

Aldol Reactions of Formaldehyde in Non-aqueous Media

IV.* The Mechanism of the Acid-catalyzed Reaction of 2-Butanone with Formaldehyde

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The mechanism for the formation of 5-acetyl-5-methyl-1,3-dioxane (5) from 2-butanone (1) and formaldehyde in chloroform and nitromethane solutions and in the presence of boron trifluoride etherate has been studied. Comparison of the reaction rates obtained with 2-butanone and 1,1,1,3,3-pentadeutero-2-butanone revealed that the reaction was subject to a primary kinetic isotope effect ($k_H/k_D=2-3$), in agreement with the view that enolization of 2-butanone is rate-determining for the reaction. The primary reaction product, 3-hydroxymethyl-2-butanone (2), was shown to react further with formaldehyde very rapidly. The proposed reaction mechanism involves the formation of 3-hydroxymethyl-2-butanone hemiformal (3), followed by enolization *via* a rapid intramolecular hydrogen abstraction by the hydroxyl group of 3.

The rate of formation of 1,3-dioxane 5 was found to increase with increasing dielectric constant and decreasing basicity of the reaction medium.

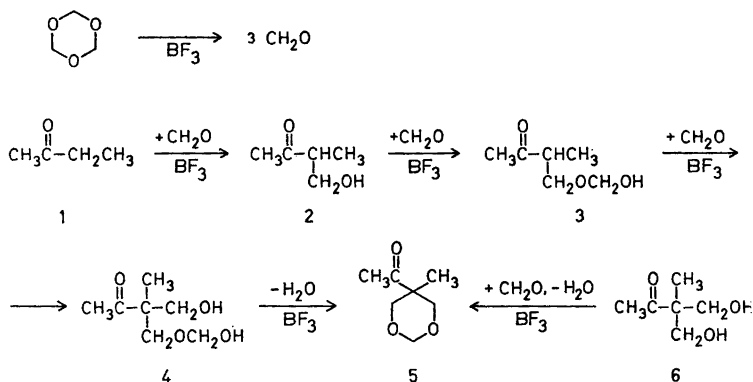
In part III of this series,¹ the formation of 5,5-disubstituted 1,3-dioxanes by acid-catalyzed aldol reaction of aldehydes and ketones with formaldehyde in refluxing chloroform solution was reported. The present paper deals with the mechanism of the formation of 5-acetyl-5-methyl-1,3-dioxane (5) from 2-butanone and trioxane, the cyclic formaldehyde trimer, in the presence of boron trifluoride etherate.

RESULTS AND DISCUSSION

According to the reaction path given in Scheme 1 the formation of the 1,3-dioxane 5 from trioxane and 2-butanone is due to two simultaneous reactions, *i.e.* the depolymerization of trioxane to formaldehyde, and the aldol

* Part III, see Ref. 1.

SCHEME 1



reaction between formaldehyde and 2-butanone to give 5. As the kinetics of the aldol reaction may depend on the amount of formaldehyde available, the depolymerization of trioxane will first be discussed in some detail.

The depolymerization of trioxane. When trioxane is treated with acid catalysts in organic solvents depolymerization to formaldehyde takes place.^{2,3} Simultaneously, trioxane as well as formaldehyde polymerize to polyoxymethylene, which under certain conditions may precipitate. These reactions are reversible.^{3,4} Depending on the relative rates of the reactions involved, the depolymerization of trioxane may then influence the formation of 1,3-dioxane 5 from 2-butanone in at least three different ways.

1. If the depolymerization of trioxane is slow in comparison with the following reactions shown in Scheme 1, the rate of formation of 5 will be governed only by the depolymerization rate.

2. If the depolymerization of trioxane as well as the polymerization to polyoxymethylene are rapid as compared with the aldol reaction, and if polyoxymethylene precipitates, the concentration of formaldehyde will be constant throughout the reaction ("ceiling concentration"),³ and the formation of 5 will be zero order with respect to trioxane.

3. If the reversible depolymerization of trioxane to formaldehyde is rapid, but precipitation of polyoxymethylene does not occur, the concentration of formaldehyde will depend on the initial concentration of trioxane, and the rate of formation of 5 will depend on the concentrations of 2-butanone (1) and formaldehyde, or 2-butanone alone, rather than on the depolymerization rate.

