

Acid Hydrolysis of γ -Hydroxybutyramide

R. BRUCE MARTIN, REGINA HEDRICK, AND ALICE PARCELL

Cobb Chemical Laboratory, University of Virginia, Charlottesville, Virginia

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In order to characterize further the unusually rapid rate of acid hydrolysis of γ -hydroxybutyramide compared with butyramide, results are reported for hydrolysis rates over ranges of temperature and acidity. Hydrolysis of protonated γ -hydroxybutyramide proceeds with an activation energy of 14.6 kcal./mole and a pre-exponential term $\log A = 7.2$. Both of these values are less than those obtained for ordinary amides. Plots of the logarithm of the observed first-order rate constant *vs.* the logarithm of activity of water yield abnormally low ω -values from 0.3 to 0.7 in perchloric acid and sulfuric acid at three temperatures. It is suggested that the results can be explained by nucleophilic attack of the hydroxy oxygen at the carbonyl carbon of the protonated amide and water-mediated proton transfer from this oxygen to the nitrogen atom. Pyrrolidone undergoes acid hydrolysis about 10^2 times slower than the corresponding straight-chain amide.

In comparing rates of hydrolysis of a series of hydroxy acid amides with their alkyl analogs of similar chain length, Zörn^{1a} observed that in 1.0 *N* hydrochloric acid γ -hydroxybutyramide, δ -hydroxyvaleramide, and ϵ -hydroxycapronamide were hydrolyzed eighteen or more times faster than normal butyramide, valeramide, and capronamide, respectively. In this paper we undertook a further study of this augmentation in rate for γ -hydroxybutyramide over ranges of acidity and temperature.

Experimental

γ -Hydroxybutyramide was synthesized from γ -butyrolactone and concentrated aqueous ammonia. Melting point of the amide was 52–53° compared with lit.^{1a} m.p. 46° and lit.^{1b} m.p. 53–54°.

Anal. Calcd. for C₄H₉NO₂: C, 46.5; H, 8.8; N, 13.6. Found: C, 46.6; H, 8.8; N, 13.5.

Hydrolysis rates were calculated directly from the decrease in amide absorption at 200 *m* μ as followed on a Cary 11 spectrophotometer and corrected for product absorption. The amide does not exhibit an absorption maximum until further out in the ultraviolet. Under our conditions molar extinction coefficients on the slope at 200 *m* μ for the amide were about 1000 in water, decreasing to about 200 in the concentrated acids, and for the product about 50. Since Zörn^{1a} deduced his rates from an estimate of liberated ammonia, both studies are measuring the rate of disappearance of amide. His single rate value obtained at 30° in 1 *M* hydrochloric acid is consistent with this study. Under the conditions of both studies, hydrolysis of amides is virtually irreversible and appearance of a lactone as an intermediate is irrelevant to the rate analysis. In acid solutions γ -butyrolactone² is hydrolyzed more rapidly than γ -hydroxybutyramide, however. Values of Hammett acidity functions³ and activity of water⁴ were taken from the indicated references.

Results

Observed first-order rate constants for hydrolysis of γ -hydroxybutyramide in solutions 1 or 2 $\times 10^{-3}$ *M* in amide and several concentrations of perchloric acid are presented in Table I. When the observed first-order rate constants are plotted against $-H_0$, a maximum occurs at about $-H_0 = 1.7$ at 25° in perchloric acid. This result is similar to that previously obtained for other amide hydrolyses in acid solutions and suggests that the observed first-order rate constant k' be expressed as

$$k' = ka_{\text{H}_2\text{O}} h_0 / (h_0 + K_a)$$

where k represents the first-order rate constant for hydrolysis of protonated amide at unit activity of water and $h_0 / (h_0 + K_a)$ specifies the fraction of amide in the protonated form. Because protonation of amide is not complete in dilute acids, k may only be determined by studies over a range of acidity and water activity.

TABLE I

OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF γ -HYDROXYBUTYRAMIDE IN PERCHLORIC ACID SOLUTIONS AT 25°

HClO ₄	$k' \times 10^3 \text{ min.}^{-1}$
1.10 pH	0.50
0.20 pH	4.0
1.47 <i>M</i>	7.1
2.40	10.8
3.38	11.9
4.31	13.2
4.38	12.9
5.66	10.3
6.21	9.5
6.36	9.5
7.51	6.1
7.66	7.1
8.30	5.4
8.45	5.0
8.75	4.2

Plots⁵ of $\log k' - \log h_0 / (h_0 + K_a)$ *vs.* $\log a_{\text{H}_2\text{O}}$ for γ -hydroxybutyramide yield straight lines if a suitable value for K_a is chosen. In 0.1 to 9 *M* perchloric acid solutions at 25°, a straight line of slope $\omega = 0.65$ is obtained when $K_a = 4$. These values of ω and K_a are consistent with the position of the maximum on the $-H_0$ scale according to a previously derived relationship relating these three quantities.⁶ From the extrapolation to unit activity of water, we calculate that $k = 1.7 \times 10^{-2} \text{ min.}^{-1}$ in perchloric acid at 25°.

