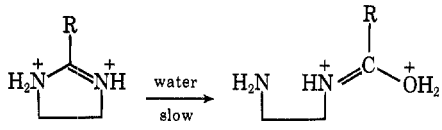
60% aqueous ethanol at 100°.[7] It would seem quite unlikely that negligible electronic effects on the rate of hydrolysis would be obtained if step 2 consisted of a direct displacement reaction by water.



Because the protonation step should exhibit a negative ρ value (protonation of substituted acetophenones has a ρ^+ value of between -2.0 and -3.0[8]) and the direct displacement step should have a negligible ρ value,[9] the overall ρ value for the reaction should be significant and negative. For example, the acid-catalyzed hydrolysis of 2-aryl-1,3-oxathiolanes, which is considered to proceed by an A2 mechanism involving a rate-determining direct displacement by water step, has a ρ value of -1.66.[10]

Acid Effect.—It has been observed that for solutions of similar water activities (and acidity) that the rates of A2 reactions are faster in hydrochloric and sulfuric acids than in perchloric acid, while the reverse is observed for A1 reactions.[11] The data of Table II indicate that the relative rates of hydrolysis of lysidine in the indicated concentrations of perchloric, sulfuric, and hydrochloric acids are 1:2.7:3.1. This order is consistent with that observed for other A2 reactions—for both amides[11b] and esters[11c] the rates of hydrolysis are twice as fast in 4 M sulfuric acid as in 4 M perchloric acid.

Solvent Isotope Effect.—The solvent deuterium isotope effects, $k_{H_2SO_4}/k_{D_2SO_4}$, of 0.71 and 0.78 on the rates of hydrolysis of lysidine in 4 and 14 M sulfuric acid (Table I) are consistent with an A2 reaction in which the preequilibrium protonation of the substrate is fast and incomplete.[10,12] These isotope effects therefore confirm the previous proposal (based on nmr data which indicated that lysidinium ion is significantly protonated only in solutions more acidic that 102% sulfuric acid) that the inverse dependence of lysidine hydrolysis rate on acid concentration above 12 M sulfuric acid is not due to substantial conversion of the substrate to the reactive dication but to the retarding effect of decreasing water activity outweighing the accelerating effect of increasing medium acidity.[1]

In contrast to lysidine, the hydrolysis of acetamide exhibits a solvent isotope effect $[k(H)/k(D)]$ of 0.7 in 0.1 N acid where acetamide is incompletely protonated and an isotope effect of 1.1 in 4 N acid where it is essentially completely protonated.[12]

Entropies of Activation.—Because of their large orientation and steric requirements, A2 reactions have entropies of activation of approximately -15 to -30 eu.[13] For example, the A2 hydrolyses of acetamide, ethyl acetate, and 2-phenyl-1,3-oxathiolane have entropies of activation of -37, -23, and -18 eu, respectively.[10,13]

From the second-order rate constants $k_1/[H_2SO_4]$ calculable from the data of Table I, entropies of activation of -26 and -31 (± 4) eu may be calculated for the hydrolysis of lysidine in 4 and 14 M sulfuric acid (the corresponding enthalpies of activation are 22 and 21 kcal/mol, respectively). These entropy values, being similar to those for known A2 reactions, are consequently consistent with the mechanism of eq 1.

Thus the four mechanistic criteria which we have applied to the acid hydrolysis of the imidazolines have given results which, being consistent with the results expected for an A2 hydrolysis mechanism, provide evidence for the hydrolysis proceeding as outlined in eq 1. The negligible electronic effects on the rates of hydrolysis of the two arylimidazolines provide good evidence for the proposition that step 2 of eq 1 represents rate-determining nucleophilic addition of water to the dication at position 2 to form a tetrahedral addition intermediate which decomposes to the hydrolysis products (or reverts to reactants by loss of water from the dication).

Additional work in this laboratory has provided similar evidence in support of Haake and Watson's[1] proposal that guanidines also hydrolyze by an A2 mechanism analogous to that of eq 1.[14]

Registry No.—Lysidine, 534-26-9.

Acknowledgments.—We are grateful to the National Institutes of Health for support of this research.

