

## Aldol Reactions of Formaldehyde in Non-aqueous Media

### VI.\* Acid-catalyzed Reaction of Formaldehyde with 2-Butanone in Acetic Acid

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The aldol reaction of 2-butanone with formaldehyde was shown to yield 5-acetyl-5-methyl-1,3-dioxane when carried out at 60° in glacial acetic acid and in the presence of sulfuric acid. The addition of formaldehyde to the enol of 2-butanone was found to be rate-determining for the reaction.

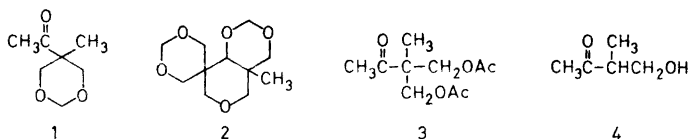
As reported previously,<sup>1,2</sup> the acid-catalyzed reaction of formaldehyde with 2-butanone in aprotic media yields 5-acetyl-5-methyl-1,3-dioxane (*I*). It was found that enolization of the ketone rather than addition of the conjugate acid of formaldehyde to the enol was rate-determining when the reaction was carried out in chloroform or nitromethane and in the presence of boron trifluoride etherate.<sup>2</sup> Noyce *et al.*<sup>3</sup> have shown that in the aldol reaction of 2-butanone with anisaldehyde in acetic acid and with sulfuric acid as a catalyst addition of the conjugate acid of the aldehyde to the enol of 2-butanone was slow relative to enolization of 2-butanone. It was suggested<sup>2</sup> that this difference between the two aldehydes with respect to their reaction with 2-butanone is due either to a medium effect or to a difference in the resonance stabilization of the conjugate acids.

In the present study the reaction of 2-butanone with formaldehyde in glacial acetic acid and with sulfuric acid as a catalyst was investigated, and this reaction was compared with the analogous reaction with anisaldehyde.

#### RESULTS AND DISCUSSION

Wöllner<sup>4</sup> reported that all hydrogen atoms at the  $\alpha$ -positions are substituted when 2-butanone is allowed to react with excess formaldehyde in refluxing acetic acid and in the presence of sulfuric acid. The main product

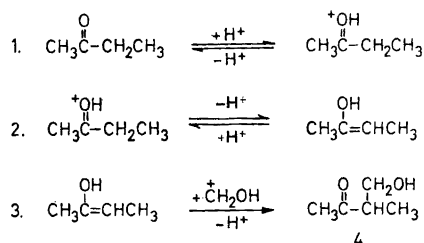
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was compound 2, in which the original keto group had undergone reduction. It has now been found, however, that bis-hydroxymethylation is favoured when the reaction is carried out at 60°, with 5-acetyl-5-methyl-1,3-dioxane (1) being obtained in high yield together with a small amount of 3,3-bis(acetoxymethyl)-2-butanone (3).

As in the cases of chloroform and nitromethane as solvents,<sup>2</sup> no mono-hydroxymethyl compound was detected in the reaction mixture. Since it was found that 3-hydroxymethyl-2-butanone (4), under the conditions used, reacts rapidly with formaldehyde to give 1,3-dioxane 1, it was concluded that in the conversion of 2-butanone to 1 the introduction of the first hydroxymethyl group was slower than the subsequent steps of the reaction.

## SCHEME 1



The first hydroxymethylation may be divided into three separate steps (Scheme 1, *cf.* Ref. 2). In order to determine which of these steps actually is the rate-controlling one, the initial rate of consumption of 2-butanone was measured for different initial concentrations of formaldehyde. The results, which are presented in Fig. 1, show clearly that the initial rate of reaction is a function of the initial formaldehyde concentration. The very strong deviation from linearity for the initial rate is presumably due to formation of acylals

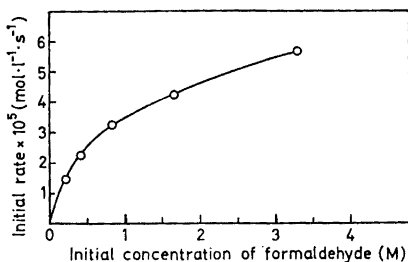


Fig. 1. Initial rate of consumption of 2-butanone in the sulfuric acid-catalyzed reaction with formaldehyde in acetic acid. Initial concentration of 2-butanone, 0.238 M; concentration of sulfuric acid, 0.267 M; temperature, 60°.

