4$,[19] bp 105–108° (lit. 105–108°,[18] 101–104°,[19] and 102–104° [20]). Reaction of 12 g of the amine with 23 g of ethyl acetate at reflux for 70 hr yielded the amide **6**: bp 105° (4 mm); neut equiv 131 ± 1, calcd 130; nmr (in D_2O) τ 6.67 (triplet, area 2.0), 7.50 (triplet, area 2.4), 7.78 (singlet, area 5.7), 8.08 (singlet, area 3.0).

Anal. Calcd for $C_6H_{14}N_2O$: C, 55.35; H, 10.84. Found: C, 55.41; H, 10.76.

2-Acetamidoethyltrimethylammonium Iodide.—A solution of 3 g (0.025 mol) of *N*-(2-dimethylaminoethylacetamide) in 5 ml of absolute methanol was placed in a 50-ml, three-neck flask equipped with a dropping funnel, a magnetic stirrer, and a reflux condenser; the system was protected from water vapor by Drierite. Over a period of 0.5 hr, 4.8 g (0.034 mol) of methyl iodide was added; a white precipitate formed after approximately half of the methyl iodide had been added. After the addition was complete, the reaction mixture was refluxed for 0.5 hr. The warm solution was transferred to an erlenmeyer flask and ether was added until the solution became cloudy; upon further cooling crystallization occurred. After three recrystallizations from absolute methanol and drying over P_2O_5 under vacuum at 100° for 24 hr, 1.7 g of nonhydroscopic, white crystals, mp 140.5–142° were obtained.

Anal. Calcd for $C_7H_{17}N_2OI$: C, 30.89; H, 6.30; N, 10.30. Found: C, 30.82; H, 6.64; N, 10.36.

2-Acetamidoethyltrimethylammonium Chloride.—Approximately 6 ml of methyl chloride (Matheson) was condensed in a graduated cylinder and added to a pressure bottle containing 4.2 g (0.032 mol) of *N*-(2-dimethylaminoethylacetamide) dissolved in 25 ml of absolute methanol; the bottle was immediately closed. There was a 4.5-g increase in the weight of the pressure bottle and its contents after the addition of the methyl chloride. After standing for 5 days, the reaction mixture had a pH of 5–6 as determined by indicator paper. Solvent was removed under vacuum at room temperature and crystallization occurred when the volume of liquid had been reduced to approximately 5 ml. The evaporation was stopped at this point and 25 ml of anhydrous ether was added to the liquid. Filtration and washing with ether yielded 5.5 g of hygroscopic crystals, mp 156–158°. Recrystallization from methanol–acetone and then from methanol–acetone–ether followed by drying 15 hr (0.1 mm), 100°, over P_2O_5 resulted in hygroscopic white needles: mp 165.0–166.5°; nmr (25 mg in 0.3 ml of D_2O) τ 5.35 (HOD), 6.2–6.5 (multiplet, area 3.9, $-CH_2CH_2-$), 6.79 [singlet, area 8.9, $-H^+-(CH_3)_3$], 7.95 [singlet, area 3.0, $CH_3C(O)-$].

Anal. Calcd for $C_7H_{17}N_2OCl$: C, 46.53; H, 9.49; Cl, 19.6. Found: C, 45.66; H, 9.33. After redrying: C, 45.81; H, 9.54; Cl, 18.7. (The differences are probably due to water; inclusion of $^1/_6H_2O$ gives calcd: C, 45.81; H, 9.51; Cl, 19.3. Nmr spectra also indicated small amounts of water present in this salt.)

