

## Aldol Reactions of Formaldehyde in Non-aqueous Media

### V.\* Acid-catalyzed Reaction of 4-Hydroxy-4-methyl-2-pentanone with Formaldehyde

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The acid-catalyzed enolization of 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol) was studied by means of NMR spectroscopy in dioxane-D<sub>2</sub>O 1:1. It was found that the compound was dehydrated *via* a rate-controlling enolization in the 3-position. The observed rate constant for the enolization in the 1-position was shown to be about twice as large as that for the enolization in the 3-position. The former constant was of the same magnitude as that for the enolization in the 1-position of 4-methyl-2-pentanone. In chloroform solution diacetone alcohol reacted with formaldehyde under the influence of boron trifluoride etherate to give 5-acetyl-4,4-dimethyl-1,3-dioxane at a rate about 100 times larger than that of the formation of 5-acetyl-5-isopropyl-1,3-dioxane from 4-methyl-2-pentanone.

In Part IV<sup>1</sup> of this series a mechanism for the acid-catalyzed reaction of 2-butanone with formaldehyde in chloroform and nitromethane solutions was proposed. The high reactivity of the intermediate  $\beta$ -hydroxy ketone, 3-hydroxymethyl-2-butanone, towards formaldehyde in the non-aqueous media was explained by the assumption that the compound was rapidly converted to a hemiformal, which underwent enolization assisted by an intramolecular  $\alpha$ -hydrogen abstraction followed by cyclization with formaldehyde to the end product, 5-acetyl-5-methyl-1,3-dioxane.

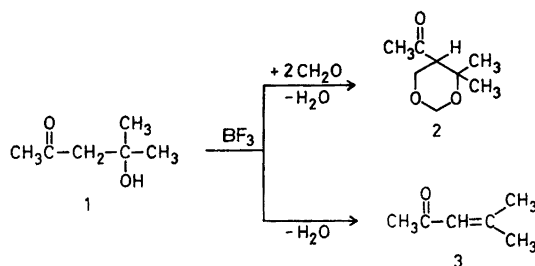
Not only hydroxymethyl compounds display an extraordinarily high reactivity towards formaldehyde in chloroform solution and in the presence of acid catalysts. In the present paper it is shown that diacetone alcohol, which is a  $\beta$ -hydroxy-ketone containing a tertiary hydroxyl group, reacts rapidly with formaldehyde in the presence of boron trifluoride etherate with the formation of a 1,3-dioxane.

\* Part IV, see Ref. 1.

## RESULTS AND DISCUSSION

Addition of a solution of diacetone alcohol (*1*, Scheme 1) in chloroform to a refluxing chloroform solution of trioxane and boron trifluoride etherate gave two major reaction products, 5-acetyl-4,4-dimethyl-1,3-dioxane (*2*), and 4-methyl-3-penten-2-one (mesityl oxide, *3*), the latter product arising from the dehydration of diacetone alcohol. The yield of the 1,3-dioxane *2* (38 %)

SCHEME 1



was found to be slightly higher than that of the dehydration product *3* (34 %). However, when the catalyst was added to a refluxing chloroform solution of the reactants, a yield of only 5 % of the 1,3-dioxane *2* was obtained while the yield of the unsaturated compound *3* amounted to about 70 %. In the latter case the trioxane content of the reaction mixture did not change appreciably during the reaction. This may be explained by the formation of a strong complex between diacetone alcohol and boron trifluoride, the latter component thus being hindered in its action as a catalyst in the depolymerization of the trioxane. Substitution of paraformaldehyde for trioxane increased the yield of the 1,3-dioxane (*2*) to 40 % with a simultaneous decrease in the yield of mesityl oxide.

