

# Acylal Hydrolysis.

## The Hydrolysis of $\gamma$ -Ethoxy- $\gamma$ -butyrolactone

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The hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone to  $\beta$ -formylpropionic acid was studied as a function of pH in water and in 50% dioxane-water at 30°. At low pH a specific hydronium ion catalyzed reaction takes place which on the basis of D<sub>2</sub>O solvent isotope effects ( $k_{D_2O}/k_{H_2O} = 2.37$ ) and the entropy of activation ( $-6.9$  e.u.) can most probably be regarded as an A-1 reaction, proceeding by a pre-equilibrium protonation followed by a unimolecular decomposition of the protonated intermediate. The pH-rate profile shows a large plateau in the pH range 5 to 9 which is most likely due to an S<sub>N</sub>1-type reaction in which the carboxylate anion acts as the leaving group. At alkaline pH values hydroxide ion catalysis occurs.

Carboxyl groups have been implicated in the action of several glycosidic enzymes.<sup>1</sup> Capon<sup>2</sup> has recently studied the nonenzymatic hydrolysis of *o*-carboxyphenyl  $\beta$ -D-glucoside and has found a facile carboxyl group participation. In both enzymatic and nonenzymatic cases, if an intermediate is formed by carboxylate anion attack at the glycosidic carbon, a mixed acetal-acylal will be formed which presumably would hydrolyze rapidly.<sup>3</sup> Skrabal, Brunner, and Airoidi<sup>4</sup> found that mixed acetal-acylals undergo rapid hydrolysis in water; however, little work has been done in the elucidation of the mechanism of hydrolysis of compounds of this type. Therefore, a study of these compounds has been undertaken with the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone described in this paper.

### Experimental

**Materials.**  $\gamma$ -Ethoxy- $\gamma$ -butyrolactone was prepared from ethyl  $\gamma,\gamma$ -diethoxybutyrate (10.2 g., 0.05 mole, b.p. 97–98° (9 mm.),  $n_D^{26}$  1.4148; lit.<sup>5</sup> b.p. 111–116° (16 mm.),  $n_D^{20}$  1.4180). The ester was added to a solution of 4.0 g. of sodium hydroxide in 50 ml. of 95% ethanol. A few drops of water were added until the solution became cloudy. The sodium salt of  $\gamma,\gamma$ -diethoxybutyric acid was collected and washed with absolute ethanol. The salt was added to a small volume of water and extracted once with ether. The aqueous extract was covered with ether and carefully acidified with hydrochloric acid to pH 4 to 5 and quickly extracted several times with ether. The ether extracts were dried over anhydrous sodium sulfate. The ether was removed by flash evaporation after standing. The

residual liquid was heated gently below the boiling point for several hours and then distilled. The  $\gamma$ -ethoxy- $\gamma$ -butyrolactone boiled at 72–73° (5 mm.),  $n_D^{21}$  1.4329; lit.<sup>6</sup> b.p. 95.5° (15 mm.),  $n_D^{20}$  1.4343. The infrared spectrum of the material had an intense band at 1790 cm.<sup>-1</sup> characteristic of five-membered ring lactones.

**Kinetic Measurements.** The kinetics of the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone were measured in water, D<sub>2</sub>O, and 50% dioxane-water (v./v.) at 30 ± 0.1° and at a constant ionic strength of 0.25 M made up with KCl. At pH values less than 3.0 the rates were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer by following the increase in optical density at 280 m $\mu$  due to the aldehyde product. The rates were generally followed to 75% of completion. Infinity points were taken at 10 half-lives and again at 20 to 30 half-lives. The pseudo-first-order constants ( $k_{obsd}$ ) were obtained from the slopes of plots of log [(O.D.<sub>∞</sub> - O.D.<sub>t</sub>)/(O.D.<sub>∞</sub> - O.D.<sub>0</sub>)] vs. time. The pH of each solution was measured on a Model 22 Radiometer pH meter. Constant temperature was maintained in the kinetic runs by circulating water at 30 ± 0.1°, from a Haake Model F constant temperature circulating bath, through a Zeiss constant temperature cell holder.