Results

Rate Measurements.—Tables I and II contain the observed first-order rate constants for the hydrolysis of lysidine ($3 \rightleftarrows 4$) in aqueous HCl and H_2SO_4 (eq 1) at 99.9°. Because the pK_a of lysidinium ion **4** is 11,[5] in acidic solutions lysidine exists essentially completely as lysidinium ion **4**. The hydrolysis of the initial

TABLE I

OBSERVED FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF LYSIDINE HYDROCHLORIDE IN HYDROCHLORIC ACID AND IN HYDROCHLORIC ACID PLUS LITHIUM CHLORIDE AT 99.9°[a]

Molarity of HCl	$k_1 \times 10^5$ (sec^{-1})	h_0 (25°)[b]	a_{H_2O} (25°)[b]
0.10	0.018	0.105	1.0
3.0	0.346	11.2	0.851
5.0	0.724	57.5	0.700
6.0	0.920	132.0	0.615
0.1 *M* HCl 5.8 *M* LiCl	0.033	4.0[c]	0.610[d]
3.0 *M* HCl 3.0 *M* LiCl	0.767	100.0[e]	0.616[c]
2.5 *M* NaBr 3.0 *M* HCl	0.4[f]		

[a] Initial concentration of substrate = 3×10^{-4} *M*. [b] The h_0 and a_{H_2O} values are from (a) J. F. Burnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961); (b) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [c] Assumed equal to the average of the water activities of 6 *M* HCl and of 6 *M* LiCl: D. Rosenthal and J. S. Dwyer, *Can. J. Chem.*, **41**, 80 (1963). [d] Assumed equal to the activity of water of 5.9 *M* LiCl (reference in footnote *c*). [e] The h_0 values for the hydrochloric acid–lithium chloride solution were calculated from the equation $H_0 = -\log [H^+] + 4 \log a_{H_2O} - B$ [electrolyte] and published data (reference in footnote *c*). For the 0.1 *M* HCl:5.8 *M* LiCl solution, *B* was assumed equal to 0.126. For the 3 *M* HCl:3 *M* LiCl solution, *B* was assumed equal to 0.109, the average of the *B* values of LiCl and HCl. [f] Because of the oxidation of the bromide ion, only the first two points, representing zero and 30% hydrolysis, were used to calculate k_1.

---

(13) G. V. D. Tiers and R. I. Coon, *J. Org. Chem.*, **26**, 2097 (1961); DSS = sodium 3-trimethylsilylpropane-1-sulfonate.

(14) D. A. Shirley, "Preparations of Organic Intermediates," Wiley, New York, N. Y., 1951, p 3.

(15) P. Haake and J. W. Watson, unpublished results.

(16) R. B. Martin and A. Parcell, *J. Amer. Chem. Soc.*, **83**, 4830 (1961).

(17) D. B. Luten, Jr., *J. Org. Chem.*, **3**, 588 (1939).

(18) R. A. Turner, *J. Amer. Chem. Soc.*, **68**, 1607 (1946).

(19) E. E. Campaigne and F. Jacoby, *Crisol*, **7**, 19 (1953); *Chem. Abstr.*, **48**, 11320*i* (1954).

(20) H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. Fr.*, 556 (1962).

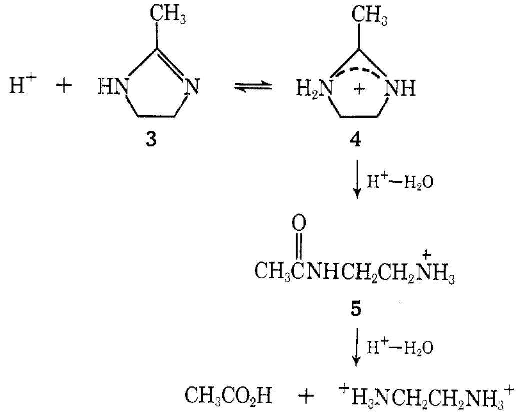
TABLE II

OBSERVED FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF LYSIDINE IN SULFURIC ACID SOLUTIONS AT 99.9° [a]

