The Acid-catalyzed Hydrolysis of 4-Dimethoxymethylpyridinium Ion

BY M. W. FULLER[1] AND W. M. SCHUBERT

First-order rate constants for the hydrolysis of 4-dimethoxymethylpyridine in 36–50% aqueous perchloric acid at 25° have been determined spectrophotometrically. The substrate is essentially all in the form of the pyridinium ion and the hydrolysis occurs by an over-all two-proton process, with a negligible contribution to the rate by a one-proton process. The plot of log k_{obs} vs. $-H_0$ is linear with slope 1.07 ± 0.01, corresponding closely to what has been found for the hydrolysis of methylal in 4–35% perchloric acid.[4,5] Insofar as a similarity of mechanism applies to the two hydrolyses, the results imply that H_+ and H_0 are parallel functions in this instance. The Bunnett w-value for the hydrolysis is -0.34 ± 0.02.

Introduction

The mechanism of the acid-catalyzed hydrolysis of acetals has been studied by a number of workers,[2-5] and it is now generally agreed that the rate-determining step is the unimolecular decomposition of the conjugate acid of the acetal. Studies of the dependence of hydrolysis rate on acidity in moderately concentrated acid solutions have, with one exception,[3] been carried out dilatometrically. This procedure requires a relatively large concentration of acetal and introduces some doubt as to whether one can consider the system as being purely aqueous.[6]

This paper reports the results of a kinetic study of the hydrolysis of the dimethyl acetal of 4-formylpyridine in aqueous perchloric acid. This compound hydrolyzes at a convenient rate in 35–50% perchloric acid at room temperature, and the reaction can be followed spectrophotometrically at concentrations sufficiently low to ensure that the substrate does not change the medium. The acetal is practically completely in the form of the pyridinium ion in these media. Thus a study of the acidity dependence of the hydrolysis reaction might contribute to a knowledge of the behavior of the H_+ acidity function, provided that in the media used the hydrolysis proceeded by a path requiring an additional proton.

Experimental

4-Dimethoxymethylpyridine.—A solution of 4-formylpyridine (58 g.) in anhydrous methanol was saturated with dry hydrogen chloride gas, and allowed to stand for several days at room temperature. The solution was then made alkaline with sodium methoxide in methanol, concentrated on a rotary evaporator, and diluted with water. The product was isolated by extraction with ether and purified by two distillations under reduced pressure. The center cut used in the kinetic work had b.p. 81.3–81.5° (7 mm.), $n^{27}D$ 1.4898 [lit.[7] b.p. 94–103° (11 mm.)]. The infrared spectrum (liquid film) showed no carbonyl absorption, and no impurities were detected by vapor phase chromatography (Aerograph Hy-Fi 600, with flame ionization detector).

Acid Solutions.—Stock solutions were prepared by diluting C.P. 70% perchloric acid, and analyzed by titration of weighed portions with 0.2 M sodium hydroxide which had been standardized against both constant boiling hydrochloric acid and potassium hydrogen phthalate.

Kinetic Procedure.—Kinetic runs were carried out in stoppered quartz cells in a constant temperature bath inserted between the photocell and monochrometer units of a Beckman DU spectro-

photometer. The temperature of the bath was controlled to $\pm 0.02°$ by means of a Sargent Thermonitor unit. Before carrying out a run, the cells were filled with acid of the desired concentration and placed in the cell-holder. After thermal equilibrium was re-established, a small sample of the acetal was quickly introduced, and the increase in the optical density at 282 mμ recorded as a function of time.

Results

In 35–50% perchloric acid, the product of the hydrolysis of 4-dimethoxymethylpyridine is an equilibrium mixture of 4-formylpyridinium ion and its hydrate, 4-dihydroxymethylpyridinium ion. Experiments with 4-formylpyridine showed that the hydrate equilibrium is established very rapidly. Thus the rate of hydrolysis of the acetal could be obtained directly from the increase in optical density with time in the region of the developing spectral peak of the aldehyde.