At pH values greater than 3.0 rates were measured titrimetrically at constant pH with a Radiometer TTT-1 Autotitrator and Radiometer Titrigraph utilizing a Metrohm EA 115X electrode in an airtight, three-necked  $\frac{3}{8}$  Metrohm microtitration cell. Solutions 1.5 to 2.0 ml. in volume were titrated by addition of base (0.03 M KOH in 0.22 M KCl solution) from a syringe (0.4 ml. capacity) by way of a glass capillary which extended into the cell to just above a small bar magnet stirrer. Constant temperature was maintained by circulating water at 30 ± 0.1°, from a Haake Model F constant temperature bath, through the water jacket. At high pH values the cell was thoroughly swept out with nitrogen before commencement of the rate measurement. The rates measured titrimetrically were followed to completion and the pseudo-first-order rate constants were obtained by the method of Guggenheim.<sup>7</sup>

Rates were also measured spectrophotometrically utilizing imidazole and acetate buffers at an ionic strength of 1.0 M with no significant buffer catalysis being observed.

In buffered solutions, even at high buffer concentrations, a slight pH drop generally occurred during the course of the reaction due to the formation of acid from the lactone. For example, with an imidazole buffer (2.31 M) the initial pH was 7.26 and the final pH 7.17. This pH drop would have no effect on the

(1) S. Ono, K. Hiromi, and Y. Yoshikawa, *Bull. Chem. Soc. Japan*, **31**, 957 (1958); B. H. J. Hofstee, *J. Am. Chem. Soc.*, **80**, 3966 (1958).

(2) B. Capon, *Tetrahedron Letters*, **14**, 911 (1963).

(3) A postulated mechanism for  $\alpha$ -amylase action involves such a process: E. H. Fischer and E. A. Stein in "The Enzymes," Vol. 4, P. D. Boyer, H. Lardy, and K. Myrback, Ed., Academic Press Inc., New York, N. Y., 1960, Chapter 19, p. 340.

(4) A. Skrabal, E. Brunner, and H. Airoidi, *Z. physik. Chem. (Leipzig)*, **111**, 109 (1924).

(5) R. M. Acheson, *J. Chem. Soc.*, 4232 (1956).

(6) G. O. Schenck, *Ann.*, **584**, 156 (1953).

(7) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

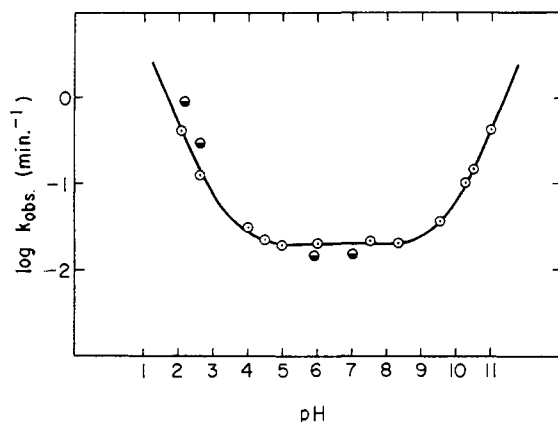


Figure 1. Plot of  $\log k_{\text{obs}}$  vs. pH for the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone in  $\text{H}_2\text{O}$  ( $\odot$ ) and in  $\text{D}_2\text{O}$  ( $\ominus$ , pH = pD) at  $30^\circ$  and  $\mu = 0.25 M$ . The solid line was constructed using the rate constants recorded in Table III and eq. 1.

rate of the reaction since the reaction is pH independent in the range studied.

In a series of runs utilizing the autotitrator at pH 7.0 ionic strength was maintained at 1.0  $M$  with varying amounts of potassium acetate and KCl. Changing the concentration of acetate ion had no effect on the rate.

In work utilizing 99.8%  $\text{D}_2\text{O}$  as the solvent the glass electrode correction formula of Fife and Bruce<sup>8</sup> was employed in the determination of  $a_{\text{D}}$ . The kinetic results are presented in Tables I and II and Figures 1 and 2.