(14) S. Limatibul and J. W. Watson, *J. Org. Chem.*, **36**, 3805 (1971).

(7) H. H. Jaffé, *Chem. Rev.*, **53**, 202 (1953).

(8) (a) G. C. Levy, J. D. Cargioli, and W. Racela, *J. Amer. Chem. Soc.*, **92**, 6238 (1970); (b) R. Stewart and K. Yates, *ibid.*, **80**, 6355 (1958).

(9) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 18.

(10) N. C. De and L. R. Fedor, *J. Amer. Chem. Soc.*, **99**, 7266 (1968).

(11) (a) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 934 (1969); (b) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *ibid.*, 1099 (1968); (c) C. A. Bunton, J. H. Carbtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

(12) M. L. Bender, *Chem. Rev.*, **60**, 67 (1960).

(13) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

The Mechanism of Acid Hydrolysis of Guanidines

SUMET LIMATIBUL AND JOSEPH W. WATSON*

Department of Chemistry, University of California, San Diego, La Jolla, California 92038

Received April 13, 1971

On the basis of the nmr spectra of lysidine, 2-methylimidazoline, in concentrated sulfuric acid solutions and the curvilinear dependence of the rate of hydrolysis of lysidine on sulfuric acid concentration, Haake and Watson proposed that imidazolines and similar strong bases, such as guanidines, hydrolyze in acid solutions by rate-determining nucleophilic attack by water on the diprotonated substrate.[1] In a recent paper we have reported additional data which support their proposed mechanism for the acid hydrolysis of amidines.[2] We report in this communication experimental results which indicate that guanidines hydrolyze by an analogous mechanism as proposed by Haake and Watson[1] (eq 1).

The rates of hydrolysis of 1,1,3,3-tetramethylguanidine, TMG, and its expected hydrolysis products, 1,1-dimethyl- and tetramethylureas, were determined by nmr spectroscopy by following the disappearance of the substrate methyl singlet and the formation of the

(1) P. Haake and J. W. Watson, *J. Org. Chem.*, **35**, 4063 (1970).

(2) S. Limatibul and J. W. Watson, *ibid.*, **36**, 3803 (1971).

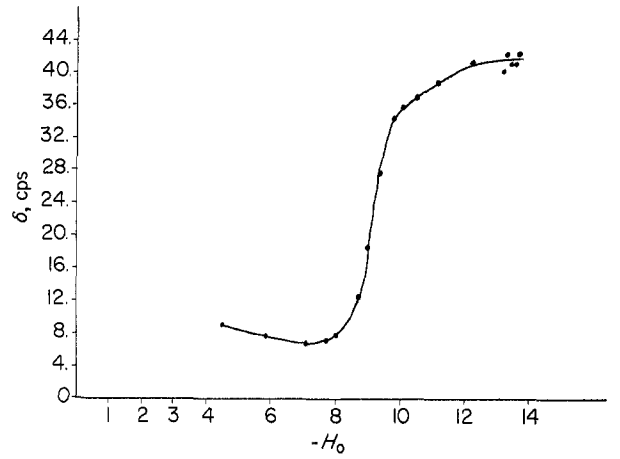
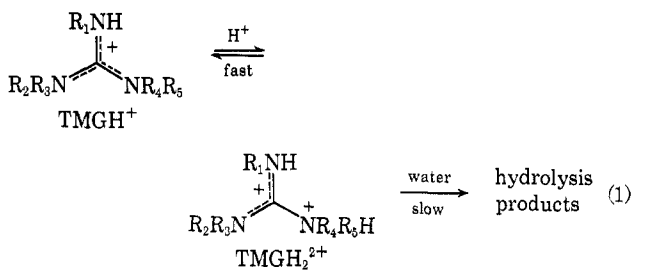


Figure 1.—Plot of the chemical shifts of the methyl protons of TMG relative to the methyl protons of dimethylammonium ion in sulfuric acid *vs.* H_0.

triplet of the hydrolysis product dimethylammonium ion.