When trioxane was treated with boron trifluoride etherate in refluxing chloroform solution, about 35 % of the initial amount of trioxane (0.32 M) disappeared in a rapid reaction, followed by a considerably slower further decrease of the trioxane content (Fig. 1). No solid polyoxymethylene was formed. Apparently an equilibrium between trioxane on one side and other oligomers as well as monomeric formaldehyde on the other side was rapidly established (*cf.* item 3 above), and the subsequent slow consumption of trioxane was caused by the loss of gaseous formaldehyde from the system. The same

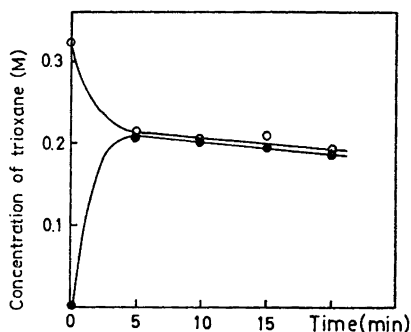


Fig. 1. Depolymerization of trioxane (O), and formation of trioxane from paraformaldehyde (●) in refluxing chloroform. Boron trifluoride etherate, 3 % by volume.

equilibrium mixture was obtained when paraformaldehyde was treated in a similar manner (Fig. 1). The formation of trioxane from paraformaldehyde under the influence of boron trifluoride etherate in nitrobenzene solution has previously been reported by Jaacks.³

The equilibrium amounts of trioxane present in refluxing chloroform solutions containing boron trifluoride etherate are given in Fig. 2 as a function of the initial trioxane content. The equilibrium concentration of trioxane was found to be approximately proportional to the initial trioxane concentration up to about 1.3 M, where solid polyoxymethylene precipitated from the solution. Fig. 3 shows the equilibrium at 50°. At this temperature polyoxymethylene precipitated at a lower initial trioxane concentration (1.0 M).

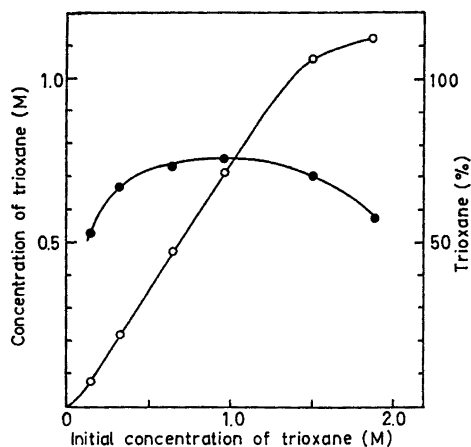


Fig. 2. The equilibrium between trioxane and formaldehyde in refluxing chloroform and in the presence of boron trifluoride etherate (3 % by volume): Concentration of trioxane at equilibrium (O); trioxane at equilibrium in per cent of initial trioxane concentration (●).

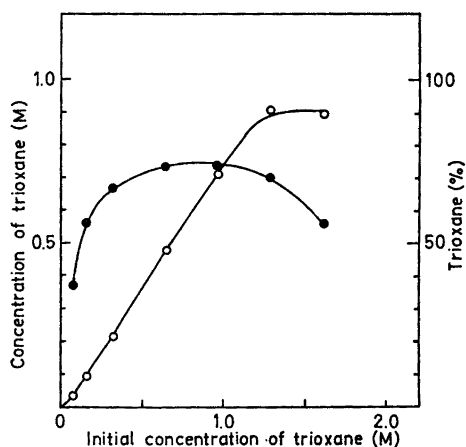


Fig. 3. The equilibrium between trioxane and formaldehyde in chloroform at 50° in the presence of boron trifluoride etherate (3 % by volume): Concentration of trioxane at equilibrium (O); trioxane at equilibrium in per cent of initial trioxane concentration (●).

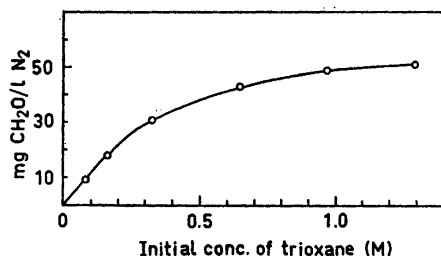


Fig. 4. Vapour pressure of formaldehyde over solutions of trioxane in chloroform at 50° in the presence of boron trifluoride etherate (3 % by volume).