The reactivity of diacetone alcohol towards aqueous formaldehyde in the presence of sulfuric acid was found to be very low. The acid catalyst only caused dehydration of the alcohol, as in the case of 3-hydroxymethyl-2-butanone,<sup>1</sup> and mesityl oxide (*3*) was obtained together with unchanged diacetone alcohol. Since enolization of the ketone component is believed to be the first step in acid-catalyzed aldol reactions of ketones with aldehydes,<sup>2-3</sup> it was of interest to obtain some information on the rate and direction of the enolization of diacetone alcohol in aqueous medium. This was accomplished by the technique used for 3-hydroxymethyl-2-butanone,<sup>1</sup> *i.e.* deuteration of the  $\alpha$ -positions of the ketone by deuterium oxide and analysis of the reaction mixture by means of NMR spectroscopy.<sup>1,4-8</sup> The experiments were carried out with DCl in dioxane-D<sub>2</sub>O 1:1 (*cf.* Ref. 7), where the expected dehydration product *3* is easily soluble. The following results were obtained (Fig. 1).

1. Diacetone alcohol was dehydrated to mesityl oxide (*3*), and equilibrium between the two compounds was practically established during the experiment.

2. The observed rate of deuteration in the 3-position of diacetone alcohol was almost zero at first, but increased during the reaction.

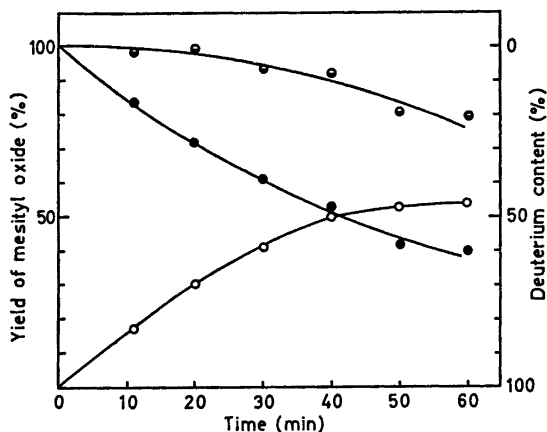
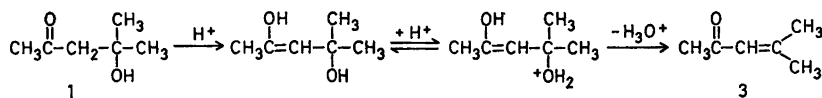


Fig. 1. Treatment of diacetone alcohol (1) with DCl (2.1 M) in dioxane-D<sub>2</sub>O 1:1. Formation of mesityl oxide (3), ○; deuteration in the 1-position, ●; deuteration in the 3-position, ●.

3. The rate of deuteration in the 1-position was greater than that in the 3-position.

Pressman, Brewer and Lucas<sup>9</sup> have shown that the rate of the acid-catalyzed dehydration of diacetone alcohol is proportional to the concentration of the catalyst. In a paper concerning the dehydration of  $\beta$ -hydroxy ketones<sup>10</sup> Noyce and Reed point out, on the basis of their own and of other authors' results, that the rate of dehydration of an alcohol *via* a carbonium ion mechanism should be proportional to Hammett's acidity function  $h_0$ . Those  $\beta$ -hydroxy ketones, however, which are dehydrated with rates proportional to the concentration of the catalyzing acid, *i.e.* the hydrogen ion concentration, are dehydrated *via* a rate-determining enolization (*cf.* Ref. 3, p. 121, and Ref. 11). Thus, the latter mechanism is valid for the dehydration

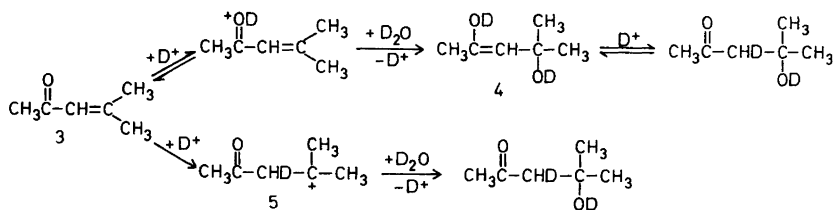
## SCHEME 2



of diacetone alcohol (Scheme 2). Additional evidence for this view is provided by the present results (Fig. 1) which show that the rate of the deuteration of diacetone alcohol in the 3-position was practically zero in the beginning of the reaction (item 2), *i.e.* reversal of the enolization did not occur. The increasing rate of deuteration in the 3-position is explained by the fact that the reversible dehydration of diacetone alcohol to mesityl oxide almost reached equilibrium during the experiment (item 1). As the concentration of mesityl

oxide increases, its hydration will take place to an increasing extent during the experiment, either *via* the enol 4 or the carbonium ion 5<sup>9</sup> (Scheme 3), either way introducing deuterium into the 3-position of the diacetone alcohol.