The hydrolysis reaction usually was followed to 70–90% completion in each medium. The first-order rate constants, obtained from the slopes of the plots of log $(D_\infty - D)$ against time, are recorded in Table I. Instability of the "infinity" readings, due apparently to slow air-oxidation of the product, was occasionally troublesome in the slower runs and prevented extension of rate measurements to lower perchloric acid concentrations.
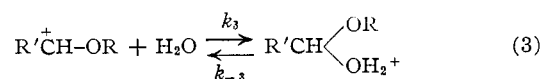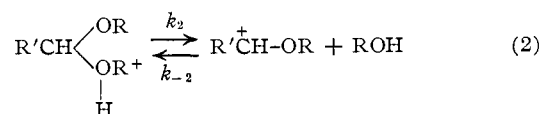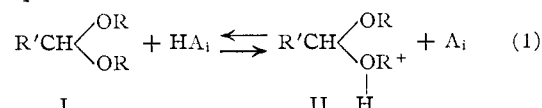
TABLE I

VALUES OF k_{obs} FOR THE HYDROLYSIS OF 4-DIMETHOXYMETHYL-PYRIDINIUM ION IN HClO4 AT 25.00°

HClO4, %	$-H_0{}^a$	$10^4 k_{obs}$, sec.$^{-1}$
36.59	2.04	2.84, 2.92, 2.95, 2.95
39.68	2.31	5.78, 6.03
43.35	2.69	14.1, 14.3, 14.8, 15.2, 15.4, 15.4
44.61	2.83	20.1, 20.8, 21.7
47.27	3.22	54.8, 55.0
49.40	3.53	112, 113, 119
43.35^b	2.69	53.3, 54.1, 53.7
43.35^c	2.69	166, 169, 172, 183, 186, 189

^{a} Values of Paul and Long.[8] ^{b} Values at 35.00°; $\Delta H^{\ddagger} = 22.6 \pm 0.2$ kcal./mole; $\Delta S^{\ddagger} = +4.5 \pm 0.6$ e.u. at 25°. ^{c} Values at 45.00°. The reaction was too fast at this temperature for precise duplication of k_{obs}.

Discussion

Acetal hydrolysis in acid solution may be represented by the eq. 1–4.[2-4]

$$R'CH{\big\langle}^{OR}_{OR} + HA_i \rightleftarrows R'CH{\big\langle}^{OR}_{\underset{\underset{H}{|}}{OR^+}} + A_i \quad (1)$$

$$\text{I} \qquad\qquad \text{II}$$

$$R'CH{\big\langle}^{OR}_{\underset{\underset{H}{|}}{OR^+}} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} R'\overset{+}{C}H\text{-}OR + ROH \quad (2)$$

$$R'\overset{+}{C}H\text{-}OR + H_2O \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} R'CH{\big\langle}^{OR}_{OH_2{}^+} \quad (3)$$

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(2) (a) J. N. Brönsted and C. Grove, J. Am. Chem. Soc., **52**, 1394 (1930); (b) J. N. Brönsted and W. F. K. Wynne-Jones, Trans. Faraday Soc., **25**, 59 (1929); (c) J. M. O'Gorman and H. J. Lucas, J. Am. Chem. Soc. **72**, 123 (1956); (d) F. Stamsiuk, W. A. Sheppard and A. N. Bournes, Can. J. Chem. **34**, 123 (1956); (e) A. Skrabal and H. H. Eger, Z. physik. Chem., **122**, 349 (1926); (f) A. Skrabal and R. Skrabal, ibid., **A181**, 449 (1938); (g) P. M. Leininger and M. Kilpatrick, J. Am. Chem. Soc., **61**, 2510 (1939).

(3) (a) M. M. Kreevoy and R. W. Taft, Jr., ibid., **77**, 5590 (1955); (b) **77**, 3146 (1955).

(4) D. McIntyre and F. A. Long, ibid., **76**, 3240 (1954).

(5) F. A. Long and D. McIntyre, ibid., **76**, 3243 (1954).

