

investigated with the purpose of obtaining a method for selective isolation of fragments of the carbon chain of butyrate. The products of the oxidation, carbon dioxide, acetic acid, acetone, acetaldehyde, propionaldehyde, and an unidentified non-volatile compound have been determined quantitatively and their  $C^{13}$  contents measured. Identification of the acetaldehyde and propionaldehyde is tentative.

From  $CH_3CH_2CH_2C^{13}OOH$  the only products that contained excess  $C^{13}$  were carbon dioxide and the non-volatile fraction. The other products, therefore, are formed from the  $\alpha$ ,  $\beta$  and  $\gamma$  carbons of the butyric acid. From  $CH_3C^{13}H_2CH_2C^{13}OOH$  each product was found to contain excess  $C^{13}$ . The excess  $C^{13}$  in the acetone was determined by iodoform degradation to be

exclusively in the carbonyl group. Using this type of degradation the  $C^{13}$  in the carboxyl and  $\beta$  positions of the butyrate can be measured quantitatively. The average of the  $\alpha$  and  $\gamma$  carbons is also obtained.

The exact origin of the acetic acid and acetaldehyde could not be definitely established. It will be necessary to oxidize butyrate which is labelled at either the  $\alpha$  or  $\gamma$  position to obtain this information.

The  $CH_3C^{13}H_2CH_2C^{13}OOH$  was isolated from butyl alcohol fermentations of corn mash to which  $CH_3C^{13}OOH$  was added. The distribution of the  $C^{13}$  in the molecule supports the suggestion that butyl alcohol is formed by a condensation of acetic acid or its derivative.

AMES, IOWA

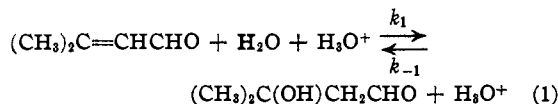
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[CONTRIBUTION NO. 973 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

## The Hydration of Unsaturated Compounds. XII. The Rate of Hydration of $\beta,\beta$ -Dimethylacrolein and its Equilibrium with $\beta$ -Hydroxyisovaleraldehyde<sup>1</sup>

BY H. J. LUCAS, W. T. STEWART AND D. PRESSMAN

The reaction involved in the hydration of  $\beta,\beta$ -dimethylacrolein is shown by Eq. 1



We have measured the rate constants,  $k_1$  and  $k_{-1}$  of the hydration and dehydration reactions, respectively, and the equilibrium constant,  $K$ , at 20°, 25° and 35° in 0.5 and 1.0 *N* nitric acid solutions of various ionic strengths as regulated by potassium or sodium nitrate.

The hydration reaction was found to be first order with respect to the concentration of the hydronium ion since at constant ionic strength the initial slopes of the curves obtained by plotting  $(1-x)$  against  $t$  are proportional to the hydronium ion concentrations (Fig. 1). Here  $x$  is the fraction of the  $\beta,\beta$ -dimethylacrolein which has been hydrated at time  $t$ . The value of the slope is 0.014 at 1.04 *N* nitric acid and 0.007 at 0.52 *N* nitric acid and 0.52 *N* potassium nitrate.

The reversibility of the reaction was shown indirectly by permitting reaction mixtures to come to equilibrium at 15 or 25°. When the temperature was then raised to 35° the fraction of unsaturation became greater, approaching by dehydration the value of  $(1-\epsilon)$  determined by direct hydration at 35°.

The hydration and dehydration reactions are first order with respect to  $\beta,\beta$ -dimethylacrolein and  $\beta$ -hydroxyisovaleraldehyde, respectively. This is shown by the straight line character of

the curves obtained by plotting  $\log_{10} \epsilon/(\epsilon-x)$  against  $t$  (Fig. 2), which is the case for two first order reactions coming to equilibrium according to the integrated equation, Eq. 2

$$\log_{10} \epsilon/(\epsilon-x) = (k_1 + k_{-1})t/2.303 \quad (2)$$

The data of Table I, plotted in Figs. 1 and 2, are typical values.