The results shown in Figs. 2 and 3 also imply that the concentration of formaldehyde (comprising monomeric formaldehyde and soluble oligomers other than trioxane) in the solution is approximately proportional to the initial trioxane concentration, provided that the latter concentration is < 1.0–1.1 M.

The concentration of monomeric formaldehyde in the solution is proportional to the vapour pressure of formaldehyde, according to Henry's law. The vapour pressure of formaldehyde over chloroform solutions, determined at 50° and expressed as mg CH₂O/l N₂ (see Experimental Part), is given in Fig. 4 as a function of the initial trioxane concentration of the solution. The strong deviation from linearity is presumably due to an increasing proportion of soluble polymeric formaldehyde with increasing initial trioxane concentration.⁵ It is evident, however, that the concentration of monomeric formaldehyde strongly depends on the initial trioxane concentration at concentrations < 0.45 M.

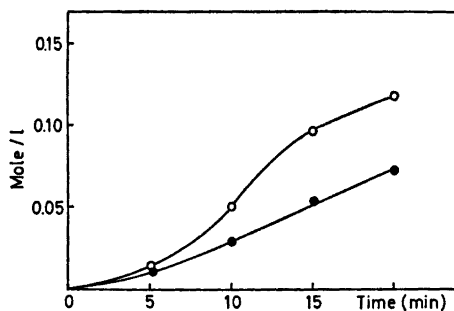


Fig. 5. Consumption of trioxane (O) and formation of 1,3-dioxane 5 (●) in the reaction of 2-butanone (0.24 M) with trioxane (0.15 M) in refluxing chloroform. Boron trifluoride etherate, 3 % by volume.

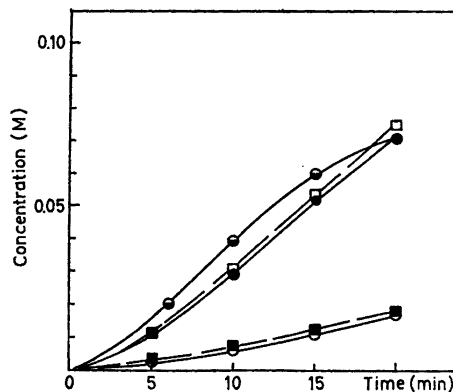


Fig. 6. Formation of 1,3-dioxane 5 from 1,1,1,3,3-pentadeutero-2-butanone and trioxane (O, ■) and from 2-butanone and trioxane (●, □, ⊙) in refluxing chloroform. Deutero-2-butanone, 0.242 M; trioxane, 0.146 M (O), and 0.242 M (■). 2-Butanone, 0.242 M; trioxane 0.146 M (●), 0.242 M (□), and 0.437 M (⊙). Boron trifluoride etherate, 3 % by volume.

A comparison of Figs. 1 and 6 clearly indicates that, under the conditions used, the depolymerization of trioxane proceeds at a considerably higher rate than the formation of 1,3-dioxane 5 (Scheme 1). These findings are in agreement with the alternative given in item 3 above. It should be noted that the curves in Fig. 6 indicate a low initial rate of formation of compound 5. This was found to be due to slow initial depolymerization of the trioxane in the presence of 2-butanone. After about 5–10 min, however, the depolymerization rate increased to a rate greater than the rate of formation of 5, until equilibrium was reached after a reaction time of 10–15 min (Fig. 5). The depolymerization of trioxane cannot accordingly be rate-determining for the formation of 1,3-dioxane 5 under the conditions used.