(6) Unpublished work by W. M. Schubert and D. W. Brownawell in these laboratories has shown that during the hydrolysis of methylal at dilatometric concentrations in aqueous acids the H_0 value of the solution changes significantly in the course of the reaction.

(7) A. C. J. Opfermann, British Patent 783,430 (September 25, 1957).

(8) M. A. Paul and F. A. Long, Chem. Revs., **57**, 1 (1957).

$$R'CH\diagdown_{\substack{OR\\OH_2^+}} + A_i \rightleftharpoons R'CH\diagdown_{\substack{OR\\OH}} + HA_i \quad (4)$$
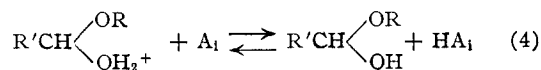
Equations 1 and 4 represent rapid proton-transfer equilibria. Steps 2 and 3 are in principle reversible,[9] with k_{-2} and k_3 and likewise k_2 and k_{-3} of similar orders of magnitude. However, under the conditions of the kinetic runs, i.e., acetal in spectrophotometric concentrations, the very large excess of water over methanol concentration ensures that the *velocity* of step 3-forward is much greater than that of step 2-reverse,[10] making step 2-forward the rate-controlling step in hemiacetal formation. Hydrolysis of the hemiacetal is believed to occur by the same type of mechanism, but at a much faster rate than hydrolysis of acetal to hemiacetal, so that step 2-forward can be considered as the rate-controlling step of the entire hydrolysis.[2-4]

The fact that the observed first-order rate constants for the hydrolysis of 4-dimethoxymethylpyridine increase sharply in 35.6 to 49.4% perchloric acid (Table I) is indicative of an over-all two-proton process, starting with the free pyridine. The substrate in these media is essentially 4-dimethoxymethylpyridinium ion (I, $R=CH_3$, $R' = 4-C_5H_4NH^+$).[11] In fact, protonation of the pyridine is practically complete even in fairly dilute acids. The value of pK_{BH^+} has not been measured, but should not differ greatly from that of 4-methylpyridine, reported[12] as 5.98.

Strictly speaking, the rate constants quoted in Table I contain a small contribution from the "one-proton" hydrolysis of 4-dimethoxymethylpyridine. If the accepted mechanism of acetal hydrolysis applies, then the one-proton process involves unimolecular decomposition of the oxygen conjugate acid of the pyridine (II, $R = CH_3$, $R' = 4-C_5H_4N$), present in small amounts in equilibrium with the 4-dimethoxymethylpyridinium ion. Under the conditions that pertain (i.e., concentration of the pyridinium ion, SH^+, much greater than that of the free pyridine, S), it can be shown that the first-order rate constant for the one-proton process has the simple form of eq. 5, where f_{SH^+} is the activity coefficient of the pyridinium ion and f_{tr^+} is that of the one-

$$k = \text{const.} f_{SH^+}/f_{tr^+} \quad (5)$$

proton transition state.[13] Since the ratio of activity coefficients of the similarly constituted species SH^+ and tr^+ should not vary greatly with medium, it is believed that the one-proton process makes a negligible contribution to the rate constants of Table I. This conclusion is fortified by the fact that solutions of 4-dimethoxymethylpyridine in 0.5 M perchloric acid, in which the pyridine nitrogen is surely practically completely protonated, are stable for several hours at 25°.