M H_2SO_4	$k_1 \times 10^5$ (sec^{-1})	h_0 (25°)[b]	a_{H_2O} (25°)[b]
4.0	0.503	70.7	0.721
4.5	0.556	115	0.666
5.0	0.596	191	0.603
6.0	0.767	575	0.478
7.0	0.943	2,090	0.364
8.0	1.04	7,410	0.259
9.0	1.19	25,100	0.173
10.0	1.30	77,600	0.108
11.0	1.30	3.2×10^5	0.061
12.0	1.29	2.6×10^6	0.016
14.0	0.55	2.0×10^7	0.0059
15.0	0.285	7.6×10^7	0.0019
16.0	0.11	4.0×10^8	0.00049

[a] [Lysidine] = 2×10^{-4} M initially. [b] For sulfuric acid solutions below 11 M in concentration, and a_{H_2O} and h_0 values, see Table I, ref a in footnote *b*. For acid solutions more concentrated than 10 M, h_0 values are from (a) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963), and a_{H_2O} values are from (b) W. F. Giange, E. W. Homung, J. E. Kunzler, and T. R. Rubin, *J. Amer. Chem. Soc.*, **82**, 62 (1960). Concentrations expressed as percentages or as molalities were converted to molarities with the aid of the data from the "Handbook of Chemistry and Physics," 38th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1956, p 1927. Linear dependencies of h_0 and of a_{H_2O} on molarity of sulfuric acid were assumed when values were not available for an acid concentration.

product of lysidine hydrolysis, *N*-(2-ammoniumethyl)-acetamide (**5**), can have little effect on the calculated rates of hydrolysis of lysidine because amide **5** and its hydrolysis products absorb less than $^1/_{50}$ as strongly as lysidine in the 230–236-mμ region used to follow the lysidine hydrolysis;[21] the considerably faster rate of hydrolysis of amide **5** (compare Tables I, II, and III) further minimizes the possible effect of its hydrolysis.



(1)

$CH_3CO_2H + {}^+H_3NCH_2CH_2NH_3{}^+$

Although lysidine was a likely contaminant of amide **5** (see Experimental Section) and its extinction coefficient is $\gtrsim 10^3$ while that of the amide is $\sim 10^2$ at 208–215 mμ,[21] lysidine contamination would have only a small effect on the rate constants for hydrolysis of amide **5** reported in Table III because amide **5** hydrolyzes approximately 10^2 times faster than lysidine. Thus after ten half-lives for the hydrolysis of amide **5** approximately 94% of the lysidine originally contaminating the amide **5** would still be present and would contribute to the absorbance A_∞ along with the hydrolysis products, acetic acid and ethylenediammonium ion. The A_∞'s, the absorbance after ten half-lives, varied from 5 to 20% of the absorbances at zero time, A_0. If it is assumed that A_∞ is totally due to 94% of the lysidine originally present as a contaminant of amide **5** and A_∞ is 20% of A_0, then the rate constants calculated from A_0, A_∞, and the absorbances at one and two half-lives would be calculated to be too small by 2 and 4%, respectively. The calculated error is less if A_∞ is less than 20% of A_0 and if one considers that a considerable fraction of A_∞ is due to absorbance by the hydrolysis product acetic acid (at 210 mμ, acetamide and acetic acid have extinction coefficients of $\sim$400 and $\sim$40, respectively[21]).

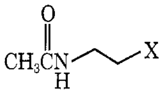
TABLE III

RATES OF ACID HYDROLYSIS OF AMIDES **5–8**[a]

Molarity of HCl	$10_5\,k$ (sec^{-1}), observed rate constants: Amide 8	Amide 5	Amide 6	Amide 7
0.10[b]	1.91	3.46	4.06	3.56
0.50[b]	7.1	21.0	25.5	22.3
1.0[b]	11.7	46.0	50.9	47.0
2.0	14.5	88.4	93.5	90.8
3.0	16.2	110	142	131
4.0	14.4	129	160	148
4.5		128	170	148
5.0	12.3	113	151	145
6.0	10.4	91.9	131	123

[a] At 99.8° with initial concentrations of amides in range 0.001–0.003 M. [b] For amides **5** and **8**, the actual concentrations of HCl were 0.0976, 0.489, and 0.976 M. The tabulated values for these amides therefore need to be increased by $\sim$3% to be valid for 0.1, 0.5, and 1.0 M HCl.