Results for experiments performed at three temperatures in 5 to 9.6 *M* sulfuric acid are shown in Fig. 1 where $-\log k'$ is plotted against $-\log a_{\text{H}_2\text{O}}$. The plots are extrapolated to unit activity of water. Obtaining more experimental points at water activities nearer unity would not aid the extrapolation because a suitable value of K_a would have to be evaluated as the line passes into the region where the amide is not fully protonated. At 15.0°, 25.0°, and 35.0° we obtain $\omega = 0.37, 0.55, \text{ and } 0.30$, and $k = 0.8, 1.8 \text{ and } 4.3 \times 10^{-2} \text{ min.}^{-1}$, respectively. These last three rate constants yield an activation energy of 14.6 kcal./mole, a pre-

(1) (a) L. Zörn, *Ann.*, **631**, 56 (1960); (b) T. C. Bruice and F. H. Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962).

(2) F. A. Long, F. B. Dunkle, and W. F. McDevit, *J. Phys. Colloid Chem.*, **55**, 829 (1951).

(3) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(4) Appendix of first paper of ref. 5.

(5) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

(6) R. B. Martin, *ibid.*, **84**, 4130 (1962).

exponential $\log A = 7.2$, and an activation entropy of about -28 entropy units. Agreement between the two k values in different acids at 25° is satisfactory. Our corresponding values of ω and activation entropy fall far off a plot relating these two quantities for many reactions.⁵

The acid-catalyzed hydrolysis of pyrrolidone or butyrolactam also was studied in sulfuric acid solutions. A plot similar to that of Fig. 1 at 25° yields two straight line portions. From $0.15 < -\log \alpha_{\text{H}_2\text{O}} < 0.3$, $\omega \simeq 1.9$ and $k \simeq 21 \times 10^{-6} \text{ min.}^{-1}$, while from $0.4 < -\log \alpha_{\text{H}_2\text{O}} < 0.75$, $\omega \simeq 0.45$ and the extrapolated value of $k \simeq 7 \times 10^{-6} \text{ min.}^{-1}$. These acid hydrolysis rates for the lactam are about 10^2 times slower than those for straight-chain amides.

Discussion

The kinetically inferred value of $K_a \simeq 4$ is less than the value estimated from a plot of absorption at $200 \text{ m}\mu$ vs. $-H_0$ for γ -hydroxybutyramide. This difference parallels that in other amides. The difficulties associated with equilibrium spectrophotometric determination of K_a in amides have been mentioned⁶; the kinetically determined value is preferable in this case. Evidently the protonation of amides does not follow precisely the Hammett acidity function.⁷ None of the discussion that follows is dependent upon the precise K_a value.

Acid hydrolyses of straight-chain amides exhibit activation energies of about 20 kcal./mole , factors of $\log A \simeq 9.5$, and activation entropies of about -15 e.u. ⁸ Thus the acid hydrolysis of γ -hydroxybutyramide is characterized by comparatively lower activation energies and pre-exponential factors, or a more negative entropy of activation. The greater rate of acid hydrolysis of γ -hydroxybutyramide compared with its straight-chain analog is evidently due to a pronounced lowering of the activation energy which more than offsets a relatively unfavorable pre-exponential or entropy of activation term.⁹

Since successive removal of the hydroxy group from γ - and δ -, to ϵ -positions from the amide function increases ratios of hydrolysis rates for hydroxy amides as compared with alkyl analogs,¹ simple inductive effects cannot account for the augmentation in rates. Some kind of ring formation consistent with a more negative entropy of activation for hydroxyamide hydrolysis is indicated. Nucleophilic attack of the hydroxy group at the carbonyl carbon of the amide protonated at the carbonyl oxygen is suggested because other combinations of reactive groupings would involve intermediate rings of greater than seven members in the case of ϵ -hydroxycapronamide hydrolysis. Considering the results for acid hydrolysis of other amides,¹⁰ we also assume that once nucleophilic attack has occurred loss of amide