Table I. The Hydrolysis of  $\gamma$ -Ethoxy- $\gamma$ -butyrolactone in Water and Deuterium Oxide at  $30^\circ$ <sup>a</sup>

Water		Deuterium oxide	
pH	$k_{\text{obsd}}$ , min. <sup>-1</sup>	pD	$k_{\text{obsd}}$ , min. <sup>-1</sup>
2.07 <sup>b</sup>	0.419	2.16 <sup>b</sup>	0.919
2.62 <sup>b</sup>	0.132	2.60 <sup>b</sup>	0.302
4.00	0.0313	4.89	0.0195
4.49	0.0230	5.89	0.0152
4.99	0.0202	6.98	0.0157
6.01	0.0207		
7.51	0.0218		
8.30	0.0206		
9.52	0.0379		
10.22	0.106		
10.48	0.151		
11.00	0.445		

<sup>a</sup>  $\mu = 0.25 M$ . <sup>b</sup> Lactone concentration varied from 0.05  $M$  to 0.10  $M$  in the spectrophotometric rate determinations.

Table II. Effect of Temperature on the Hydrolysis of  $\gamma$ -Ethoxy- $\gamma$ -butyrolactone in Water<sup>a</sup>

Temp., °C.	$k_{\text{obsd}}$ , min. <sup>-1</sup>	
	pH 2.07	pH 6.01
13	0.0791	
20	0.184	
30	0.419	0.0207
40	0.893	0.0550
50		0.130
60		0.274

<sup>a</sup>  $\mu = 0.25 M$ . The rate constant at each temperature is an average of three determinations.

(8) T. H. Fife and T. C. Bruce, *J. Phys. Chem.*, **65**, 1079 (1961).

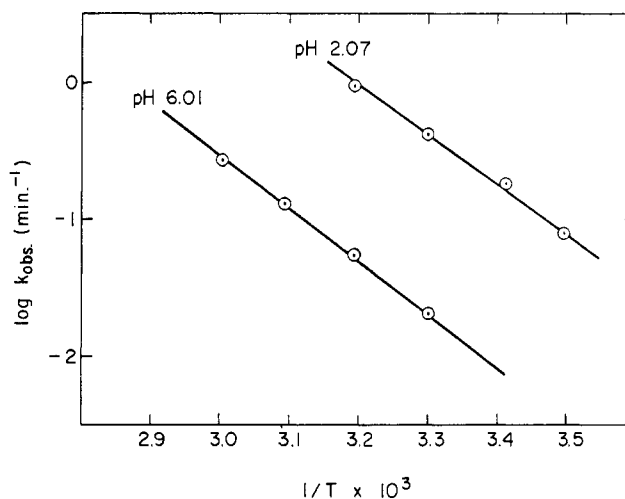


Figure 2. Plot of  $\log k_{\text{obsd}}$  vs.  $1/T \times 10^3$  for the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone at pH 2.07 and 6.01 in  $\text{H}_2\text{O}$ ,  $\mu = 0.25 M$ .

**Alcoholysis Reaction.**  $\gamma$ -Ethoxy- $\gamma$ -butyrolactone (1.2 g.) was added to 75 ml. of anhydrous ethanol. The flask was protected against moisture with a calcium chloride drying tube. The solution was allowed to stand for 24 hr. at room temperature. The ethanol was then removed by flash evaporation. The residual liquid (1.2 g.) had an infrared spectrum identical with starting material. After refluxing for 91 hr. in 75 ml. of absolute ethanol and removal of the ethanol by flash evaporation, the residual liquid still had strong absorption at  $1790 \text{ cm.}^{-1}$  but new bands of approximately equal intensity had appeared at  $1735$  and  $1715 \text{ cm.}^{-1}$ . The region from  $3500$  to  $2500 \text{ cm.}^{-1}$  was typical of a carboxylic acid.

## Results and Discussion

The pH-rate profile for the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone at  $30^\circ$  and  $\mu = 0.25 M$  is shown in Figure 1. It can be seen that there are three important pH regions, one in which an acid-catalyzed reaction takes place, a pH-independent region, and a region in which the reaction is hydroxide ion catalyzed. The equation that is followed is

$$k_{\text{obsd}} = k_0 + k_{\text{H}}a_{\text{H}} + k_{\text{OH}}(\text{OH}^-) \quad (1)$$

where  $k_0$  is the rate constant for the uncatalyzed reaction,  $k_{\text{H}}$  is the second-order rate constant for the acid-catalyzed reaction,  $a_{\text{H}}$  is activity of hydronium ion, and  $k_{\text{OH}}$  is the second-order rate constant for the hydroxide ion catalyzed reaction. The kinetic constants and activation parameters are recorded in Tables III and IV.