The very similar hydrolysis rate patterns for amides **5**, **6**, and **7** provide additional evidence against lysidine significantly affecting the observed rate of hydrolysis of amide **5** (Table III).



Amide	X	
5	NH_2	protonated in acid
6	NMe_2	protonated in acid
7	$NMe_3{}^+$	
8	CH_3	

Nmr Spectra.—Table IV contains the chemical shifts of lysidinium ion **4** relative to the center of the methyl resonance of $(CH_3)_2HN_2{}^+$. It is very improbable that solvation effects are responsible for the large downfield shifts of the methylene and methyl signals of lysidinium ion in media more acidic than 102% sulfuric acid: (1) the data of Table V show that the relative chemical shifts of the four methyl ammonium ions vary only slightly in the 99.5–105.7% sulfuric acid region in spite of quantitative and qualitative differences in their abilities to be solvated by hydrogen bond donation to the solvent, and (2) both lysidinium ion and dimethylammonium ions have two acidic protons and should therefore show roughly the same solvation effects on chemical shift.

Below 102% H_2SO_4, both CH_3 and CH_2 signals of lysidine are sharp singlets, but at higher acidity the signals are broadened. The methyl signal sharpens again in 105.7% H_2SO_4, but the methylene signal is

---

[21] P. J. Ferm, J. L. Riebsomer, E. L. Martin, and G. H. Daub, *J. Org. Chem.*, **18**, 642 (1953); I. M. Claesson, *Ark. Kemi*, **10**, 1 (1956).

TABLE IV

CHEMICAL SHIFTS AND SIGNAL WIDTHS OF THE METHYL AND METHYLENE PROTONS OF LYSIDINIUM ION IN SULFURIC ACID[a]

		Methylene		Methyl		
% H_2SO_4	M, H_2SO_4	$-\delta^b$	Width[c]	δ^b	Width[c]	$-H_0{}^d$
32.0	68.3	2.0	32.0		2.0	1.85
44.0	68.3	2.0	33.0		2.0	2.76
63.0	66.8	2.0	34.5		1.5	4.83
76.0	65.9	1.5	35.8		2.0	6.71
88.0	65.0	2.0	37.3		2.0	8.61
95.0	64.7	2.0	37.3		2.0	9.85
99.4	65.2	2.0	37.1		1.5	11.06
100.0	65.2	1.5	37.0		2.0	12.20
101.0	64.8	2.0	37.0		2.0	12.92
102.0	65.8	3.0	35.8		3.5	13.16
102.4	66.2	3.5	36.0		4.0	13.26
103.0	66.4	5.0	35.2		5.0	13.38
103.5	72.1	10.0	25.4		12.5	13.47
104.0	74.0	12.0	20.0		11.0	13.57
105.1	77.1	14.5	17.9		7.0	13.73
105.7	81.7	15.0	15.8		4.0	13.80
105.9	79.6	17.0	16.0		4.0	13.83
107.65	84.6	17.5	14.2		2.0	14.06

[a] Concentration of lysidine hydrochloride was about 0.06 g/ml. ml. [b] Chemical shifts in cps downfield from the central peak of the dimethylammonium chloride triplet. [c] Width in cps at half-height of signal; the $(CH_3)_2NH_2{}^+$ standard showed a width of 1 cps. [d] For H_0 values below 60% H_2SO_4, see Table I, ref a in footnote *b*. For H_0 values between 60 and 100% H_2SO_4, see Table II, ref a in footnote *b*. H_0 values for 100% H_2SO_4 and above are obtained by adding -1.10 H_0 units to the H_0 values given in Table I, ref b in footnote *b* as suggested in Table II, ref a in footnote *b*.