TABLE I  
EXPERIMENTAL DATA OF HYDRATION OF  $\beta,\beta$ -DIMETHYLACROLEIN AT 25° AT IONIC STRENGTH 1.04<sup>a</sup>

HNO <sub>3</sub> , 1.04 <i>N</i> , $\epsilon = 0.28$ Time, hr.	$(1-x)$	HNO <sub>3</sub> , 0.521 <i>N</i> , $\epsilon = 0.28$ Time, hr.	$(1-x)$
0.58	0.991	1.74	0.989
1.08	.985	4.63	.968
1.48	.978	18.42	.897
1.95	.974	26.67	.867
2.40	.967	43.74	.814
2.85	.964	68.08	.766
3.35	.961	94.90	.732
4.00	.950	117.00	.718
4.68	.945	139.00	.710
5.17	.939	162.70	.701
5.83	.935	187.00	.698
13.63	.868	212.00	.695
47.68	.748	234.13	.689
101.87	.717	283.77	.689
147.57	.704	331.00	.687
217.57	.690		

<sup>a</sup> Regulated by potassium nitrate.

The determination of  $\epsilon$  was complicated by the fact that there was a slow decrease in unsaturation even after equilibrium should have been reached (Fig. 1). On this account  $\epsilon$  could not be deter-

(1) Previous communication, XI. THIS JOURNAL, 64, 1953 (1942).

TABLE II

KINETIC DATA FOR THE HYDRATION OF  $\beta,\beta$ -DIMETHYLACROLEIN AND THE DEHYDRATION OF  $\beta$ -HYDROXYISOVALERALDEHYDE

Temp., °C.	$\mu$ , N	(H <sub>3</sub> O <sup>+</sup> ), N	$\beta,\beta$ -Dimethyl- acrolein, initial M	$\epsilon$	K	$k_1$ hr. <sup>-1</sup>	$k_{-1}$ hr. <sup>-1</sup>	$k_1/(H_3O^+)$	$k_{-1}/(H_3O^+)$
20	1.04 <sup>a</sup>	0.520	0.019	0.32	0.47	0.00440	0.00935	0.00849	0.0180
20	1.04	1.040	.018	.32	.47	.00893	.0190	.00859	.0182
25	0.52	0.520	.021	.30	.43	.00664	.0155	.0128	.0298
25	1.04 <sup>b</sup>	.520	.021	.28	.39	.00705	.0181	.0136	.0348
25	1.04 <sup>a</sup>	.520	.021	.28	.39	.00705	.0181	.0136	.0348
25	1.04	1.04	.021	.28	.39	.0135	.0346	.0130	.0332
25	1.88 <sup>a</sup>	0.922	.022	.27	.37	.0105	.0284	.0114	.0306
35	0.52	.520	.018	.26	.35	.0200	.0567	.0385	.109
35	1.04 <sup>b</sup>	.520	.017	.25	.33	.0193	.0579	.0371	.111
35	1.04 <sup>a</sup>	.520	.017	.25	.33	.0202	.0604	.0387	.116
35	1.04	1.04	.018	.25	.33	.0376	.1125	.0362	.108
35	1.88 <sup>a</sup>	0.922	.020	.24	.32	.0334	.1060	.0362	.115

<sup>a</sup> Potassium nitrate added. <sup>b</sup> Sodium nitrate added.

mined directly. Moreover, it was not possible because of the nature of the data to determine  $\epsilon$  precisely by the analytical method involving choice of  $\epsilon$  to give the best straight line in a plot of  $\log_{10} \epsilon/(\epsilon - x)$  against time such as in Fig. 2.

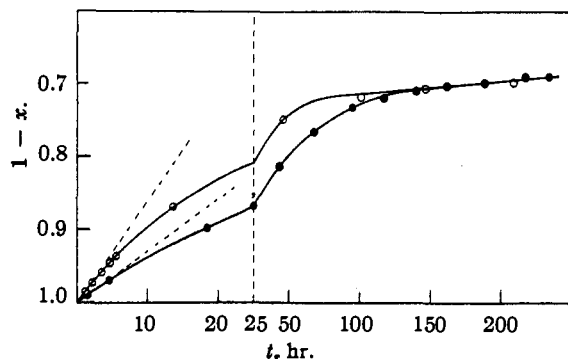


Fig. 1.—Hydration of  $\beta,\beta$ -dimethylacrolein at 25° at ionic strength 1.04: ○, HNO<sub>3</sub> = 1.04 N; ●, HNO<sub>3</sub> = 0.52 N.