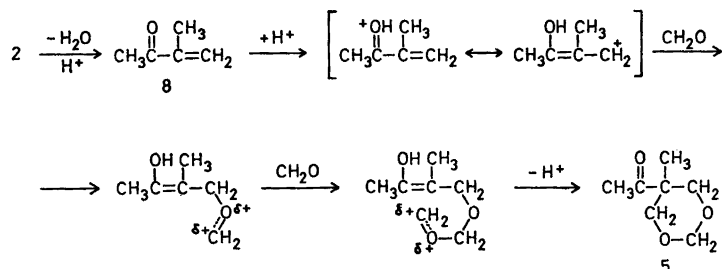
The aldol reaction of 2-butanone with formaldehyde. The formation of the 1,3-dioxane 5 from 2-butanone and formaldehyde (Scheme 1) is proposed to involve the intermediate hydroxymethyl compounds 2 and 4, as well as the hemiformal 3. As mentioned before,¹ no intermediates have actually been detected in the reaction mixture. It was found, however, that the mono- and bis-hydroxymethyl compounds 2 and 6, when treated with trioxane and boron trifluoride etherate, were converted into the 1,3-dioxane 5 much more rapidly than the butanone 1. Consequently, compounds 2–4 may be intermediates, which, however, will not accumulate in the reaction mixture. Thus, in the sequence 1→5, the first hydroxymethylation (1→2) is the slow reaction. The formation of the hemiformal 3 prior to the introduction of the second hydroxymethyl group seems probable, as the acetalization 6→5 is a very rapid reaction under the conditions used.

It is commonly believed that acid-catalyzed aldol reactions of ketones,⁶ as well as their halogenation⁷ and their acylation with acid anhydrides,⁸ proceed through enolization of the ketone, followed by the addition of an electrophile — in aldol reactions the conjugate acid of a carbonyl compound — to the double bond of the enol. This view has been supported by the work of Noyce *et al.*⁹ who found the slow step in the acid-catalyzed aldol reaction of anisaldehyde with 2-butanone to be the addition of the conjugate acid of the aldehyde to the enol of the 2-butanone.

It could not be taken for granted, however, that the analogous addition of the conjugate acid of formaldehyde to the enol form of 2-butanone is the rate-controlling step in the formation of the hydroxymethyl compound 2. The latter reaction (1→2 in Scheme 1) may be divided into three separate steps (Scheme 2). One approach used to answer the question which of these steps is the rate-controlling one, was to investigate whether or not the overall reaction, *i.e.* the formation of 1,3-dioxane 5 (Scheme 1), was subject to a primary kinetic hydrogen isotope effect.

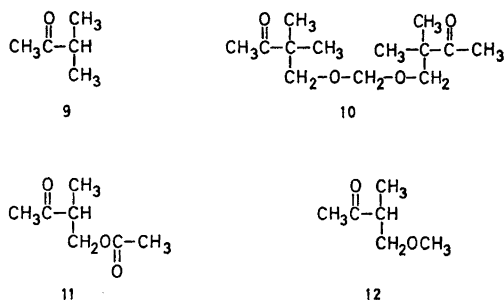
The first step, *i.e.* coordination of boron trifluoride with the carbonyl oxygen atom of the ketone, presumably is a rapid equilibrium reaction (Eqn. 1 a), and neither the position of the equilibrium nor the reaction rates will be affected by substituting deuterium for hydrogen in the α -positions of the ketone, as far as primary isotope effects are concerned. It is possible, however, that the effective catalyst is not boron trifluoride but rather a complex acid resulting from the reaction of boron trifluoride with a co-catalyst such as water (Eqn. 1 b₁).¹⁰ In that case the position of the equilibrium of the reaction given

SCHEME 4



ketone **8** reacts further with formaldehyde with the formation of the 1,3-dioxane **5** (Scheme 4). It was found that the hydroxymethyl compound **2**, in refluxing chloroform and in the presence of sulfuric acid was rapidly dehydrated. Under the same conditions, however, the formation of 1,3-dioxane **5** from the α,β -unsaturated ketone **8** and formaldehyde was found to be a slow reaction. With boron trifluoride etherate in refluxing chloroform the dehydration of compound **2** was slow and the formation of 1,3-dioxane **5** from the unsaturated ketone **8** and formaldehyde was negligible. The α,β -unsaturated ketone **8** cannot accordingly be an intermediate in the formation of 1,3-dioxane **5**.