SCHEME 3



The dehydration of diacetone alcohol, which proceeds at a rate determined by the rate of enolization in the 3-position, consumes one of the hydrogen atoms in the 3-position with the formation of water; the remaining hydrogen is found in the 3-position of the mesityl oxide formed. The back-reaction, *i.e.* the hydration of mesityl oxide, introduces deuterium instead of hydrogen in the 3-position of diacetone alcohol, and since deuterium does not enter into the NMR integrals, the observed rate of the enolization will be equal to the rate of disappearance of hydrogen atoms in the 3-position, diacetone alcohol and mesityl oxide being counted together. The reaction follows the integrated pseudofirst-order rate equation<sup>6</sup>

$$-\ln \frac{(\text{H})_3}{(\text{H}_0)_3} = k_{\text{obs. CH}_3} \times t$$

where  $(\text{H})_3$  is the normalized NMR integral of the hydrogen atoms in the 3-positions of diacetone alcohol and mesityl oxide (the integrals of the 4- $\text{CH}_3$  groups of the two compounds together counted as six),  $(\text{H}_0)_3$  the normalized integral of the hydrogens in the 3-position present at the start of the experiment, and  $k_{\text{obs. CH}_3}$  the observed rate constant for enolization in the 3-position. The rate constant for enolization in the 1-position of diacetone alcohol,  $k_{\text{obs. CH}_3}$ , is given by the integrated rate equation

$$-\ln \frac{(\text{H})_1}{(\text{H}_0)_1} = k_{\text{obs. CH}_3} \times t$$

where  $(\text{H})_1$  is the normalized integral of the hydrogen atoms remaining in the 1-position of diacetone alcohol (the integral of the 4- $\text{CH}_3$  groups of diacetone alcohol counted as six), and  $(\text{H}_0)_1$  the normalized integral of the hydrogens present in the 1-position at the start of the experiment. As can be seen in Fig. 2, which gives the results of the deuteration experiment, the observed rate constant for enolization in the 1-position is about twice as large as that for the 3-position.

According to Rappe and Sachs<sup>7</sup> 4-methyl-2-pentanone (12), which lacks the hydroxyl group of diacetone alcohol, is deuterated and brominated under

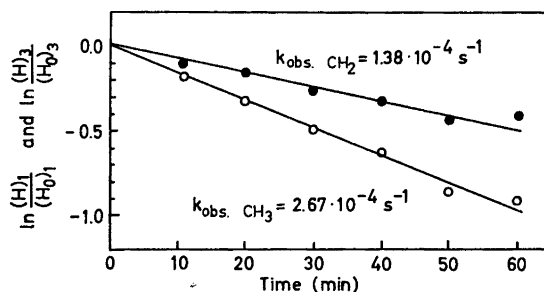


Fig. 2. First-order plot of DCl-catalyzed enolization of diacetone alcohol (I). Temperature, 37°; acid concentration, 2.1 M. Enolization in the 1-position, ○; enolization in the 3-position, ●.

acid conditions in aqueous medium at similar rates in both  $\alpha$ -positions. The rate constant for 1-deuteration is of the same magnitude as that found for the 1-deuteration of diacetone alcohol, provided that the former constant is re-calculated with respect to the acid concentration used in the latter case. Furthermore, the rate constant for deuteration in the 3-position of ketone 12 was found by the same authors to be about half that found for deuteration in the 3-position of 2-butanone. The rates of deuteration in the 3-positions of 2-pentanone and 2-hexanone were found to be of intermediate order. In Fig. 3 time-yield curves are given for the formation of 1,3-dioxanes (9–11, and 13–14; Scheme 4) from trioxane and 2-butanone (6), 2-pentanone (7), 2-hexanone (8), and 4-methyl-2-pentanone (12), respectively, in refluxing chloroform and in the presence of boron trifluoride etherate,<sup>12</sup> as well as for the forma-