The independence of the rate of hydrolysis of urea and ethylurea of acid concentration above 3 *M* H_2SO_4[3] and the observed first-order rate constants listed in Tables I and II indicate that dimethyl- and tetramethylureas

TABLE I

OBSERVED FIRST-ORDER RATES OF HYDROLYSIS OF 1,1-DIMETHYLUREA AND 1,1,3,3-TETRAMETHYLUREA IN SULFURIC ACID[a]

Compd	H_2SO_4, *M*	Temp, °C	10^5k_1, sec^{-1}
1,1-Dimethylurea	4	108.1	1.8
1,1-Dimethylurea	4	138.5	42.7
1,1,3,3-Tetramethylurea	7.5	108.1	7.85
1,1,3,3-Tetramethylurea	7.5	138.5	89.0

[a] Rates determined by nmr with initial concentrations of ureas approximately 0.3 *M*.

hydrolyze considerably faster than TMG hydrolyzes in all the acid concentrations investigated. Therefore, there should be no complication of the determination of the rate of hydrolysis of TMG from a buildup of dimethyl- or tetramethylureas during the course of the TMG hydrolysis.

Because solvation effects on the chemical shifts are expected to be small and $TMGH^+$ has a pK_a of 13.6,[4] the large downfield shift in the methyl singlet of tetramethylguanidine above 84% H_2SO_4 (Table III) suggests protonation of $TMGH^+$ to a diprotonated tetramethylguanidine, $TMGH_2^{2+}$.[1] A plot of the chemical

(3) V. C. Armstrong, E. W. Farlow, and R. B. Moodie, *J. Chem. Soc. B*, 1099 (1968).

(4) I. M. Koltloff, M. K. Chantooni, and S. Blowmik, *J. Amer. Chem. Soc.*, **90**, 23 (1968); S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1968).

TABLE II

OBSERVED FIRST-ORDER RATE CONSTANTS FOR THE ACID HYDROLYSIS OF 1,1,3,3-TETRAMETHYLGUANIDINE[a]

H_2SO_4, *M*	Temp, °C	10^5k_1, sec^{-1}
1	138.5	0.056
2.3	138.5	0.130
3.5	138.5	0.211
4.0	108.1	0.0179
4[b]	108.1	0.0231
4.0	132.0	0.143
4.0	138.5	0.254
4[b]	138.5	0.302
5.0	138.5	0.30
6.0	138.5	0.35
7.5	138.5	0.42
9.0	138.5	0.44

[a] Initial concentration of TMG was approximately 0.3 *M*. [b] In D_2SO_4.

TABLE III

CHEMICAL SHIFTS OF THE METHYL PROTONS OF 1,1,3,3-TETRAMETHYLGUANIDINE IN SULFURIC ACID[a]

% H_2SO_4	δ,[b] cps	$-H_0$[c]
59 (9.0 *M*)	9.2	4.46
70	7.8	5.80
78	6.8	7.03
82	7.2	7.66
84	8.0	7.97
88	12.4	8.61
90	18.4	8.92
92	27.6	9.29
94	34.4	9.68
96	35.6	10.03
98	36.8	10.41
99.5	38.4	11.12
100.0	41.2	12.20
102.0	40.	13.16
102.5	42.	13.29
103.0	40.8	13.38
103.5	40.8	13.47
105	42.	13.71

[a] Concentrations of dimethylamine hydrochloride and tetramethylguanidine were ~0.05 and ~0.03 *M*, respectively. [b] Chemical shifts are in cycles per second downfield from the central peak of the dimethylammonium ion triplet. [c] H_0 values below 60% H_2SO_4 are from (i) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). H_0 values between 60 and 100% H_2SO_4 are from (ii) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963). H_0 values for 100% and above H_2SO_4 are obtained by adding −1.10 H_0 units to the H_0 values of ref i as suggested in ref ii.

shift data, Figure 1, has the appearance of a titration curve with the $TMGH^+$ being half-protonated to the dication in approximately 91% H_2SO_4 (H_0 = −9.1).[5] Treatment of the data by the method of Bunnett and Olsen[6] yields an estimated pK_a of −11 for $TMGH_2^{2+}$ with a ϕ of −0.2. Nmr evidence for diprotonation of guanidines in FSO_3H–SbF_5 has been reported.[7]

The data of Tables II and IV are consistent with the A-2 type mechanism given in eq 1 and are very similar to the results observed for the acid hydrolysis of amidines[1,2] indicating that guanidines and amidines hydrolyze by similar mechanisms in acid solution.