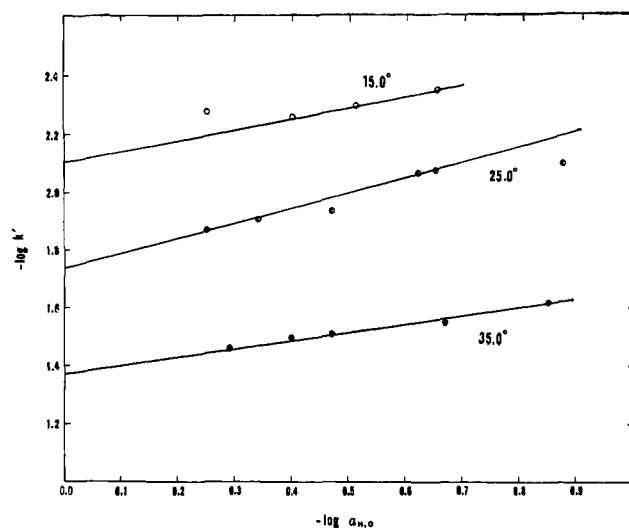


Fig. 1.—Plot of negative logarithm of first-order rate constant in min.^{-1} vs. negative logarithm of activity of water for hydrolysis of γ -hydroxybutyramide in aqueous sulfuric acid solutions at three different temperatures.

function is inevitable; there is no appreciable reversion to reactant.

According to the Bunnett criterion for the role of water in the rate-determining step, $\omega < 0.0$ implies no involvement of water, $+1.2 < \omega < +3.3$ indicates water acting as a nucleophile, and $\omega > +3.3$ suggests water acting as a proton transfer agent.⁵ In the acid hydrolysis of ordinary amides $\omega = 1.2$ to 2.6 indicative of water acting as a nucleophile.⁵ In pyrrolidone hydrolysis the ω -value of about 2 at relatively high water activities is within the usual range for amides. We offer no explanation for the ω -value of about a half for the cyclic amide observed at low activities of water.

For γ -hydroxybutyramide the observed values of $\omega = 0.37$ to 0.65 fall into none of Bunnett's categories. The values are too high for no involvement of water, and in any case a role for water is indicated by the usual explanation given for a maximum in the observed rate constant vs. $-H_0$ plot. We have already concluded that the oxygen atom of the γ -hydroxy group functions as a nucleophile so that the only role remaining for water is that of a proton transfer agent. If this analysis is correct the acid hydrolysis of γ -hydroxybutyramide exhibits the lowest ω -value observed⁵ for participation of water as a proton transfer agent with substrates protonated on oxygen or nitrogen. Can we rationalize ω -values at least 3 units lower than expected for water functioning as a proton transfer agent?

In perchloric acid solutions⁵ hydrolysis of γ -butyrolactone exhibits a value of $\omega = 8.5$ while for the reverse reaction the lactonization of γ -hydroxybutyric acid $\omega = 2.2$. Since water is the nucleophile in hydrolysis while alcohol is the nucleophile in lactonization, there are reasons⁶ for supposing that the difference in ω -values for hydrolysis and lactonization should be 1.2 to 3.3 units, corresponding to that for water functioning as a nucleophile. The observed difference, greater than expected by 3 – 5 units of ω , has been explained by unusual hydration changes brought about mainly by the already heavily hydrated γ -hydroxy group.⁵ We might expect that a similarly hydrated hydroxy group in γ -hydroxybutyramide would yield observed ω -values 3 – 5 units lower in perchloric acid than normal

(7) J. T. Edward and I. C. Wang, *Can. J. Chem.*, **40**, 966 (1962).

(8) B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **20B**, 73 (1942).

(9) We are comparing activation entropies of two pseudo first-order rate constants, and no problems concerning the choice of standard state arise. In comparing activation entropies for similar intramolecular and intermolecular reactions M. Bender [*Chem. Rev.*, **60**, 53 (1960)] has ignored a contribution of about -8 e.u. to activation entropies calculated from second-order rate constants due to the choice of standard state.

(10) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955); C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chem. Ind. (London)*, 1154 (1954).

for water acting as a proton transfer agent. Addition of 3–5 units of ω to our observed value in perchloric acid of 0.65 yields a derived $\omega = 3.6$ –5.7, well within the range suggested for water acting as a proton transfer agent. Thus we conclude that water is involved as a proton transfer agent in the rate-limiting step for acid hydrolysis of γ -hydroxybutyramide.

In a discussion of the results of Zürn,^{1a} Witkop¹¹ suggested a nucleophilic attack of hydroxy oxygen on the carbonyl carbon of the protonated amide and direct

(11) B. Witkop, *Advan. Protein Chem.*, **16**, 221 (1961).

transfer of hydroxy hydrogen proton to nitrogen. In order to accommodate a role for water as a proton transfer agent as indicated in this study, we suggest that the proton transfer from oxygen to nitrogen is mediated by one or more water molecules. Water removes the proton from the hydroxy oxygen and donates another proton to the nitrogen atom.