Correlation with H_0.—For the over-all two-proton process, application of the mechanism of eq. 1–4, with the second step rate-controlling, leads to the rate expression

$$k_{obs} = (k_2/K_{SH_2^{++}}) a_{H^+} f_{SH^+}/f_{tr_2^{++}} \quad (6)$$

In this equation, $K_{SH_2^{++}}$ is the thermodynamic ionization constant of the doubly protonated intermediate

(II, $R = CH_3$, $R' = 4-C_5H_4NH^+$), f_{SH^+} is the activity coefficient of 4-dimethoxymethylpyridinium ion (I, $R = CH_3$, $R' = 4-C_5H_4NH^+$) and $f_{tr_2^{++}}$ is the activity coefficient of the two-proton transition state. Taking the logarithm of eq. 6 and substituting in H_+, the Hammett acidity function for the protonation of a cationic base (eq. 8),[14] leads to eq. 7.

$$\log k_{obs} = \text{const.} -H_+ + \log(f_{SH^+}f_{CH^{++}}/f_{tr^{++}}f_{C^+}) \quad (7)$$
$$H_+ = -\log a_{H^+} f_{C^+}/f_{CH^{++}} \quad (8)$$

If one makes the standard simplifying assumption that the ratios of activity coefficients of similarly constituted species vary with medium in the same manner, i.e. that $f_{SH^+}/f_{tr_2^{++}} = f_{C^+}/f_{CH^{++}}$, then a plot of log k_{obs} against $-H_+$ should be linear and of unit slope.[14,15] However, there are no values of H_+ available for the perchloric acid range under consideration. Nevertheless, there is reasonable justification for assuming that, outside the very dilute acid range, the various acidity functions, H_+, H_0 and H_- are parallel functions of solvent acid concentration, provided that the indicators used in their determination are structurally similar and the electrical charge is not conjugated with the site of protonation. Protonation of the H_+ bases 2-amino-5-nitroanilinium ion and 4-acetylanilinium ion in 30-55 and 75-95% sulfuric acid, respectively,[16] of a series of nitroanilinesulfonate ions in 2–8 molar perchloric acid[17] and of 4-nitroaniline-3-sulfonate ion in 2–7 molar hydrochloric acid[17] follow the H_0 function based on substituted nitroaniline bases.[8] Similarly, protonation of 3-nitroanilinium ion in fuming sulfuric acid follows the H_0 function based on the protonation of nitrobenzene, 4-nitrotoluene and 2,4-dinitrotoluene.[18,19] On the other hand, the H_- functions based on the structurally different cyanocarbon anions[20] and phosphonate ions[21] show quite different behavior with changing acid concentration.

Figure 1 shows a plot of log k_{obs} vs. $-H_0$ for the hydrolysis of 4-dimethoxymethylpyridinium ion in 36–50% perchloric acid at 25°. The linear correlation between log k_{obs} and $-H_0$ is good, the slope of the least squares regression line being 1.07 ± 0.01. The deviation of the slope from unity could be attributed either to H_+ being a slightly steeper function than H_0 in 36–50% perchloric acid, or to a slight increase, linear with H_0, in log $(f_{SH^+}f_{CH^{++}}/f_{tr^{++}}f_{C^+})$.

Alternatively, log k_{obs}, rather than being expressed in terms of H_+, can be expressed directly in terms of H_0, as in eq. 9, where f_B and f_{BH^+} are activity coefficients for the neutral indicator base (or bases) used in 36–50% perchloric acid. Insofar as the mechanistic assignment

$$\log k_{obs} = \text{const.} -H_0 + \log (f_{SH^+}f_{BH^+}/f_{tr^{++}}f_B) \quad (9)$$

is correct and the H_0 and the k_{obs} values accurate,[22] the 0.07 deviation from unit slope is entirely attributable to an increase in log $(f_{SH^+}f_{BH^+}/f_{tr^{++}}f_B)$ with increasing acid percentage. In this connection, it is to be noted that Long and McIntyre reported that for the hydrolysis of methylal in 5–35% perchloric acid at 25°, the slope of the plot of log k_{obs} against $-H_0$ is 1.08. The additional slope was attributed to medium effects on

(9) The reversibility of the system was utilized in the preparation of 4-dimethoxymethylpyridine from 4-formylpyridine in a large excess of anhydrous methanol and hydrogen chloride as the catalyst (see Experimental section).

(10) Some reversal of step 2 has been found to occur in the hydrolysis of methyl formal in dilatometric kinetic runs, in which the original concentration of acetal is relatively high, ca. 0.25 molar; unpublished results, W. M. Schubert and D. W. Brownawell.