The concept of hyperconjugation has been commonly used to explain differences in rates and directions of enolization of ketones.^{7,14,17,18} Provided that 2-butanone and the hydroxymethyl compound **2** are protonated or complex bound to boron trifluoride to the same extent in chloroform, one would expect **2** to enolize at the 3-position at a greater rate than 2-butanone, since the double bond of its 3-enol is stabilized by hyperconjugation with eight C—H bonds, whereas the double bond of the corresponding enol of 2-butanone is hyperconjugated with only six C—H bonds. One would also expect 3-methyl-2-butanone (**9**), in which the double bond of the 3-enol will be stabilized by hyperconjugation with nine C—H bonds, to enolize and probably react with formaldehyde in the 3-position at about the same rate as **2**. However, when compounds **2** and **9** were allowed to compete for a limited amount of trioxane in refluxing chloroform and in the presence of boron trifluoride etherate, the hydroxymethyl compound **2** reacted exclusively, 1,3-dioxane **5** being formed



in a high yield. In the absence of 2 the reaction of 9 with trioxane yielded the methylene ether 10. Furthermore, the acetate (11) and the methyl ether (12) of 2, which are equivalent to 2 with regard to hyperconjugative stabilization of the enols, were found to react with trioxane considerably more slowly than compound 2. Consequently, the high reactivity of 2 towards formaldehyde in chloroform solution cannot be explained by hyperconjugative stabilization of its enol.

As already mentioned (p. 2089), the initial reaction of 2 with formaldehyde under the conditions used is probably the formation of the hemiformal 3 (Scheme 1). In fact, it seems possible to understand the high rate of the conversion of aldol 2 to the 1,3-dioxane 5 on the basis of the initial formation of this hemiformal (3) (Scheme 5). In a medium such as chloroform the polar hydroxyl and ether groups of the solutes are much less solvated than in aqueous media, and the hydroxyl group of the hemiformal 3 may easily come in close proximity to the 3-hydrogen atom and intramolecularly abstract it with the formation of the 3-enol 14 (Scheme 5). Proton abstraction from 2-butanone as well as from 9, 11, and 12 can only occur intermolecularly by the bases present in the reaction mixture, *e.g.* the starting ketones, diethyl ether, formaldehyde, and trioxane, which all are less basic and presumably less active than a hydroxyl group.¹⁹ The intramolecular proton abstraction from 3 may also account for the selective 3-substitution in the reaction of 2 with formaldehyde. As mentioned before, the 1,3-dioxane 5 is formed from 2 in nearly quantitative yield, and no signs of 1,3-disubstituted 2-butanones have been detected. The transition state 13*a* (Scheme 5), involving the 3-hydrogen atom of 3, exhibits a six-membered ring configuration in which the reacting α -C—H orbital easily can assume the conformation most favourable for elimination, *i.e.* perpendicular to the nodal plane of the π -electron system of the carbonyl group.^{13,20} The isomeric transition state 13*b*, where a hydrogen atom in

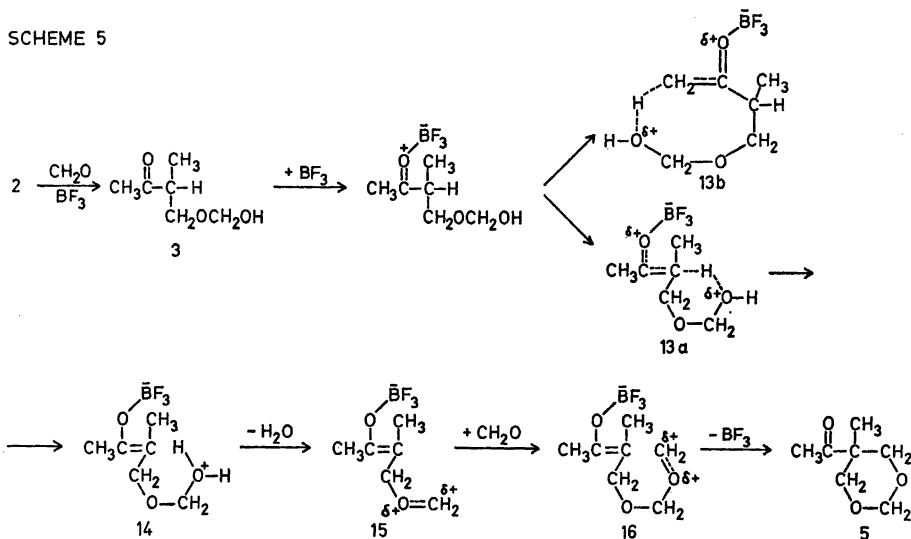


Table 1. Solvents used in the reaction of 2-butanone with trioxane.