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The Chemistry of 7-Substituted Norbornenes. The Reaction of Bicyclo[2.2.1]hept-2-en-7-one with Peracid^{1,2}

P. G. GASSMAN AND P. G. PAPE³

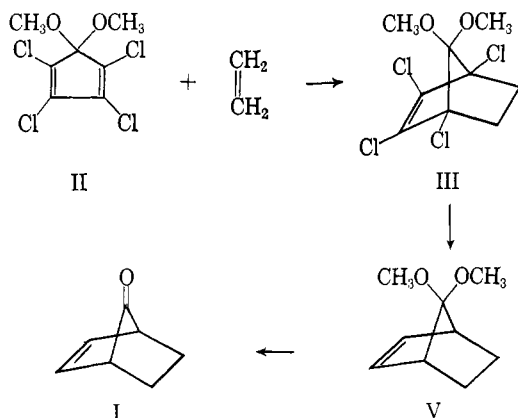
The Department of Chemistry, The Ohio State University, Columbus 10, Ohio

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A short synthetic route to 7-substituted bicyclo[2.2.1]hept-2-enes has been developed. Bicyclo[2.2.1]hept-2-en-7-one has been prepared and was found to react with perbenzoic acid to give the epoxide (XI) rather than the Baeyer–Villiger product, indicating that there is very little interaction between the carbonyl and the non-conjugated double bond.

Although much is known about the chemistry of norbornenes, a relatively small amount of this recorded knowledge deals with the reactions of 7-substituted bicyclo[2.2.1]hept-2-enes. This paucity of information is due to the lack of a simple synthetic route to these relatively unknown compounds. We describe herein a simple four-step synthesis of bicyclo[2.2.1]hept-2-en-7-one (I). Certain reactions of I are discussed. Of particular interest is the reaction of this unsaturated ketone with perbenzoic acid.

Ethylene reacts with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (II) in an inert atmosphere at 180° to yield the expected Diels–Alder adduct (III).⁴ Dechlorination of III according to the procedure of Winstein⁵ gave partial reduction of the double bond



(1) (a) Presented in part before the Division of Organic Chemistry, Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, p. 53M; (b) a preliminary communication of part of this work has appeared: P. G. Gassman and P. G. Pape, *Tetrahedron Letters*, **No. 1**, 9 (1963).

(2) We are indebted to the National Science Foundation, Grant 25221, for partial support of this research.

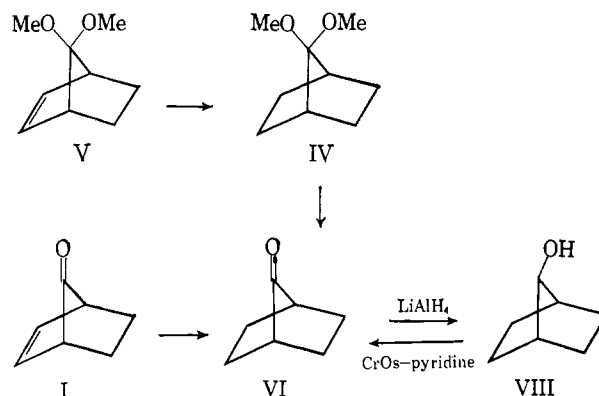
(3) National Science Foundation Summer Fellow, 1962.

(4) P. E. Hoch, *J. Org. Chem.*, **26**, 2066 (1961).

(5) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

resulting in a mixture of saturated and unsaturated ketals, IV and V, respectively. Although this mixture could be separated by extraction of the unsaturated ketal (V) with aqueous silver nitrate solution, this extra purification step was undesirable. Substitution of sodium for lithium in the dechlorination reaction gave pure 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V), which on hydrolysis under acidic conditions gave bicyclo[2.2.1]hept-2-en-7-one (I). The over-all yield of I from II was 45%.

The conversion of bicyclo[2.2.1]hept-2-en-7-one to well characterized compounds was considered to be an essential part of establishing the structure of I. Catalytic hydrogenation of I gave a 92% yield of bicyclo[2.2.1]heptan-7-one (VI), a compound described in the literature as an oil⁶ and as a solid.⁷ Although our sample of the saturated ketone corresponded in melting point to that given in the literature,⁷ the melting point of its 2,4-dinitrophenylhydrazone (VII) did not agree with the literature values.^{6,7} Whereas both Walborsky and Norton list a melting point in the range 133–135°



(6) H. M. Walborsky and D. F. Loncrini, *J. Org. Chem.*, **22**, 1117 (1957).

(7) C. Norton, thesis, Harvard University, 1955.

(8) Norton (ref. 7) reports 134–135° while we have found 137.2–137.8° for the melting point of the 2,4-dinitrophenylhydrazone of I.