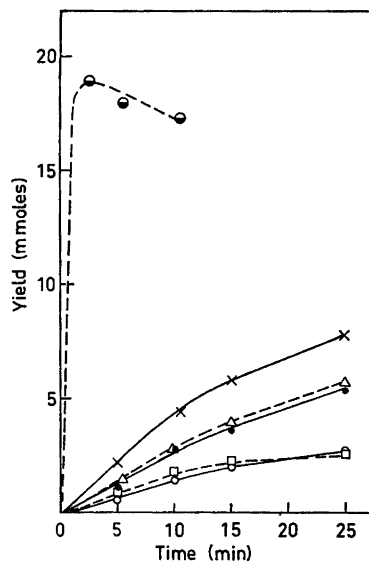
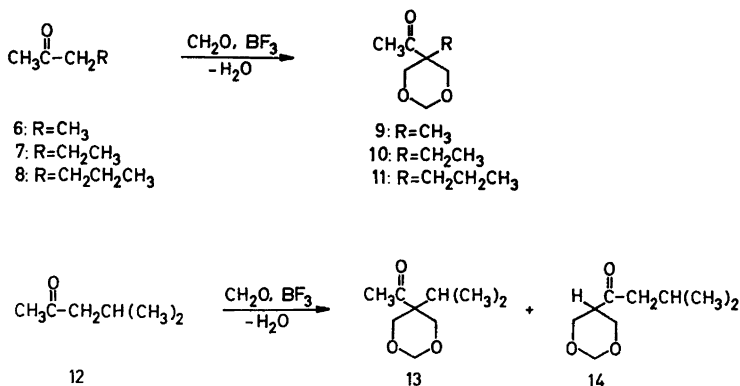


Fig. 3. Formation of 5-acetyl-4,4-dimethyl-1,3-dioxane (2), ●; 5-acetyl-5-methyl-1,3-dioxane (9), ×; 5-acetyl-5-ethyl-1,3-dioxane (10), ●; 5-acetyl-5-propyl-1,3-dioxane (11), △; 5-acetyl-5-isopropyl-1,3-dioxane (13), ○; and 5-isovaleryl-1,3-dioxane (14), □. Refluxing chloroform; boron trifluoride etherate as catalyst.

SCHEME 4



tion of 5-acetyl-4,4-dimethyl-1,3-dioxane (2) from diacetone alcohol (1) and paraformaldehyde under similar conditions.

It may be noted that the rates of formation of 1,3-dioxanes 9–11 and 13–14 did not change on changing the initial trioxane concentration, which determines the concentration of formaldehyde and linear formaldehyde oligomers (this concentration being lower than the "ceiling concentration" of formaldehyde, according to Ref. 1), or on substituting paraformaldehyde for trioxane. The relative rates of formation of the 1,3-dioxanes were found to be of about the same order as those given for deuteration<sup>7</sup> and bromination<sup>13</sup> of the corresponding ketones. It may therefore be concluded that enolization of the ketones is rate-determining for the formation of the 1,3-dioxanes, as previously shown for the formation of 5-acetyl-5-methyl-1,3-dioxane (9) from 2-butanone (6).<sup>1</sup>