Solvent	Dielectric constant ²¹
Cyclohexane	2.02
Benzene	2.27
Diisopropyl ether	3.88
Chloroform	4.81
Ethyl acetate	6.02
1,2-Dichloroethane	10.4
2-Nitropropane	25.5
Nitroethane	28.0
Nitromethane	35.9

the 1-position of **3** is involved, exhibits an eight-membered ring configuration, and therefore must be considered less favoured than **13a**.

The oxonium ion **14**, formed *via* transition state **13a**, may easily lose water to yield the resonance-stabilized carbonium ion **15**, which on reaction with formaldehyde gives the ion **16**. Intramolecular addition of this ion to the enol double bond forms the six-membered ring of the 1,3-dioxane **5**. The formation of ion **16** according to this mechanism would be alternative to the formation of 3,3-bis(hydroxymethyl)-2-butanone hemiformal (**4**, Scheme 1).

Solvent effects. The boron trifluoride-catalyzed reaction of 2-butanone with trioxane has been studied in some non-aqueous solvents other than chloroform (Table 1). Time-yield curves for the formation of 1,3-dioxane **5** are given in Fig. 7. The solvents used may be divided into three groups with regard to their dielectric constants and base strengths ¹⁹ with respect to boron trifluoride. The first group consists of solvents with low base strengths and with increasing dielectric constants: Chloroform, 1,2-dichloroethane, 1-nitropropane, nitroethane and nitromethane. The rates of formation of **5** increased in the same order as the dielectric constants, *i.e.* with increasing ionizing ability of the medium. The solvents of the second group, benzene and cyclohexane, have dielectric constants lower than chloroform, and still lower base strengths than the first group; the rates of formation of **5** were larger than in

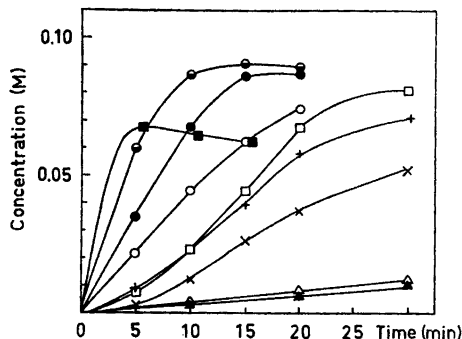


Fig. 7. Formation of 1,3-dioxane **5** from 2-butanone (0.242 M) and trioxane (0.146 M) in various solvents at 60° in the presence of boron trifluoride etherate (3% by volume): Chloroform (×), 1,2-dichloroethane (+), 1-nitropropane (○), nitroethane (●), nitromethane (⊙), benzene (□), cyclohexane (■), diisopropyl ether (Δ), and ethyl acetate (▲).

chloroform solution. The acidity of the catalyst is probably higher in these solvents than in chloroform, thus enhancing the reaction rates in spite of the low dielectric constants. The third group, diisopropyl ether and ethyl acetate, have about the same dielectric constants as chloroform, but are stronger bases. These solvents are known to form stable complexes with boron trifluoride (Ref. 10, p. 516). They obviously compete with 2-butanone and trioxane for the catalyst, the resulting low catalyst activity being the reason for the low reaction rates.

The results obtained indicate that the rate of formation of the 1,3-dioxane 5 from 2-butanone and trioxane in the presence of boron trifluoride etherate increases with increasing dielectric constant, and decreases with increasing Lewis base strength of the medium.

In order to examine whether the reaction mechanism changes with changing solvent, the reaction of 2-butanone with trioxane was investigated in nitromethane solution in the same manner as in chloroform. Nitromethane was chosen as solvent since the rate of the formation of 1,3-dioxane 5 was high and there was no initial period of low reaction rate. The formation of the monohydroxymethyl compound 2 was found to be the slow reaction, as in chloroform. The rate constants for the formation of the 1,3-dioxane from 2-butanone and 1,1,1,3,3-pentadeutero-2-butanone, respectively, at 60° were determined by plotting the initial rate of formation of the 1,3-dioxane against the initial ketone concentration, at constant trioxane concentration (Fig. 8). Evidently, the reaction was subject to a primary kinetic isotope effect of the magnitude of $k_H/k_D=1.9$. The initial trioxane concentration had no influence on the initial reaction rate (Fig. 9), and therefore it was concluded that enolization of 2-butanone (in the 3-position) was overall rate-controlling as in chloroform solution.