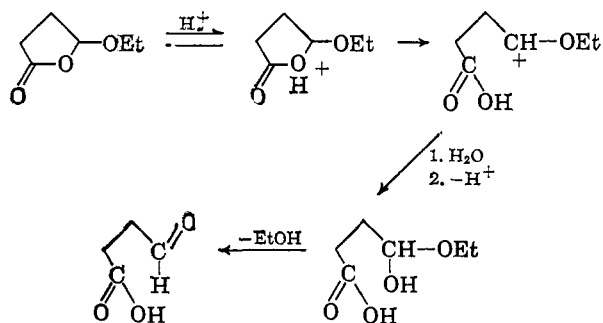
Table III. Rates of Hydrolysis for  $\gamma$ -Ethoxy- $\gamma$ -butyrolactone<sup>a</sup>

Solvent	$k_0$ , min. <sup>-1</sup>	$k_{\text{H}}$ , l. mole <sup>-1</sup> min. <sup>-1</sup>	$k_{\text{OH}}$ , l. mole <sup>-1</sup> min. <sup>-1</sup>
$\text{H}_2\text{O}$	$2.04 \times 10^{-2}$	53.7	294.8
$\text{D}_2\text{O}$	$1.55 \times 10^{-2}$	127.3	
Dioxane- $\text{H}_2\text{O}$ (50%)	$4.12 \times 10^{-4}$	10.5	

<sup>a</sup>  $30 \pm 0.1^\circ$ ,  $\mu = 0.25 M$ .

At low pH the rates were measured spectrophotometrically at 280 m $\mu$  by following the increase in absorption due to the aldehyde product. At pH values above 3.0 the rates were measured titrimetrically on a Radiometer TTT-1 autotitrator.

As can be seen from Figure 1, at low pH values the plot of  $\log k_{\text{obsd}}$  vs. pH is linear with slope of  $-1.0$ , showing the reaction in that pH range to be hydronium ion catalyzed. The D<sub>2</sub>O solvent isotope effect ( $k_{\text{H}^{216}\text{O}}/k_{\text{H}^{16}\text{O}}$ ) of 2.37 is characteristic of a reaction involving a pre-equilibrium protonation followed by a rate-determining, unimolecular decomposition of the protonated intermediate.<sup>9</sup> Supporting evidence for this supposition can be found in the entropy of activation for the acid-catalyzed reaction. The small negative value of  $-6.9$  e.u. would indicate that water is not involved in the transition state,<sup>10</sup> although as pointed out by Whalley<sup>11</sup> this type of evidence cannot be regarded as conclusive since A-2 reactions can have  $\Delta S^*$  values close to zero or even positive due to the positive entropy change associated with protonation. The small negative value of  $\Delta S^*$  for  $\gamma$ -ethoxy- $\gamma$ -butyrolactone differs from the positive values found for other known A-1 reactions.<sup>10</sup> Possible explanations for negative  $\Delta S^*$  values in A-1 reactions of cyclic compounds are: high solvation of the conjugate acids or transition states, or restriction of rotation about the breaking bond in the transition state.<sup>10</sup> It is quite possible that effects such as these are occurring in the present case.<sup>12</sup> The  $\Delta S^*$  value for the acid-catalyzed hydrolysis of  $\gamma$ -butyrolactone, a reaction which is certainly A-2, is  $-20.9$  e.u.,<sup>13</sup> considerably more negative than that for  $\gamma$ -ethoxy- $\gamma$ -butyrolactone. The value of  $\Delta S^*$  in the present case, therefore, reinforces the conclusion of an A-1 reaction derived from the D<sub>2</sub>O solvent isotope effect. Thus, the acid-catalyzed hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone resembles an acetal hydrolysis much more closely than it does an ester hydrolysis proceeding by the common AAC2 mechanism. The most likely scheme, therefore, for the acid-catalyzed reaction is



The most striking feature of the pH-rate profile shown in Figure 1 is the large plateau, extending from approximately pH 5 to 9, the rate of the reaction being pH independent in that range. This profile can be contrasted with that for the hydrolysis of  $\gamma$ -butyrolactone,

(9) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

(10) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

(11) E. Whalley, *Trans. Faraday Soc.*, **55**, 798 (1959).