(11) No *measurable* amount of diprotonated species is detectable in the ultraviolet spectrum.

(12) R. J. L. Andon, J. D. Cox and E. F. G. Herrington, *Trans. Faraday Soc.*, **50**, 918 (1954).

(13) Reactions to which eq. 5 applies are under active investigation in these laboratories, as a means of directly evaluating medium effects on the activity coefficient ratio.

(14) L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, Chapter 9.

(15) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1937).

(16) T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 364 (1957).

(17) M. W. Fuller, unpublished work.

(18) J. C. D. Brand, W. C. Horning and M. B. Thornley, *J. Chem. Soc.*, 1374 (1952).

(19) J. C. D. Brand, *ibid.*, 997 (1950).

(20) R. H. Boyd, *J. Am. Chem. Soc.*, **83**, 4288 (1961).

(21) J. N. Phillips, *Austral. J. Chem.*, **14**, 183 (1961).

(22) For the values of log k_{obs} in the acid concentration at the two extremes to define a line of unit slope requires that the value of k_{obs} in 49.4% HClO₄ be 20% smaller, or the value of k_{obs} in 35.6% be 25% greater, or some combination of these changes.
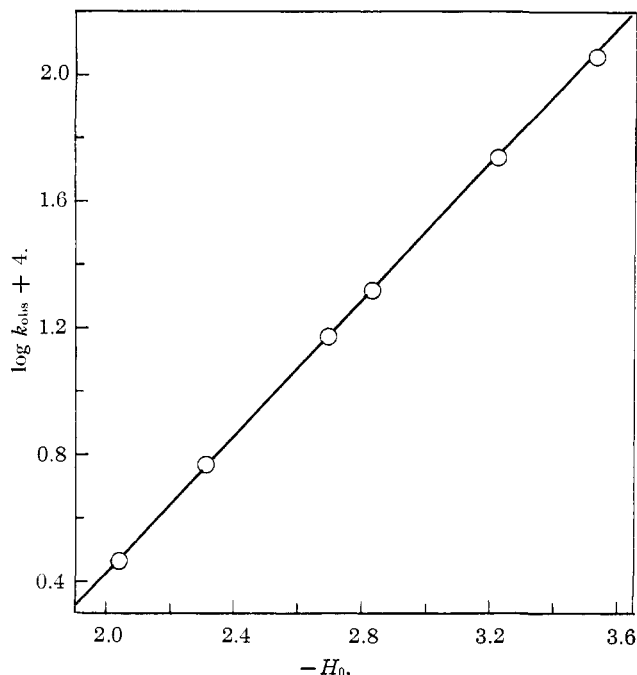
Fig. 1.—Log k_{obs} vs. $-H_0$ for the hydrolysis of 4-dimethoxy-methylpyridinium ion in perchloric acid at 25°

log $(f_M f_{BH^+}/f_{tr} + f_B)$, more specifically to salt effects on f_M, the activity coefficient of neutral methylal, and f_B, that of the indicator base used to measure H_0.[4,5] The similarity between the slopes for methylal and 4-dimethoxymethylpyridium ion hydrolyses implies that d $\log(f_{SH^+}/f_{tr_1^{++}})/dH_0 \cong$ d $\log(f_M/f_{tr_2^+})/dH_0$. This is provided, of course, that d $\log(f_B/f_{BH^+})/dH_0$ is the same for the indicator bases used to measure the H_0 values in the two instances.[23]

The value of $\Delta H^{\ddagger}$ in 43.35% perchloric acid, determined from rate constants at three temperatures

(23) That d $\log(f_B/f_{BH^+})/dH_0$ be the same for all indicator bases is, of course, basic to the entire Hammett scale. However, this can be experimentally verified only for "adjoining" indicator bases over a narrow region of overlap of mineral acid concentrations.[14,15] Whether it remains true for the indicator bases used between 4 and 35% perchloric acid (acid region used for methylal hydrolysis) as compared to those used between 36 and 50% perchloric acid (acid region used for 4-dimethoxymethylpyridinium ion hydrolysis), is a moot question.[15]