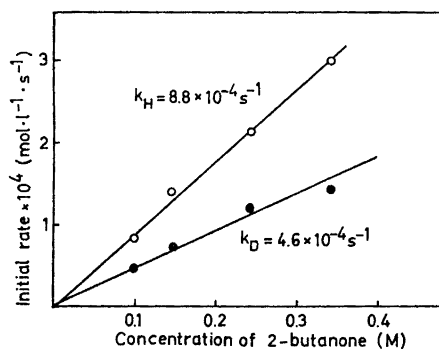


Fig. 8. Initial rates of 1,3-dioxane formation from 2-butanone and trioxane (O), and from 1,1,1,3,3-pentadeutero-2-butanone and trioxane (●) in nitromethane at 60°. Trioxane, 0.146 M; boron trifluoride etherate, 3 % by volume.

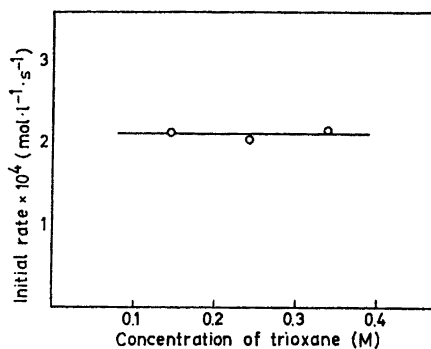


Fig. 9. Initial rates of 1,3-dioxane formation from 2-butanone (0.242 M) and trioxane in nitromethane at 60°. Boron trifluoride etherate, 3 % by volume.

EXPERIMENTAL

Samples of trioxane, paraformaldehyde (99.5 % CH_2O), and 3,3-bis(hydroxymethyl)-2-butanone were supplied by Perstorp AB, Perstorp, Sweden. 3-Hydroxymethyl-2-butanone was synthesized according to Landau and Irany.²² Commercial purum grade chemicals generally were 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. Melting and boiling points are uncorrected.

Depolymerization of trioxane. Solutions (100 ml) of varying amounts of trioxane in chloroform were heated to reflux, or in a thermostat at $50^\circ \pm 0.05^\circ$ with stirring, and boron trifluoride etherate (3.0 ml) was added. Samples were withdrawn at 5 min intervals, cooled rapidly to 0° and neutralized with sodium bicarbonate. The concentrations of trioxane were determined by VPC. The equilibrium concentrations of trioxane were obtained by extrapolation to zero time to correct for losses of formaldehyde by evaporation from the system. The results are given in Figs. 1, 2, and 3.

Formation of trioxane from paraformaldehyde. Paraformaldehyde (3.0 g, 0.10 mole) was suspended in chloroform, and chlorobenzene (2.5 ml) was added as internal standard. The suspension (total volume 100 ml) was heated to reflux, and boron trifluoride etherate (3.0 ml) was added. Samples were withdrawn at 5 min intervals, cooled rapidly to 0° , and neutralized with sodium bicarbonate. The trioxane concentration in the samples was determined by VPC. The results are presented in Fig. 1.

*Determination of formaldehyde vapour pressure.*²³ Solutions (100 ml) of varying amounts of trioxane in chloroform were equilibrated for 20 min in a thermostat at $50^\circ \pm 0.05^\circ$, and boron trifluoride etherate (3.0 ml) was added. Nitrogen was passed through the solutions by means of a glass filter disc at a rate of 30 ml/min, and the formaldehyde present in the gas stream was absorbed in a mixture of 40 ml ethanol and 2 ml 1 M aqueous potassium hydroxide solution. The connecting glass tubings were kept at about 100° which prevented the deposition of paraformaldehyde. Three consecutive samples were collected 10 min after the addition of the catalyst, each over a period of 10 min. The alcoholic solutions were neutralized with 0.1 N sulfuric acid against thymolphthalein, and after the addition of 50 ml of 1 M sodium sulfite solution the formaldehyde content of the solutions was determined by titration with 0.1 N sulfuric acid (Ref. 5, p. 486). The results are given in Fig. 4.