(12) Positive  $\Delta S^*$  values were found for the acid-catalyzed hydrolysis of methoxymethyl acetate and ethoxymethyl acetate: P. Salomaa, *Acta Chem. Scand.*, **11**, 239 (1957). The acid-catalyzed hydrolysis reactions of a series of cyclic 1,3-dioxolone derivatives, however, have recently been reported to have  $\Delta S^*$  values ranging from  $-4.0$  to  $-8.7$  e.u.: P. Salomaa, *Suomen Kemistilehti*, **37B**, 86 (1964).

(13) F. D. Coffin and F. A. Long, *J. Am. Chem. Soc.*, **74**, 5767 (1952).

Table IV. Activation Parameters for Hydrolysis of  $\gamma$ -Ethoxy- $\gamma$ -butyrolactone in H<sub>2</sub>O<sup>a</sup>

Rate constant	$\Delta H^*$ , kcal./mole	$\Delta S^*$ , <sup>b</sup> e.u.
$k_0^c$	16.9	-18.5
$k_{\text{H}^+}^d$	15.7	-6.9

<sup>a</sup>  $\mu = 0.25$ . <sup>b</sup> Calculated at 30°. <sup>c</sup> Rate constant has the units sec.<sup>-1</sup>. <sup>d</sup> Rate constant has the units l. mole<sup>-1</sup> sec.<sup>-1</sup>.

which shows an acid-catalyzed reaction<sup>14</sup> and a base-catalyzed reaction<sup>15</sup> but no pH independent region.<sup>13</sup>

The plateau rate could be due to: (1) attack of both hydronium ion and hydroxide ion, (2) a water-catalyzed reaction, or (3) a spontaneous uncatalyzed decomposition of substrate. The possibility that the reaction involves catalysis by both H<sub>3</sub>O<sup>+</sup> and -OH can be regarded as highly unlikely. Such a process would have a probable high negative  $\Delta S^*$ . It can be calculated, however, that if an acid-base-catalyzed reaction were occurring, the plateau rate would be characterized by a  $\Delta S^*$  even more favorable than for the hydronium ion catalyzed reaction. From Figure 2 it can be seen that the activation energy at pH 6.01, on the plateau, is slightly higher than that for the acid-catalyzed reaction at pH 2.07. The  $\Delta S^*$  calculated for  $k_{\text{obsd}}$ <sup>16</sup> at pH 6.01 has the value  $-18.5$  e.u.

Attack of water at the carbonyl of the lactone is an unlikely explanation of the plateau rate since the only possibility for facilitation of such a reaction by the  $\gamma$ -ethoxy group would be through an electronic effect. Electron withdrawal would make attack at the carbonyl carbon easier. However, if water can function in such a manner then it would seem likely that general bases such as acetate ion and imidazole could do likewise. Imidazole is approximately 10<sup>8</sup> times more basic than water. No significant catalysis of the reaction could be observed, however, at a concentration of 2.31 M total imidazole at pH 7.26, or 1.0 M acetate ion at pH 7.0. If attack by these bases does take place it must be at a rate which cannot compete with the uncatalyzed reaction. Bruice and Bruno<sup>17</sup> found that imidazole did function as a catalyst for the hydrolysis of  $\gamma$ -butyrolactone and  $\delta$ -valerolactone at 78°, but at 30° catalysis would occur at only very slow rates.

The postulation of attack of water at the  $\gamma$ -carbon in an S<sub>N</sub>2 type reaction is subject to similar difficulties. If water is attacking at that position then it would be expected that other nucleophiles would do so as well. The hydrolysis of  $\beta$ -lactones has been shown to proceed by a pH-independent reaction<sup>18</sup> with this being attributable to a reaction with water at the  $\beta$ -carbon. Gresham, Jansen, and Shaver<sup>19</sup> found that a variety of nucleophilic reagents could react with  $\beta$ -propiolactone. In the neutral reaction the rate constant for attack by

(14) P. Henry, *Z. physik. Chem.*, **10**, 96 (1892); A. Kailan, *ibid.*, **94**, 111 (1920); *ibid.*, **101**, 63 (1922).

(15) D. S. Hegen and J. H. Wolfenden, *J. Chem. Soc.*, 508 (1939).

(16)  $k_{\text{obsd}}$  in sec.<sup>-1</sup>.