However, at any one temperature  $d\epsilon/dt$ , the rate of drift of  $\epsilon$  was approximately the same at the different hydrogen ion concentrations and ionic strengths. It was 0.00004, 0.00011 and 0.00022 hr.<sup>-1</sup> at 20, 25 and 35°, respectively. Therefore,  $\epsilon$  was determined from plots of  $(1 - x)$  against time, by extrapolating to zero time. Smooth curves such as in Fig. 1 were drawn through the experimental points. Using the above values of  $d\epsilon/dt$ , extrapolation was made to zero time from the point at which the hydration had progressed 99% toward equilibrium. The 99% point was taken at a time thrice as long as was required for the reaction to go 80% toward equilibrium. The latter can be determined much more precisely. The factor 3 is general in any equilibrium between two opposing first order or pseudo first order reactions. The values of  $\epsilon$  thus derived are in Table II.

The rate constants of the hydration and dehydration reactions, *viz.*,  $k_1$  and  $k_{-1}$ , respectively,

were calculated by the use of Eqs. 2 and 3

$$K = k_1/k_{-1} = \epsilon/(1 - \epsilon) \quad (3)$$

The values of  $(k_1 + k_{-1})$  were determined from the slopes of plots of  $\log_{10} \epsilon/(\epsilon - x)$  against  $t$ . The values of  $K$ ,  $k_1$  and  $k_{-1}$  are in Table II. Also

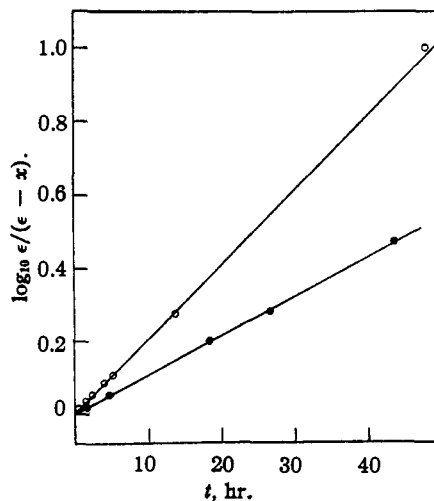


Fig. 2.—Hydration of  $\beta,\beta$ -dimethylacrolein at 25° at ionic strength 1.04: ○, HNO<sub>3</sub> = 1.04 N; ●, HNO<sub>3</sub> = 0.52 N.

in Table II are listed the values of  $k_1/(H_3O^+)$  and of  $k_{-1}/(H_3O^+)$ . The good agreement at the same temperature and same ionic strength between different values of  $k_1/(H_3O^+)$  shows that the hydration is first order with respect to hydronium ion concentration. A similar conclusion holds for the dehydration.

The hydronium ion concentration was taken as equal to the total hydrogen ion concentration. No correction was made for the amount combined as oxonium complex with the aldehydes since we estimate that this would be less than 1%, similar to the case of the mesityl oxide-diacetone alcohol system.<sup>2</sup>

(2) D. Pressman, L. Brewer and H. J. Lucas, *THIS JOURNAL*, **64**, 1117, 1122 (1942).

**Effect of Hydronium Ion and Salts on the Reaction Constants.**—The equilibrium constant,  $K$ , was found to be constant at any one temperature at constant ionic strength. This indicates that the basic strength, *i. e.*, the tendency to coordinate with the proton in aqueous solution, is the same at constant ionic strength, within the experimental error of  $\pm 3\%$  for  $\beta, \beta$ -dimethylacrolein and for  $\beta$ -hydroxyisovaleraldehyde.<sup>2</sup>

No appreciable difference in effect was observed when the ionic strength was regulated by sodium nitrate or potassium nitrate. However, when the ionic strength is increased at constant hydronium ion concentration, the value of  $K$  decreases.