Acid Concentration Effect.—The rate of hydrolysis of TMG increases linearly with acid concentration up

(5) G. C. Levy, J. D. Cargioli, and W. Racela, *J. Amer. Chem. Soc.*, **92**, 6238 (1970).

(6) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899 (1966).

(7) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **90**, 6087 (1968).

TABLE IV
OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF 1,1,3,3-TETRAMETHYLGUANIDINE IN DIFFERENT ACIDS AT 138.5°

Acid	H_0[a]	Log a_{H_2O}[b]	10^5k_1, sec^{-1}
3.5 *M* $HClO_4$	−1.47	−0.106	0.0289
4 *M* HCl	−1.40	−0.107	0.118
3.5 *M* H_2SO_4	−1.62	−0.111	0.211

[a] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956 (1961).

to 6 *M* sulfuric acid suggesting that the transition state for acid hydrolysis consists of a proton, water, and the substrate which is $TMGH^+$ ($pK_a = 13.6$). In solutions more concentrated than 7.5 *M* H_2SO_4, the observed second-order rate constants decreased and the occurrence of a side reaction of undetermined nature was indicated by the nmr spectra of the reaction solutions.

Solvent Isotope Effect.—In 4 *M* sulfuric acid the solvent isotope effects, $k_{H_2SO_4}/k_{D_2SO_4}$, of 0.78 and 0.83 at 108.1 and 138.5°, respectively, are consistent with fast preequilibrium protonation of the substrate as indicated in eq 1. For the hydrolysis of lysidine in 4 *M* sulfuric acid at 90°, $k_{H_2SO_4}/_{D_2SO_4}$ is 0.71.[2]

Entropies of Activation.—From the rates of hydrolysis of TMG in 4 *M* sulfuric acid at 108.1 and 138.5°, activation parameters of $\Delta S = -25$ eu and $\Delta H = 27$ kcal/mol may be calculated for the second-order rate constant $k_1/[H_2SO_4]$. The entropy of activation is very similar to that observed for the acid hydrolysis of lysidine, −26 eu, and other A2 reactions.[2]

Acid Effect.—It has been observed that A2 reactions are faster in sulfuric and hydrochloric acids than in perchloric acid solutions of comparable acidity and water activity.[3] The ratio of hydrolysis rates of TMG in perchloric, hydrochloric, and sulfuric acids of 1:4:7 (Table IV) is consequently consistent with the A2 mechanism of eq 1. The relative order observed for the hydrolysis of lysidine of 1:3.1:2.7 is slightly different.[2]

Thus our experimental results are consistent with the proposal that guanidines hydrolyze by an A2 mechanism as outlined in eq 1 and support the proposition that compounds, such as amidines and guanidines, which form highly resonance-stabilized conjugate acids undergo acid hydrolysis by nucleophilic attack by water on the diprotonated compounds.[1] The present experimental data are not considered sufficient to justify our speculating on whether the nucleophilic attack by water on the diprotonated guanidine consists of nucleophilic addition of water to form a tetrahedral intermediate (as favored for the amidine hydrolysis[2]) or a direct displacement (SN2) reaction analogous to the mechanism proposed for the acid hydrolysis of carbamates.[8a]

Experimental Section

Nmr spectra were determined on a Varian T-60 spectrometer. Acid solutions were standardized as previously described.[1]

Dimethylurea was synthesized from dimethylamine and potassium cyanate[9a] and recrystallized from ethanol, mp 182–183° (lit.[9b] mp 182–183°). Aldrich 1,1,3,3-tetramethylurea was purified by distillation, bp 174–175° (lit.[10] bp 174–177°). Aldrich 1,1,3,3-tetramethylguanidine was purified by distillation, bp 164° [lit.[11] bp 159.5° (745 mm)]. The nmr spectra of the compounds were consistent with their structures.