TABLE V

CHEMICAL SHIFTS (IN CPS) OF THE METHYL PROTONS OF AMMONIUM IONS FROM Me_4N^+

Solvent[a]	$MeNH_3{}^+$	$Me_2NH_2{}^+$	Me_3NH^+
0.98 N HCl	35.7	28.5	17.5
0.90 M H_2SO_4	34.5	27.5	17.5
60% H_2SO_4	26.8	22.5	14.2
95.5% H_2SO_4	17.3	15.0	10.3
98.8% H_2SO_4	16.7	14.8	10.2
102.4% H_2SO_4	17.1	15.0	10.3
105.7% H_2SO_4	17.0	14.1	9.9

[a] The concentrations of the ammonium salts were $MeNH_3{}^+Cl^-$, 2.0 M; $Me_2NH_2{}^+Cl^-$, 1.3 M; $Me_3NH^+Cl^-$, 0.8 M and $Me_4N^+Cl^-$, 0.6 M.

still broad with some indication of separation into two signals.

After 20 hr at room temperature, the spectrum of the 103.5% H_2SO_4 solution was essentially unchanged: two broad signals at -71.3 and 25.2 cps. After dilution with water to give 88% H_2SO_4, the spectrum showed two sharp singlets at 64.8 and 36.9 cps. These chemical shifts are within experimental error of those observed immediately in 88% H_2SO_4 (Table III). Therefore, the reactions indicated by the chemical shift changes in very strong acid are rapidly reversible.

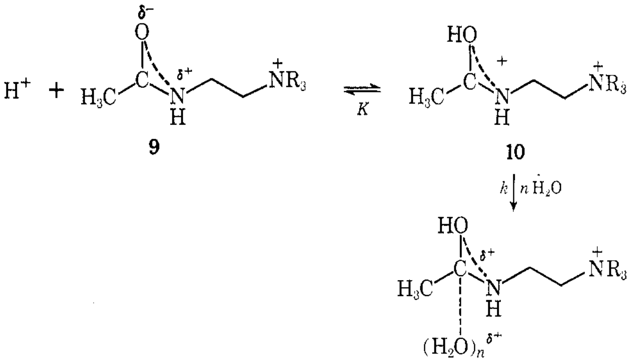
Discussion

Amide Hydrolysis.—The generally accepted mechanism of acid hydrolysis of amides is rate-determining nucleophilic attack of water on the protonated amide.[22]

Thus the two to three times faster rate of hydrolysis of the ammonium amides **5**, **6**, **7** compared to *N*-propylacetamide **8** in dilute acid suggest that the ammonium groups increase the rate of water attack on the protonated amide two to three times more than they increase the acidity of the protonated amide group. This result is probably a consequence of the approximately 40% dipolar character of the amide group[23] which results in a significant destabilizing amide nitrogen–ammonium group interaction in **9** and a high degree of bond formation and charge dispersal to water in the transition state **11** which relieves this positive nitrogen–positive nitrogen interaction.

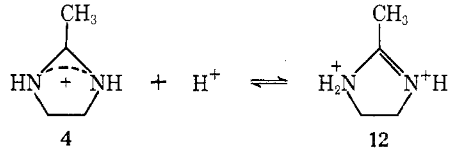
In contrast to the amide hydrolysis results, the acid hydrolysis of 2-trimethylammonium ethyl acetate is 6.7 times slower than that of ethyl acetate in dilute acid.[24] Thus the ammonium group increases the rate of attack of water on the protonated ester group $^1/_7$ as much as it increases the acidity of the protonated ester group.