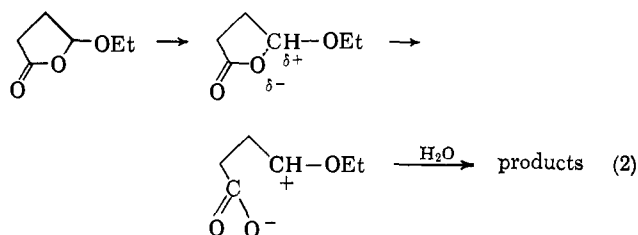
(17) T. C. Bruice and J. J. Bruno, *J. Am. Chem. Soc.*, **83**, 3494 (1961).

(18) A. R. Olson and R. J. Miller, *ibid.*, **60**, 2687 (1938); F. A. Long and M. Purchase, *ibid.*, **72**, 3267 (1950).

(19) T. L. Gresham, J. E. Jansen, and F. W. Shaver, *ibid.*, **70**, 1001 (1948); T. L. Gresham, J. E. Jansen, F. W. Shaver, and J. T. Gregory, *ibid.*, **70**, 999 (1948); T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory, and W. L. Beears, *ibid.*, **70**, 1004 (1948); T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, W. L. Beears, and M. G. Prendergast, *ibid.*, **71**, 661 (1949); T. L. Gresham, J. E. Jansen, F. W. Shaver, and R. A. Bankert, *ibid.*, **71**, 2807 (1949).

acetate ion is considerably larger than that for water,<sup>20</sup> in contrast to the lack of any effect by acetate ion in the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone. Other ions which are good nucleophiles toward  $sp^3$ -carbon attack  $\beta$ -propiolactone readily in aqueous solution but produce only a small effect on the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone. The rate constant for reaction of iodide ion with  $\beta$ -propiolactone in water is considerably greater than that for reaction with water,<sup>20</sup> and is 17.0 times larger than that for chloride ion.<sup>20</sup> Potassium iodide, however, at a concentration of 1.0 *M* increases the titrimetrically determined rate of hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone, at pH 6.02, by only 26% over the rate measured under identical conditions but with 0.25 *M* KCl. Increasing the concentration of KCl from 0.25 to 1.0 *M* produces an identical effect. Sodium thiosulfate attacks  $\beta$ -propiolactone 1050 times faster than chloride ion,<sup>20</sup> but  $\gamma$ -ethoxy- $\gamma$ -butyrolactone hydrolyzes only 2.05 times faster in the presence of 1.06 *M* sodium thiosulfate at pH 7.52 (30°) than with 0.25 *M* KCl added. Such small differences can be regarded as due to ionic strength effects. These experiments in aqueous solution demonstrate conclusively that the tremendous reactivity of nucleophiles toward  $\beta$ -lactones is not present in the hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone. Thus, it is evident that the mechanism for the plateau rate in the present case is quite different than that for the water reaction of  $\beta$ -lactones.

The most logical possibility for the plateau rate is an uncatalyzed elimination of the carboxylate anion as shown in eq. 2. The first-order decomposition would be aided



by several factors: (1) the carboxylate anion being expelled is resonance stabilized and therefore a good leaving group, (2) the carbonium ion formed at the  $\gamma$ -carbon is resonance stabilized by the neighboring ethoxy group, and (3) unimolecular ring cleavage would give rise to a more random state and lead, therefore, to a favorable  $\Delta S^*$  compared to that expected for a bimolecular reaction involving water as a reactant. The actual prediction of  $\Delta S^*$  is, of course, difficult since the developing charges in the transition state will enhance the solvation of the transition state compared to the ground state. The  $\Delta S^*$  value of  $-18.5$  e.u.<sup>16</sup> indicates a high degree of solvation for the transition state. As a consequence, it is possible that some solvent interaction with the incipient carbonium ion is taking place, but it seems clear that bond breaking far exceeds bond making.

Liang and Bartlett<sup>21</sup> found a similar lack of susceptibility to nucleophilic attack in the hydrolysis of  $\beta$ -isovalerolactone and postulated that an  $S_N1$  type ionization was occurring. The stability afforded the carbonium ion at the  $\beta$ -position by the presence of two substituent methyl groups is, therefore, sufficient to change

(20) P. D. Bartlett and G. Small, *J. Am. Chem. Soc.*, **72**, 4867 (1950).