In the acid solutions employed for the rate determinations, the ureas and 1,1,3,3-tetramethylguanidine absorbed at the same chemical shift and on hydrolysis gave rise to an upfield triplet which was confirmed to be due to dimethylammonium ion. For example, in 4 *M* H_2SO_4 the ureas and the tetramethylguanidine gave singlets at 3.3 ppm upfield from the solvent signal and dimethylammonium ion gave a triplet of 3.5 ppm upfield from the solvent signal. The rates of hydrolysis were determined from plots of $\ln A_R/(A_R + A_P)$ *vs.* time, where A_R is the area of the reactant (urea or guanidine) singlet and A_P equals the area of the product dimethylammonium ion triplet. Linear plots consisting of four to five points and covering approximately 2 half-lives were obtained. The nmr determination of the protonation of tetramethylguanidinium ion was performed as previously described.[1,5]

Registry No.—1,1-Dimethylurea, 598-94-7; 1,1,3,3-tetramethylurea, 632-22-4; sulfuric acid, 7664-93-9; 1,1,3,3-tetramethylguanidine, 80-70-6.

(8) (a) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 934 (1969); (b) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *ibid.*, 1099 (1968); (c) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

(9) (a) F. Arndt, *Org. Syn.*, **15**, 48 (1935); (b) F. Kurzer, *ibid.*, **32**, 61 (1952).

(10) H. Z. Lecler and K. Gubernator, *J. Amer. Chem. Soc.*, **75**, 1087 (1953).

(11) M. L. Anderson and R. N. Hammer, *J. Chem. Eng. Data*, **12**, 442 (1967).

Formation of 2-Alkyl-5-phenyltetrazoles from 1-Alkyl-5-phenyltetrazoles

TYÛZÔ ISIDA,*[1a] SINPEI KOZIMA,[1b] KIYOSHI NABIKA,[1c] AND KEIITI SISIDO[1c]

Department of Industrial Chemistry and College of Liberal Arts and Sciences, Kyôto University, Kyôto, 606, Japan

Received March 29, 1971

It is generally recognized that the reaction of a 1,5-disubstituted tetrazole with alkyl halide or alkyl benzenesulfonate gives a 1,4,5-trisubstituted tetrazolium salt.[2-9] We have found, however, that treatment of 1-alkyl-5-phenyltetrazole with alkyl iodide at 130° gave no tetrazolium salt but rather 2-alkyl-5-phenyltetrazole. To elucidate this novel isomerization process, some experiments were carried out at lower temperatures.

On heating 1-methyl-5-phenyltetrazole (**1**) with methyl iodide at 130° for 10 hr, 2-methyl-5-phenyltetrazole (**2**) was obtained in a quantitative yield. The presence of methyl iodide was essential to this reaction, since there was no conversion without methyl iodide.

Treatment of the 1-methyl isomer **1** with methyl iodide at 70° for 20 hr gave the 2-methyl isomer **2** together with the usual product, 1,4-dimethyl-5-phenyl-

(1) (a) To whom correspondence should be addressed: Department of Industrial Chemistry. (b) College of Liberal Arts and Sciences. (c) Department of Industrial Chemistry.

(2) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, **86**, 1865 (1964).

(3) A. C. Rochat and R. A. Olofson, *Tetrahedron Lett.*, 3377 (1969).

(4) F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Amer. Chem. Soc.*, **73**, 4457 (1951).

(5) G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)*, 1355 (1955).

(6) H. R. J. Waddington, G. F. Duffin, and J. D. Kendall, British Patent 785,334 (1957); *Chem. Abstr.*, **52**, 6030*i* (1958).

(7) S. Hünig and K.-H. Oette, *Justus Liebigs Ann. Chem.*, **641**, 94 (1961).

(8) E. K. Harville, C. W. Roberts, and R. M. Herbst, *J. Org. Chem.*, **15**, 58 (1950).

(9) R. Stolle, F. Pollecoff, and Fr. Henke-Stark, *Chem. Ber.*, **63**, 965 (1930).