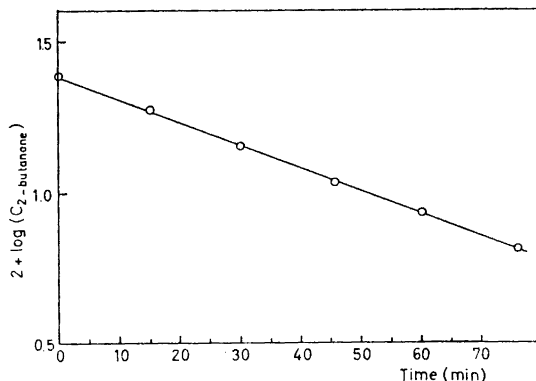


Fig. 2. First-order plot of the sulfuric acid-catalyzed reaction of 2-butanone with formaldehyde (initial concentration 3.3 M) in acetic acid. Concentration of sulfuric acid, 0.267 M; temperature, 60°.

from formaldehyde and acetic acid ( $\text{AcOCH}_2\text{OAc}$  and  $\text{AcOCH}_2\text{OCH}_2\text{OAc}$ )<sup>5</sup> as well as polyoxymethylene monoacetates (Ref. 5, p. 345), which causes a non-linear dependence of the concentration of monomeric formaldehyde on the total concentration of formaldehyde (*cf.* Ref. 2). Furthermore, the rate of consumption of 2-butanone was shown to obey pseudofirst-order kinetics (Fig. 2) when formaldehyde was present in a large excess (molar ratio formaldehyde/2-butanone=14). The results obtained are thus in accordance with the view that the third step in Scheme 1, *i.e.* the addition of the conjugate acid of formaldehyde to the enol of 2-butanone, is the rate-determining step. This would be analogous to the acid-catalyzed aldol reaction between 2-butanone and anisaldehyde, in which addition of the latter aldehyde to the enol of 2-butanone is rate-determining.<sup>3</sup>

Additional evidence for this view was obtained when the reaction of 2-butanone with formaldehyde was conducted in deuterated acetic acid ( $\text{CH}_3\text{COOD}$ ), and the reaction mixture analyzed by means of NMR spectroscopy. It was found (Fig. 3) that exchange of  $\alpha$ -methylene protons for deuterons in 2-butanone was faster than formation of 5-acetyl-5-methyl-1,3-dioxane (I), which was the only reaction product observable by NMR. Consequently, the "3-enol" of 2-butanone is in equilibrium with the ketone under the conditions used in the reaction with formaldehyde.

Accordingly, there is a difference in the relative rates of the consecutive enolization and addition steps between the chloroform- $\text{BF}_3$  system investigated previously<sup>2</sup> and the acetic acid- $\text{H}_2\text{SO}_4$  system used in the present investigation. In the former system enolization of the 2-butanone was rate determining.

The enolization (Scheme 1) involves conversion of the ketone to its conjugate acid (eqn. 1), followed by removal of an  $\alpha$ -proton by a base (eqn. 2), which, in the acetic acid- $\text{H}_2\text{SO}_4$  system, may be solvent molecules. Chloroform would be practically inert in that respect, and in this solvent proton abstraction would be accomplished by the solutes. Reversal of the enolization, *i.e.*

re-ketonization, is effected by a reaction of the enol with a proton donating agent. In the acetic acid- $\text{H}_2\text{SO}_4$  system the concentration of proton donating agents should be much higher than in the chloroform- $\text{BF}_3$  system, and accordingly the rate of re-ketonization should be much greater than in chloroform- $\text{BF}_3$ . Since re-ketonization competes with the addition of formaldehyde for the enol, the higher rate of re-ketonization in acetic acid thus partly can explain the difference in the relative rates of the enolization and addition steps between the two systems.

The rates of the addition step (Scheme 1, eqn. 3) may also differ considerably in the two systems, one of the possible reasons being a difference in the state of the formaldehyde. In the acetic acid- $\text{H}_2\text{SO}_4$  system the concentration of free, monomeric formaldehyde will be comparatively low due to its reaction with the solvent to form monomeric and polymeric acetates, as mentioned previously. In the chloroform- $\text{BF}_3$  system, however, the concentration of free formaldehyde may be expected to be comparatively high. Thus in the latter system the rate of reaction of formaldehyde with the enol of 2-butanone would be greater than in the acetic acid- $\text{H}_2\text{SO}_4$  system, and the enol of 2-butanone would be consumed as fast as it is formed.