The opposing effect of the ammonium group on the rates of hydrolysis of amides and esters can be attributed to the greater dipolar character of amides (40% *vs.* 15%)[23] and, because of the greater reactivity of protonated esters, a possibly higher degree of bond formation (with concomitant greater charge dispersal) in the transition state for addition of water to the protonated amide group.



9 **10** **11**

Diprotonation of Lysidine.—The nmr data of Table IV are consistent with significant conversion of lysidinium ion **4** to the dication **12** with slow proton transfers above 102% sulfuric acid. Formation of the dication **12** should cause downfield shifts in the methyl and methylene signals. A plot of the chemical shifts *vs.* H_0 has the general appearance of a titration curve.[25,26] However, because it is uncertain whether lysidinium ion behaves as a Hammett base[27] and the chemical shift changes have not leveled off at the highest acid concentration investigated, it can only



4 **12**

---

[22] K. Yates and J. C. Riordan, *Can. J. Chem.*, **43**, 2328 (1965); R. B. Martin, *J. Amer. Chem. Soc.*, **84**, 4130 (1962); M. L. Bender, *Chem. Rev.*, **60**, 66 (1960).

[23] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, pp 276, 281.

[24] G. Aksnes and J. E. Prue, *J. Chem. Soc.*, **103** (1959).

[25] P. Haake and G. H. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966).

[26] P. Haake, R. D. Cook, and G. H. Hurst, *ibid.*, **89**, 2650 (1967).

[27] P. J. Brignell, C. D. Johnson, A. R. Katritzky, N. Shakir, H. Tarhan, and G. Walker, *J. Chem. Soc. B*, 1233 (1967).

be stated that lysidium ion is half protonated in >102% sulfuric acid ($H_0 = 13.16$).

Slow interconversion of lysidinium ion **4** and the dication **12** would explain the broadening of the methyl and methylene signals around 103.5% sulfuric acid. At higher acid concentrations the methyl resonance resharpens but the methylene resonance remains broad. This is probably due to nearly complete conversion to **12** with proton exchange sufficiently slow so that **12** does not have C_{2v} symmetry by nmr (two different CH_2's and coupling would give a broad CH_2 signal).

Hammond and Neuman have presented evidence for the exchange of the NH protons of N,N'-dimethylacetamidinium ion with sulfuric acid solutions occurring *via* the diprotonated amidine.[28]

Heterocyclic dications have been proposed as intermediates in the nitration of quinolines and imidazoles and the proton exchange reactions of methylpyridines and pyridine N-oxides.[29] The extent of diprotonation of heterocyclic bases as a function of H_0 has been investigated.[27] Diprotonated ureas, thioureas, and guanidines in FSO_3H-SbF_5 mixtures have been observed by nmr spectroscopy.[30] The nmr spectra of biguanides in concentrated sulfuric acid has been interpreted in terms of slow proton exchange and trication formation.[31]

Mechanism of Acid-Catalyzed Hydrolysis.—Figure 1 gives the dependence of the first-order rate constants (Tables I and II) for hydrolysis of lysidinium ion on acid concentration. The rate is linearly dependent on acid concentration up to 10 M sulfuric acid.

The rate of hydrolysis increases by a factor of 50 as the HCl concentration increases from 0.1 M to 6.0 M HCl. The first, fourth, fifth, and sixth entries of Table I indicate that the rate of hydrolysis is not dependent on the chloride concentration but on the acidity of the medium (as measured by H_0) and the activity of water. Since lysidine is essentially completely present in the acid solutions as lysidinium ion, the rate dependence on acid concentration cannot be due to increasing conversion of lysidine to lysidinium ion.

The linear dependence of the first-order rate constant on acid concentration rather than on H_0 and the rate maximum observed in sulfuric acid are consistent with hydrolysis *via* a transition state composed of lysidinium ion, a proton, and water.[24,32,33]

On the basis of the nmr evidence for diprotonation of lysidine and the rate dependence on acid concentration which indicates incorporation of a proton and water in the transition state, preequilibrium protonation of lysidinium ion followed by rate-determining nucleophilic attack by water on the dication is tentatively proposed as the mechanism for acid hydrolysis of lysidine.