No consistent effect of hydronium ion concentration or of ionic strength was observed on the values of  $k_1/(H_3O^+)$  or of  $k_{-1}/(H_3O^+)$ . The average of the per cent. mean deviation in these values at any given ionic strength and temperature is  $\pm 2\%$ . Thus any effect due to exchanging positive ions is limited to this range.

**Drift of the Position of Equilibrium.**—The amount of unsaturation did not reach a final constant equilibrium value, but decreased at a low steady rate. This reasonably may have been due to dissociation of the hydroxyaldehyde to acetone and acetaldehyde, to oxidation of the aldehydes by nitric acid and/or polymerization of the aldehydes. When the initial concentration of  $\beta, \beta$ -dimethylacrolein was increased to twice the value in the runs reported (Table II), a slight cloudiness actually developed after sixteen hours. This probably was a polymer. Perchloric acid seemed to cause the formation of cloudiness more rapidly than nitric acid. In the nitric acid solutions a faint positive test for oxides of nitrogen was obtained with iodide ion. The presence of oxides of nitrogen has the effect of accentuating the drift since they liberate iodine during the analysis.

**Thermochemistry.**—In Table III are values for the heat of hydration,  $\Delta H$ , and for heats of activation of hydration and dehydration,  $\Delta H_1^\ddagger$ , and  $\Delta H_{-1}^\ddagger$ , respectively. For the temperature interval 25 to 35°, five values of  $\Delta H$  were cal-

culated by the integrated van't Hoff equation from data at different acidities and ionic strengths. Two values of  $\Delta H$  were obtained from the slopes of the plots of  $\log_{10} K$  (at 20, 25 and 35°) against the reciprocal of the absolute temperature. The over-all mean, giving equal weight to all values, is  $-3.2$  kcal.

Values for heats of activation were calculated from  $k_1$  and  $k_{-1}$  in an analogous manner using the integrated Arrhenius equation for the data at 25 and 35°, and the slopes of the plots of  $\log_{10} K$  against the reciprocal of the absolute temperature for the data at 20, 25 and 35°. The average activation energies are:  $\Delta H_1^\ddagger$ , 19.1 kcal./mole;  $\Delta H_{-1}^\ddagger$ , 22.4 kcal./mole.

### Experimental

**$\beta, \beta$ -Dimethylacrolein.**—The preparation followed the method of Fischer, Ertel and Löwenberg<sup>3</sup> through the steps, isovaleraldehyde,  $\alpha$ -bromoisovaleraldehyde,  $\alpha$ -bromoisovaleraldehyde diethyl acetal,  $\beta, \beta$ -dimethylacrolein diethyl acetal and hydrolysis of this to  $\beta, \beta$ -dimethylacrolein. Unfortunately this aldehyde is difficult to keep, due to its pronounced tendency to polymerize. However, the acetal was found to be satisfactory since it hydrolyzes rapidly in dilute aqueous acid.

**$\beta, \beta$ -Dimethylacrolein Diethyl Acetal.**—This was purified by distillation through a fractionating column at 60 mm. The fraction distilling at 89.5–90.0° had  $n_D^{20}$  1.4200. By the bromine absorption method described later the compound analyzed 1.02 double bond per mole. This material was set aside in sealed ampoules and remained unchanged until needed.

The hydrolysis of the acetal in dilute aqueous acid is so rapid that it can be used in place of the aldehyde as the starting material. When 0.2 ml. of the acetal was shaken with 10 ml. of water, two phases resulted and the amount of acetal which dissolved was negligible. When 1 drop of 6 *N* sulfuric acid was added to the mixture and this was again shaken vigorously, the organic phase disappeared almost immediately. The acid concentration here was very much lower than in the actual hydration experiments, while the acetal concentration was much higher. Thus the hydrolysis of the acetal would be essentially complete before the hydration measurements were started.

**Preparation of Solutions.**—Solutions of known acidity and ionic strengths were prepared from standard nitric acid and sodium nitrate or potassium nitrate solutions, diluting with water if necessary. A definite volume of a solution having the desired acidity and ionic strength was brought to the desired temperature and then a measured amount of the acetal was added. No correction was made for the change in volume on the addition of the aldehyde, about 2 ml. per liter. This change was essentially the same in all experiments. The solution was vigorously shaken for ten seconds and placed in the thermostat controlled within  $\pm 0.05^\circ$ . Duplicate samples were removed immediately for analysis. The course of the hydration was followed by analysis of other samples at suitable intervals.