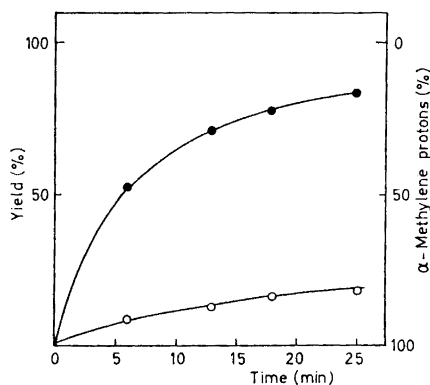


Fig. 3. Sulfuric acid-catalyzed reaction of 2-butanone with formaldehyde in  $\text{CH}_3\text{COOD}$  at  $60^\circ$ . Formation of 5-acetyl-5-methyl-1,3-dioxane (I),  $\circ$ ; amount of  $\alpha$ -methylene protons,  $\bullet$ .

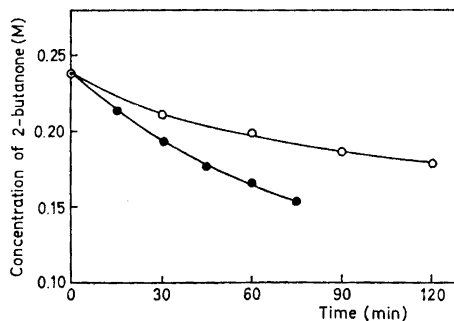
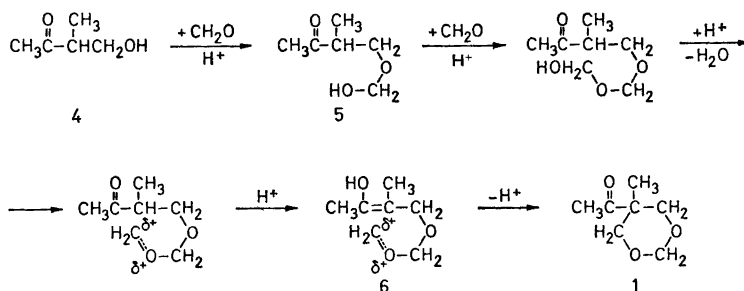


Fig. 4. Sulfuric acid-catalyzed reaction of 2-butanone with formaldehyde ( $\circ$ ) and anisaldehyde ( $\bullet$ ). Initial concentrations of aldehydes, 0.215 M; concentration of sulfuric acid, 0.267 M; temperature,  $60^\circ$ .

As mentioned above, the further reaction of 3-hydroxymethyl-2-butanone (4) with formaldehyde is considerably more rapid than the corresponding reaction of 2-butanone. By comparing rates of formation of HOAc by NMR spectroscopy on treatment of the ketones with DOAc in the presence of sulfuric acid (0.05 M), the rate of enolization of 2-butanone was found to be about twice the rate of enolization (and dehydration)<sup>2</sup> of ketone 4. However, since the enolizations of both ketones are rapid under the conditions used in the reaction with formaldehyde, it is not possible to tell whether the presence of formaldehyde affects the rate of enolization of ketone 4, as was proposed

SCHEME 2



in the cases of chloroform and nitromethane as solvents.<sup>2</sup> Apparently, the  $\beta$ -hydroxyl group of **4** greatly facilitates the aldol addition of formaldehyde (Scheme 2), presumably by the formation of a hemiacetal (**5**), which on reaction with formaldehyde and enolization may yield the ion **6**. Intramolecular addition of the carbonium ion end of the molecule to the enol double bond gives the 1,3-dioxane **1**.

Comparison of the rates of the reactions of 2-butanone with formaldehyde and anisaldehyde (Fig. 4), respectively, showed that 2-butanone is consumed more rapidly in the presence of the latter aldehyde than if an equal total concentration of formaldehyde was used. However, because the concentration of "active" formaldehyde is not known, this comparison might give a false impression of the relative reactivities of the aldehydes.

#### EXPERIMENTAL

Paraformaldehyde (98%  $\text{CH}_2\text{O}$ ) was supplied by Perstorp AB, Perstorp, Sweden. Deuterated acetic acid was prepared by hydrolyzing acetic anhydride (10.2 g, 0.1 mole) with deuterium oxide (2.0 g, 0.1 mole). Glacial acetic acid (Fisher, 99.7%) was used without further purification. Other commercial purum grade organic chemicals were generally distilled before use. NMR spectra were recorded on a Varian A-60 spectrometer. Vapour phase chromatography (VPC) was performed using a Perkin-Elmer 800 instrument.