(21) H. T. Liang and P. D. Bartlett, *ibid.*, **80**, 3585 (1958).

the mechanism from one involving attack by water, as exemplified by other  $\beta$ -lactones, to one involving a unimolecular decomposition. That carbonium ion stability is a key factor is further indicated by the present data. The rate constant,  $k_0$ , for hydrolysis of  $\gamma$ -ethoxy- $\gamma$ -butyrolactone at 30°, is one-fourth as large as the corresponding rate constant for  $\beta$ -isovalerolactone at 25°,<sup>21</sup> so increasing ring strain increases the rate of unimolecular ring cleavage as would be expected. The  $k_0$  values associated with both  $\gamma$ -ethoxy- $\gamma$ -butyrolactone and  $\beta$ -isovalerolactone are greater than for  $\beta$ -butyrolactone or  $\beta$ -propiolactone<sup>21</sup> where water is attacking the lactone.

The effect of changing the dielectric constant of the solvent is striking, the plateau rate being one-fiftieth as fast in 50% dioxane-water as in water. This difference most probably represents the difficulty of charge separation in the solvent of lower dielectric constant. The acid-catalyzed reaction is one-fifth as fast in 50% dioxane-water as in water.

Mixed acetal-acylals have previously been found to undergo reaction with alcohols to give mixtures of esters and acetals.<sup>22</sup> The isolation of acetals in high yield indicates that alcohol is attacking at the carbon bearing the two oxygen substituents in these compounds, although on the basis of these experiments nothing can be ascertained about the relative importance of bond breaking and bond making in the transition state. The alcoholysis reaction was carried out with  $\gamma$ -ethoxy- $\gamma$ -butyrolactone in anhydrous ethanol with no catalyst present. The solution was allowed to stand at room temperature for 24 hr. The infrared spectrum of the isolated material (quantitative recovery) was identical with that of the starting material, showing the alcoholysis reaction to be extremely slow in comparison with the uncatalyzed reaction in water, again demonstrating the importance to the reaction of the dielectric constant of the solvent. Even after 91 hr. at reflux temperature in absolute ethanol the infrared spectrum of the isolated material still had strong absorption due to lactone at 1790  $cm^{-1}$ , but other bands of about equal intensity were then evident at about 1735 and 1715  $cm^{-1}$ , indicating that a reaction had occurred. Alcohols, on the other hand, react at a much more rapid rate with  $\beta$ -propiolactone<sup>19</sup> where nucleophilic attack is undoubtedly occurring. Heating  $\beta$ -propiolactone in excess ethyl alcohol with no added catalyst at 65° for only 16 hr. gave 73% alkoxy acid, 2% alkoxy ester, and 15% polymeric residue.<sup>19</sup>

## Conclusions

The data presented in this paper show that mixed acetal-acylals such as  $\gamma$ -ethoxy- $\gamma$ -butyrolactone undergo a facile reaction at neutral pH in which the rate-determining step is probably unimolecular ring cleavage.<sup>23</sup> Thus, the hydrolysis of this compound, in which the structural features of both an acetal and a simple ester have been incorporated into the same molecule, is much favored at neutral pH values over that of simple compounds of either type. The formation of such an intermediate in an enzyme-catalyzed hydrolysis of a

(22) M. F. Shostakovskii and N. A. Gershstein, *J. Gen. Chem. USSR*, **21**, 1602 (1951).

(23) Salomaa<sup>12</sup> has recently suggested that 2-methyl-substituted 1,3-dioxolones may undergo a similar reaction.

glycoside where a carboxyl group at the active site of the enzyme is participating in the reaction could, therefore, lead to significant catalysis.

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## Alkylation and Carbonation of Ketones by Trapping the Enolates from the Reduction of $\alpha,\beta$ -Unsaturated Ketones

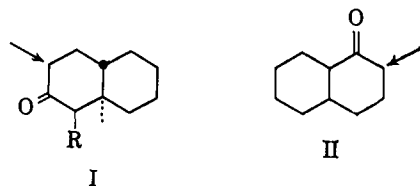
Gilbert Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji

Contribution from the Chandler Laboratories, Columbia University, New York 27, New York. Received August 31, 1964