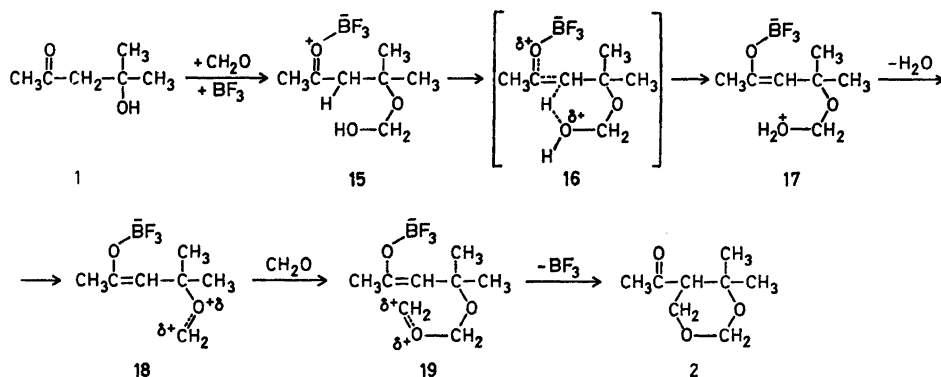
In aqueous medium, both diacetone alcohol (1) and 4-methyl-2-pentanone (12) enolize at similar rates in their 1- and 3-positions, enolization in the 1-positions being only slightly favoured. However, there is a striking difference, in chloroform solution, between the two ketones with respect to their reactivity towards formaldehyde as well as the orientation of the formaldehyde attack. 4-Methyl-2-pentanone (12) reacts in both  $\alpha$ -positions, yielding 5-acetyl-5-isopropyl-1,3-dioxane (13) and 5-isovaleryl-1,3-dioxane (14) at equal rates (*cf.* Ref. 12). Under similar conditions, diacetone alcohol reacts exclusively in the 3-position to give 5-acetyl-4,4-dimethyl-1,3-dioxane (2) at a rate more than 100 times greater than that of the formation of 1,3-dioxane 13 from 4-methyl-2-pentanone (12). It may also be noted that 4,4-dimethyl-2-pentanone, which has a methyl group instead of the hydroxyl group of diacetone alcohol, previously has been shown to react slowly and only in the 1-position with formaldehyde in refluxing chloroform and in the presence of boron trifluoride etherate.<sup>12</sup>

Mesityl oxide (3), which is formed from diacetone alcohol together with 1,3-dioxane 2, might be regarded as a possible intermediate in the formation of the latter product (*cf.* Ref. 1). However, mesityl oxide was found to give only a small yield of 1,3-dioxane 2 on reaction with formaldehyde under the

conditions used, and accordingly this reaction cannot account for the rapid formation of 2.

The results obtained indicate that the  $\beta$ -hydroxyl group of diacetone alcohol greatly enhances the reactivity of this ketone towards formaldehyde in the chloroform- $\text{BF}_3$  system and they strongly support the view that the reaction of diacetone alcohol (1) with formaldehyde in chloroform takes place according to a mechanism (Scheme 5) similar to that proposed for the reaction of 3-

SCHEME 5



hydroxymethyl-2-butanone with formaldehyde,<sup>1</sup> involving intramolecularly assisted enolization. According to this mechanism, the hydroxyl oxygen atom of the intermediate hemiformal 15 rapidly abstracts a proton in the 3-position, and the ion 18 adds another formaldehyde molecule to give 19, which on cyclization by intramolecular addition to the enolic double bond yields the 1,3-dioxane 2.

## EXPERIMENTAL

Samples of trioxane and paraformaldehyde (95 %  $\text{CH}_2\text{O}$ ) were supplied by Perstorp AB, Perstorp, Sweden. Commercial purum grade chemicals were usually distilled before use. IR spectra were recorded on a Beckman IR-9 spectrophotometer, and NMR spectra on a Varian A-60 instrument. Vapour phase chromatography (VPC) was performed using a Perkin-Elmer 800 instrument. Boiling points are uncorrected.

**5-Acetyl-4,4-dimethyl-1,3-dioxane (2).** A solution of diacetone alcohol (58.1 g, 0.5 mole) in chloroform (50 ml) was added during 20 min to a refluxing solution of trioxane (45 g, 0.5 mole) and boron trifluoride etherate (10 g, 0.07 mole) in chloroform (250 ml). Water was continuously removed by a water trap. After a total reaction time of 60 min the solution was washed with water, neutralized with sodium bicarbonate, and then dried over anhydrous calcium sulfate. The solvent was removed together with 16.7 g (34 %) of mesityl oxide (3), determined by VPC. The residue was distilled *in vacuo* to give 5-acetyl-4,4-dimethyl-1,3-dioxane (2) (main fraction, b.p.<sub>0</sub>, 65°), characterized by IR and NMR spectra and elemental analysis. (Found: C 60.58; H 8.83. Calc. for  $\text{C}_8\text{H}_{14}\text{O}_3$ : C 60.74; H 8.92). Yield 30 g (38 %), determined by VPC before distillation.