**Analysis.**—When attempt was made to determine the amount of unsaturation by the usual bromate–bromide procedure,<sup>4</sup> the results were unsatisfactory. The amount of bromine consumed exceeded the theoretical value and this became greater, the greater the excess of bromine taken and the longer the time of bromination. Moreover the end-point was indistinct, for iodine was slowly reformed after the free iodine had been titrated with thiosulfate. This would continue for some time. The drift in the end-point was in the direction of the theoretical olefin value. These results probably were due to a slow inverse sub-

TABLE III

THERMAL DATA CONCERNING HYDRATION AND DEHYDRATION

$\mu, N$	$(H_3O^+)$	$\Delta H$ hydration, kcal.	$\Delta H_1^\ddagger$ , kcal.	$\Delta H_{-1}^\ddagger$ , kcal.
0.52	0.52	-3.6	20.2	23.8
1.04 <sup>a</sup>	0.52	-2.9	19.2	22.1
		-3.6 <sup>c</sup>	18.3 <sup>c</sup>	22.0 <sup>c</sup>
1.04 <sup>b</sup>	0.52	-2.9	18.5	21.3
1.04	1.04	-2.9	18.7	21.6
		-3.6 <sup>c</sup>	17.6 <sup>c</sup>	22.0 <sup>c</sup>
1.88 <sup>a</sup>	0.922	-2.9	21.2	24.1
	Average	-3.2	19.1	22.4

<sup>a</sup> Regulated by potassium nitrate. <sup>b</sup> Regulated by sodium nitrate. <sup>c</sup> Calculated from slope of the three-temperature curve.

(3) F. G. Fischer, L. Ertel and K. Löwenberg, *Ber.*, **64**, 30 (1931).

(4) H. J. Lucas and W. F. Eberz, *This Journal*, **56**, 460 (1934).

stitution reaction of a tribromo derivative of isovaleraldehyde produced by a substitution reaction of bromine with  $\alpha,\beta$ -dibromoisovaleraldehyde, the addition product first formed.

In the presence of mercuric sulfate<sup>5</sup> satisfactory analyses are possible by the procedure which follows. Into a 300 ml. g. s. conical flask, protected from the light by a black cloth or black coating, is pipetted 25.0 ml. (an excess) of 0.05 *N* bromate-bromide solution (0.00833 *M* in potassium bromate, *ca.* 0.1 *M* in potassium bromide). The flask is closed with a stopper carrying a stopcock and is evacuated. Then 10 ml. of 6 *N* sulfuric acid is run in and after waiting five minutes for the liberation of bromine, 15 ml. of 0.2 *N* mercuric sulfate, 2 *N* in sulfuric acid is added, followed by 25 ml. of the aqueous solution to be analyzed. The contents are well mixed by vigorous shaking and after standing for one and one-half minutes the reaction is stopped by the addition of 20 ml. of 2 *N* sodium chloride. Then 15 ml. of 20% potassium iodide is added and the liberated iodine is titrated with 0.025 *N* sodium thio-sulfate. Variation in the time of bromination from

(5) H. J. Lucas and D. Pressman, *Ind. Eng. Chem., Anal. Ed.*, **10**, 140 (1938).

one and one-half to five minutes caused no appreciable change in the analysis. The end-point did not drift with time. Known amounts of  $\beta,\beta$ -dimethylacrolein diethyl acetal gave 1.02 double bond per mole.

### Summary

$\beta,\beta$ -Dimethylacrolein hydrates in dilute aqueous nitric acid at a rate which is first order with respect to the aldehyde and to the acid catalyst. The reaction comes to equilibrium. In 1 *N* acid the hydration is 25% at 35°, 28% at 25°, and 32% at 20°. The position of equilibrium is not noticeably affected by changes in the acid concentration.