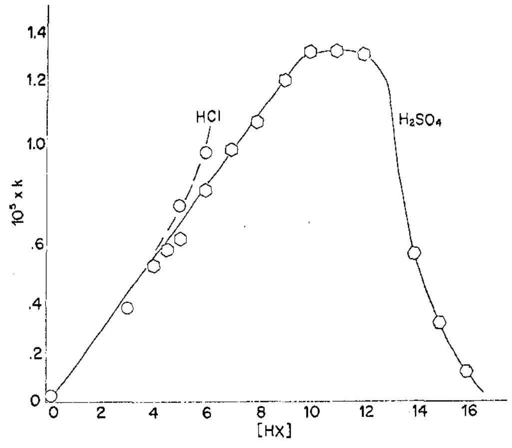
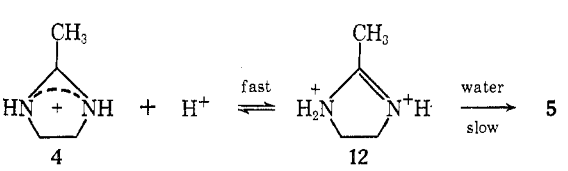


Figure 1.—Dependence of the rate of hydrolysis of lysidinium ion on concentration of acid data from Tables I and II; ○ = HCl, ○ = H_2SO_4.



This mechanism is analogous to that generally accepted for the acid hydrolysis of amides: rate-determining nucleophilic attack of water on the protonated amide.[22] In dilute acid solutions increasing the acid concentration increases the hydrolysis rate by increasing the concentration of the reactive protonated substrate. Since amides are sufficiently basic to be substantially converted to the protonated form in moderately concentrated acid, further increases in acid concentration serve only to decrease the activity of water and consequently result in a decrease in rate.[22]

This cannot be the explanation for the rate maximum in the lysidine hydrolysis because the nmr spectra indicate that lysidinium ion is not substantially protonated below 100% sulfuric acid. The rate maximum must either be the result of a change in rate-determining step[34] or the retarding effect of decreasing water activity is much greater than the accelerating effect of increasing, although negligible, conversion of lysidinium ion to the reactive dication **12** above 11 M sulfuric acid.[25]

Although guanidines are reported to be stable to acid hydrolysis,[35] the results reported here suggest that they and other compounds which form conjugate acids which are highly resonance stabilized and consequently resistant to nucleophilic attack by water may undergo hydrolysis through the dications (the dications of guanidines are known to exist in FSO_3H-SbF_5[30]).

Registry No.—**3**, 534-26-9; **3** (HCl), 26157-55-1; **5**, 1001-53-2; **6**, 3197-11-3; **7**, 26157-58-4; **8**, 5331-48-6; 2-acetamidoethyltrimethylammonium iodide, 3197-12-4; 2-acetamidoethyltrimethylammonium chloride, 26210-94-6.

---

[28] G. S. Hammond and R. C. Neuman, Jr., *J. Phys. Chem.*, 1655, 1659 (1963).

[29] A. R. Katritzky and C. D. Johnson, *Angew. Chem. Int. Ed. Engl.*, **6**, 608 (1967); W. F. Giauge, E. W. Homung, J. E. Kunzler, and T. R. Rubin, *J. Amer. Chem. Soc.*, **82**, 62 (1960), and previous papers is series.

[30] T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **41**, 2642 (1963); G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **90**, 6087 (1968).

[31] K. M. Wellman, D. L. Harris, and P. J. Murphy, *Chem. Commun.*, 568 (1967).

[32] F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

[33] J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1917 (1967).

[34] S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 241 (1967); W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 73 (1964).

[35] J. Eloranta, *Suomen Kemistilehti, B*, **34**, 107 (1961).