Evidence is given that during the course of the reduction of  $\alpha,\beta$ -unsaturated ketones with lithium in liquid ammonia the  $\beta$ -carbon atom becomes nucleophilic and can be alkylated by a suitably placed electrophilic center. In the more usual case, the  $\beta$ -carbon becomes protonated by ammonia leading to an enolate ion. Full details are given of the method briefly reported in a preliminary communication,<sup>1</sup> by which trapping of that enolate ion with an alkyl halide or carbon dioxide leads to an alkylated or carboxylated saturated ketone in which the new group appears on the carbon which was the  $\alpha$ -carbon of the original  $\alpha,\beta$ -unsaturated system. The method has been used with six- as well as five-membered unsaturated ketones, with or without a hydrogen on the  $\alpha$ -carbon. The free hydroxyl group of 4-methyltestosterone did not interfere with the reaction which led to 4,4-dimethyl-dihydrotestosterone.

Some progress in solving the problems involved in the alkylation of carbonyl compounds has been made by the introduction of the enamine alkylation method,<sup>2</sup> and later of the Schiff-base magnesium salt alkylation procedure.<sup>3</sup>

Situations not amenable to these solutions occur when an alkyl or carboxyl group must be introduced on that  $\alpha$ -carbon atom which is not substituted by these methods. Two such situations are represented by the *trans*-2-decalone (I, R = H or alkyl) and the 1-decalone (II) systems where these methods—as well as direct base alkylation of the free ketone—lead to substitution at the position marked by an arrow.<sup>4</sup> There are a number of instances where it would be synthetically useful to introduce substituents on the other  $\alpha$ -carbon, to produce III and IV.

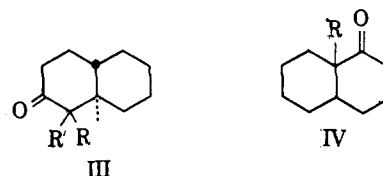


(1) G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).

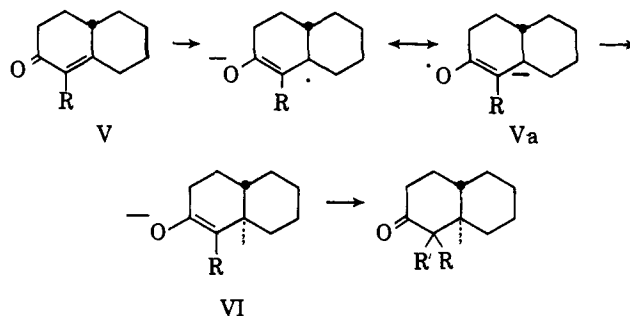
(2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(3) G. Stork and S. Dowd, *ibid.*, **85**, 2178 (1963).

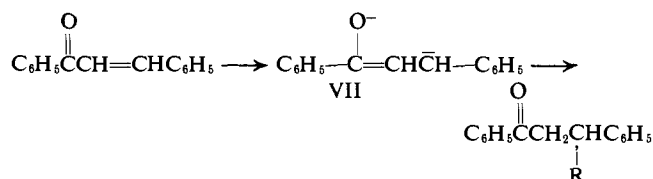
(4) Cf. (a) A. R. Pinder and R. Robinson, *J. Chem. Soc.*, 1224 (1952); (b) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).



Various methods involving the use of blocking groups to prevent enolization in the unwanted direction are available,<sup>5</sup> but we were intrigued by the possibility that one of the most useful methods for the synthesis of a ketone such as I, *i.e.* the lithium–ammonia reduction of the corresponding  $\alpha,\beta$ -unsaturated ketone V, should lead to an enolate ion VI which might be alkylated faster than it could isomerize.



Previous work by Hauser<sup>6</sup> has shown that the metal–ammonia reduction of benzalacetophenone leads to a dianion VII which undergoes monoalkylation at the more nucleophilic position,  $\beta$  to the oxygenated carbon;



but in unsaturated ketones of the type under consideration here, one would expect that a  $\beta$ -carbanion, not being stabilized by resonance with a benzene ring as in VII, should be sufficiently nucleophilic to abstract

(5) Cf. W. S. Johnson, *ibid.*, **65**, 1317 (1943); A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944); W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947); R. B. Woodward and A. A. Patchett, *J. Chem. Soc.*, 1131 (1957); R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962); T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **84**, 1750 (1962).

(6) P. J. Hamrick, Jr., and C. R. Hauser, *ibid.*, **81**, 493 (1959).