*Formation of 5-acetyl-5-methyl-1,3-dioxane (1).* A mixture (100 ml) of 2-butanone (1.80 g, 0.025 mole) and paraformaldehyde (10.8 g, 0.35 mole of  $\text{CH}_2\text{O}$ ) in acetic acid was heated with stirring to  $60^\circ$ , and 5 ml of a solution of sulfuric acid in acetic acid (5.6 M) was added. After 75 min reaction a sample was neutralized with sodium acetate, and the amounts of 2-butanone and 5-acetyl-5-methyl-1,3-dioxane (**1**) were determined by VPC, and found to be 6.8 mmoles and 14.3 mmoles, respectively. Yield of 1,3-dioxane **1** 78%, based on consumed 2-butanone. A small amount of 3,3-bis(acetoxymethyl)-2-butanone (**3**) was also identified by VPC, by comparison with authentic material.

*Reaction of 3-hydroxymethyl-2-butanone (4) with formaldehyde.* A solution (100 ml) of paraformaldehyde (5.4 g, 0.176 mole of  $\text{CH}_2\text{O}$ ) and sulfuric acid (28 mmoles) in acetic acid was heated with stirring to  $60^\circ$ . A solution (5 ml) of 3-hydroxymethyl-2-butanone (**4**; 2.55 g, 0.025 mole) in acetic acid was added during 1 min, and after further 5 min a sample was neutralized with sodium acetate. The yield of 1,3-dioxane **1** was determined by VPC, and found to be 2.81 g (78%).

*Determination of reaction rates in the reaction of 2-butanone with formaldehyde.* Mixtures (100 ml) of 2-butanone (1.80 g, 0.025 mole) and varying amounts of paraformaldehyde

(see Fig. 1) in acetic acid were heated with stirring to  $60^\circ \pm 0.05^\circ$  in a constant-temperature bath. A solution (5 ml) of sulfuric acid in acetic acid (5.4 M) was added. The solid paraformaldehyde dissolved almost instantly on addition of the acid. Samples were collected 15, 30, 45, 60, and 75 min after addition of the catalyst, neutralized with sodium acetate, and the concentrations of 2-butanone determined by VPC. From the initial slopes of the time-concentration curves the initial rates of reaction were determined. Results are given in Figs. 1 and 2.

*Reaction of 2-butanone with formaldehyde in deuterated acetic acid.* A solution of 2-butanone (0.15 g, 2.1 mmoles), paraformaldehyde (0.05 g, 1.6 mmoles) and sulfuric acid (0.28 mmole) in  $\text{CH}_3\text{COOD}$  (1 ml) was placed in an NMR tube in the NMR spectrometer at  $60^\circ$ . Spectra and integrals were recorded at intervals. The amount of 1,3-dioxane I formed as well as the consumption of protons in the 3-position of 2-butanone were determined from the spectra. Results are presented in Fig. 3.

*Deuteration of 2-butanone and 3-hydroxymethyl-2-butanone (4).* 2-Butanone (0.106 g, 1.47 mmoles) and 3-hydroxymethyl-2-butanone (0.150 g, 1.47 mmoles), respectively, were dissolved in 0.9 ml of deuterated acetic acid containing sulfuric acid (0.05 mmole), and chloroform (0.1 ml) was added as an internal standard. The solutions were placed in NMR tubes and placed in the NMR spectrometer at  $40^\circ$ . Spectra and integrals were recorded at intervals, and the amounts of HOAc formed were determined by comparison with the internal standard.

*Reaction of anisaldehyde with 2-butanone.* A solution (100 ml) of 2-butanone (1.80 g, 0.025 mole) and anisaldehyde (3.06 g, 0.0225 mole) in acetic acid was heated with stirring to  $60^\circ \pm 0.05^\circ$  in a constant-temperature bath. A solution (5 ml) of sulfuric acid in acetic acid (5.4 M) was added. Samples were collected 15, 30, 45, 60, and 75 min after the addition of the catalyst, neutralized with sodium acetate, and concentrations of 2-butanone determined by VPC. Results are given in Fig. 4, together with the results from the reaction of formaldehyde with 2-butanone under similar conditions.

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