**B.** Boron trifluoride etherate (5 g, 0.035 mole) was added to a stirred refluxing solution of diacetone alcohol (29.1 g, 0.25 mole) and trioxane (22.5 g, 0.25 mole) in chloroform (150 ml). Water was removed continuously by a water trap. The yields of mesityl

oxide (3) and 5-acetyl-4,4-dimethyl-1,3-dioxane (2) were determined by VPC and found to be 17.3 g (70 %) and 2.0 g (5 %), respectively, after 45 min reaction.

C. In an experiment similar to B, with paraformaldehyde (23.2 g, 0.75 mole) instead of trioxane as a formaldehyde source, 5.2 g (21 %) of mesityl oxide (3) and 15.7 g (40 %) of 1,3-dioxane 2 was obtained after 45 min reaction.

*Reaction of diacetone alcohol (1) with aqueous formaldehyde.* A solution of diacetone alcohol (29.1 g, 0.25 mole) in 36.5 % aqueous formaldehyde (62 g, 0.75 mole of  $\text{CH}_2\text{O}$ ) was diluted with water to 200 ml and heated to reflux. Sulfuric acid (5 ml) was added and the solution refluxed for 60 min. The solution was extracted with ethyl acetate, and the amounts of mesityl oxide and 1,3-dioxane 2 in the extract were found to be 6.2 g (25 %) and 0.72 g (1.8 %), respectively, by VPC.

*Deuteration of diacetone alcohol (1).* The hydroxyl group of diacetone alcohol was deuterated by dissolving 1 volume of the alcohol in 2 volumes of  $\text{D}_2\text{O}$ , and extracting with chloroform after 15 min. The chloroform phase was dried over anhydrous calcium sulfate and the solvent removed under reduced pressure. The acid-catalyzed deuteration was carried out in an NMR tube in the NMR spectrometer (at  $37^\circ$ ) with 0.103 g of the hydroxyl-deuterated diacetone alcohol and 1 ml of 2.1 M DCl in dioxane- $\text{D}_2\text{O}$  1:1. The reaction was followed by integrating the NMR signals from the hydrogens in diacetone alcohol as well as in its dehydration product, mesityl oxide (3), at 10 min intervals during 60 min. The 4-methyl groups of the compounds served as internal standards. The results are given in Figs. 1 and 2.

*Formation of 1,3-dioxanes (9–11, 13–14).* A. Solutions (volume 100 ml) of ketones 6–8 and 12 (0.025 mole), respectively, and trioxane (0.030 mole) in chloroform were heated to reflux, and boron trifluoride etherate (3 ml) was added. Samples were removed 5, 10, 15, and 20 min after the addition of the catalyst, neutralized with sodium bicarbonate, and the yields of 1,3-dioxanes 6–8 and 13–14, respectively (Scheme 4), were determined by VPC. The results are given in Fig. 3.

B. In a series of experiments similar to those described in A with 0.015 mole of trioxane, time-yield curves were obtained which were similar to those given in Fig. 3, apart from the appearance of a slight induction period.<sup>1</sup>

C. Mixtures (volume 100 ml) of ketones 6 and 12 (0.025 mole), respectively, and paraformaldehyde (0.090 mole of  $\text{CH}_2\text{O}$ ) in chloroform were treated as described in A. The time-yield curves obtained for 1,3-dioxanes 9, 13, and 14, respectively, were similar to those given in Fig. 3.

*Formation of 5-acetyl-4,4-dimethyl-1,3-dioxane (2).* A mixture (volume 100 ml) of diacetone alcohol (1) (0.025 mole) and paraformaldehyde (0.090 mole of  $\text{CH}_2\text{O}$ ) in chloroform was heated to reflux, and boron trifluoride etherate (3 ml) was added. Samples were removed 2.5, 5.5, and 10.5 min after the addition of the catalyst, neutralized with sodium bicarbonate, and the yields of 1,3-dioxane 2 determined by VPC. The results are given in Fig. 3.

*Reaction of mesityl oxide (3) with paraformaldehyde.* In an experiment similar to the experiment with compound 1 above, mesityl oxide (2.45 g, 0.025 mole) gave a yield of 0.16 g (4 %) of 1,3-dioxane 3 after 7 min reaction, together with considerable amounts of unchanged starting material.

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