The heat of hydration of  $\beta,\beta$ -dimethylacrolein,  $\Delta H$ , is -3.2 kcal., the heat of activation of the hydration,  $\Delta H^\ddagger$  is 19.1 kcal. and the heat of activation of the dehydration of  $\beta$ -hydroxyisovaleraldehyde,  $\Delta H^\ddagger_{-1}$ , is 22.4 kcal. per mole.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

## $\omega$ -4-Morpholinehexyl Diphenylacetate<sup>1</sup>

BY W. R. COLEMAN AND W. G. BYWATER

During the course of an investigation of the pharmacological activity of a series of esters in this Laboratory<sup>2</sup> one,  $\omega$ -4-morpholinehexyl diphenylacetate hydrochloride (S-29), was found to possess outstanding spasmolytic properties. Subsequent and more detailed study<sup>3</sup> confirmed the preliminary work and it became desirable to prepare larger quantities of this promising ester for complete toxicological studies and to initiate a clinical trial. We have, therefore, investigated its preparation in more detail in an effort to improve the yields originally obtained. Several new derivatives of *n*-hexyl diphenylacetate have been made during this investigation.

The reaction previously devised<sup>2a</sup> consisted of heating potassium diphenylacetate and hexamethylene bromide in dry xylene and, without isolating the intermediate bromoester, adding morpholine to the reaction mixture to obtain the desired ester. Employing a mole ratio of potassium diphenylacetate:hexamethylene bromide:morpholine of 1:1:2, the yields of ester varied between 10 and 36%. In the present study it has been found that the use of the potassium salt and the bromide in the molecular ratio of 1:2, isolation of the  $\omega$ -bromohexyl diphenylacetate, and then causing the latter to react with morpholine, afforded yields of 56-61%. Moreover, one troublesome by-product, 1,6-di-4-morpholinehexane, is eliminated although hexamethylene bis-diphenylacetate is formed in small quantities.

(1) Original manuscript received May 17, 1943.  
 (2) (a) Cheney and Bywater, *THIS JOURNAL*, **64**, 970 (1942);  
 (b) Rowe, *J. Am. Pharm. Assoc.*, **31**, 57 (1942).  
 (3) Chase, Lehman and Yonkman, *J. Pharmacol.*, **31**, 174 (1944).

The over-all yield from hexamethylene glycol is 41-45%.

Synthesis of the morpholine hexyl ester via hexamethylene chlorohydrin proved to be the more satisfactory method. The alcohol,  $\omega$ -4-morpholinehexanol, was prepared from hexamethylene chlorohydrin by the procedure of Anderson and Pollard.<sup>4</sup> Condensation of the alcohol with diphenylacetyl chloride gave a 91.6% yield of  $\omega$ -4-morpholinehexyl diphenylacetate hydrochloride, or an over-all yield of 48-50% based upon hexamethylene glycol.

Incidental to the study of the reaction, the products from one run in which the mole ratio of salt:bromide:morpholine was 1:1:2, were isolated and identified. As was expected, the following compounds were found:  $\alpha$ - $\omega$ -di-4-morpholinehexane dihydrochloride (21.4%), hexamethylene bis-diphenylacetate (7.6%),  $\omega$ -4-morpholinehexyl diphenylacetate hydrochloride (10%) and diphenylacetic acid (42% recovery). Unreacted hexamethylene bromide was not recovered.

### Experimental

**Hexamethylene Chlorohydrin and Chloride.**—One mole of hexamethylene glycol refluxed with 15 g. of cuprous chloride and 360 ml. of concentrated hydrochloric acid for two hours, and then continuously extracted with toluene during sixteen to eighteen hours while the reaction mixture was heated in a water-bath at 95-100°, gave 8-10% of hexamethylene chloride and 64-66% of the chlorohydrin, b. p. 114-117° (20 mm.),<sup>5,6</sup>  $n_D^{20}$  1.4550. If the mixture

(4) Anderson and Pollard, *THIS JOURNAL*, **61**, 3439, 3440 (1939).  
 (5) Boiling points were determined with 76 mm. immersion thermometers. No stem correction has been made.  
 (6) Bennett and Turner, *J. Chem. Soc.*, 814 (1938), give the b. p. as 116-117° (19 mm.).