(Table I), is 22.6 ± 0.2 kcal./mole, and $\Delta S^{\ddagger}$ at 25° is +4.5 ± 0.6 e.u. The positive entropy of activation is within the range considered normal for one-proton hydrolysis reactions proceeding via an A-1, i.e., Hammett unimolecular, mechanism.[15]

The w-Value.—Bunnett has recently proposed that the value of the parameter w, defined as the slope of the plot of log k_{obs} + H_0 vs. log a_{H_2O}, be used in the precise classification of acid-catalyzed reactions.[24] For reactions which presumably follow the Hammett mechanism, i.e., rate-controlling unimolecular decomposition of substrate conjugate acid, w lies in the range zero to —2.[24c] For the hydrolysis of 4-dimethyoxymethylpyridinium ion in 36–50% perchloric acid the w-value is —0.34 ± 0.02, whereas for methylal hydrolysis in 4-35% perchloric acid it is —2.04 ± 0.19.[24b] This difference in the w-value for two presumably mechanistically identical reactions can be rationalized in the terms used by Bunnett, namely that the w-value equals "hydration of transition state less substrate on a scale set by the 'water balance' in protonation of an indicator base."[24d] That is, one could invoke a solvation-saturation phenomenon in arguing that the increase in solvation hydration in going from a positively charged substrate to a doubly positive transition state is less than in going from a neutral substrate to a transition state having one positive charge.

Our results are pertinent to the problems of the mechanism of hydrolysis of nicotinamide, isonicotinamide and picolinamide.[25] Bunnett has pointed out that hydrolysis of these pyridinium amides has a considerably higher w-value than that of other, neutral, amides and has suggested that this may be due either to the presence of the positive charge on the substrate or to the incursion of another mechanism.[24e] The relative similarity between the w-values for the hydrolysis of methylal and 4-dimethoxymethylpyridinium ion strongly suggests that the latter explanation is the correct one.

(24) (a) J. F. Bunnett, J. Am. Chem. Soc., 82, 499 (1960); (b) 83, 4956 (1961); (c) 83, 4968 (1961); (d) 83, 4973 (1961); (e) 83, 4978 (1961).

(25) (a) H. H. G. Jellinek and A. Gordon, J. Phys. Chem., 53, 996 (1949); (b) H. H. G. Jellinck and J. R. Urwin, ibid., 57, 900 (1953).

COMMUNICATIONS TO THE EDITOR

XENON HEXAFLUORIDE[1]

Sir:

The preparations of XeF_4[2] and XeF_2[3,4] have been reported. We have found that at high excess fluorine pressures a more volatile compound is formed. Chemical and radiochemical analyses show this to be xenon hexafluoride, XeF_6.

In a typical preparation 5.25 millimoles of xenon and 110 millimoles of fluorine were heated for 16 hours at

(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.

(2) H. H. Claassen, H. Selig and J. G. Malm, J. Am. Chem. Soc., 84, 3593 (1962).

(3) J. L. Weeks, C. L. Chernick and M. S. Matheson, ibid., in press.

(4) D. F. Smith, J. Chem. Phys., in press.

300° in a nickel reaction vessel. The pressure in the vessel was calculated to be about 60 atmospheres at 300°. After the reaction the vessel was allowed to cool to room temperature, immersed in a —78° bath, and the excess fluorine pumped off. The volatile product was purified by sublimation into a trap at —78°. A number of preparations have been carried out under similar conditions and yields of XeF_6 of greater than 90% have been obtained.

The formula of the compound has been established as XeF_6 by a method described previously.[2] The hexafluoride was reduced with hydrogen and the xenon and hydrogen fluoride produced were collected and weighed. Results: (1) XeF_6 taken, 0.3934 g.; Xe found 0.2125 g., calculated 0.2106 g.; F found 0.1770 g., calculated