Formation of 5-acetyl-5-methyl-1,3-dioxane (5) from 2-butanone and trioxane. A chloroform solution (100 ml) of 2-butanone (1.80 g, 0.025 mole) and trioxane (1.35 g, 0.015 mole) was heated to reflux, and boron trifluoride etherate (3.0 ml) was added. Samples were withdrawn 5, 10, 15, and 20 min after the addition of the catalyst. The samples were rapidly cooled to 0° and neutralized with sodium bicarbonate. The concentrations of 1,3-dioxane 5 and trioxane were determined by VPC. The results obtained are given in Fig. 5.

Comparative experiments on the formation of 5-acetyl-5-methyl-1,3-dioxane (5) in chloroform solution. a) *From 2-butanone.* To a stirred refluxing solution of trioxane (4.5 g, 0.05 mole) in chloroform (100 ml) boron trifluoride etherate (4.0 g, 0.027 mole) was added. The reaction vessel was equipped with a water trap. After 3 min a solution of 2-butanone (3.6 g, 0.05 mole) in chloroform (50 ml) was added during 9 min, and after 3 more min the solution was cooled rapidly. The volume of the reaction mixture was determined, and after neutralizing with sodium bicarbonate the yield of 5 was found to be 0.80 g (12 %) by VPC.

b) *From 3-hydroxymethyl-2-butanone (2).* In an experiment similar to a) a yield of 6.3 g (88 %) of 5 was found by VPC.

c) *From 3,3-bis(hydroxymethyl)-2-butanone (6).* In an experiment similar to a) a yield of 7.2 g (100 %) of 5 was found by VPC.

Deuteration of 2-butanone. A mixture of deuterium oxide (10 g, 0.5 mole) and 2-butanone (14 g, 0.2 mole) was refluxed overnight in the presence of potassium carbonate (0.1 g). Sodium chloride was added to saturation and the organic layer was separated. Deuteration was repeated four times; after the last time the ketone was distilled through a Vigreux column to give 12.5 g of an azeotropic mixture of deuterium oxide and 1,1,1,3,3-pentadeutero-2-butanone. By NMR spectroscopy the deuterium content in the α -positions of the ketone was found to be 95 %.

Effect of deuteration on the formation of 5-acetyl-5-methyl-1,3-dioxane (5) from 2-butanone in chloroform solution. a) *Reaction of 1,1,1,3,3-pentadeutero-2-butanone with trioxane.* Chloroform was added to the azeotrope of 1,1,1,3,3-pentadeutero-2-butanone and deuterium oxide obtained on deuteration of 2-butanone (see above) and the mixture dried overnight over anhydrous calcium sulfate. The concentration of pentadeutero-2-butanone in the solution was determined by UV spectrophotometry. Samples of the solution were used to prepare chloroform solutions (100 ml) containing 0.025 mole of pentadeutero-2-butanone and 0.015 and 0.025 mole of trioxane, respectively. The solutions were heated to reflux with heating mantles. Boron trifluoride etherate (3.0 ml) was added to each solution, and samples were withdrawn 5, 10, 15, and 20 min after the addition of the catalyst. The samples were cooled rapidly to 0° and neutralized with sodium bicarbonate. The concentration of 5-acetyl-*d*₅-5-methyl-1,3-dioxane was determined by VPC. The results obtained are presented in Fig. 6.

b) *Reaction of 2-butanone with trioxane.* 2-Butanone was distilled together with water through a Vigreux column to give an azeotropic mixture of the compounds. The azeotrope was mixed with chloroform, and the mixture treated overnight with anhydrous calcium sulfate. The concentration of 2-butanone in the solution was determined by UV spectrophotometry. Samples of the solution were used to prepare chloroform solutions (100 ml) containing 0.025 mole of 2-butanone and 0.015, 0.025, and 0.045 mole trioxane, respectively. The latter solutions were treated as described under a). The concentration of 5-acetyl-5-methyl-1,3-dioxane (5) was determined by VPC. The results obtained are given in Fig. 6.

Competitive reactions of 3-hydroxymethyl-2-butanone (2) and 3-methyl-2-butanone (9) with trioxane. A solution of 2 (10.2 g, 0.10 mole) and 9 (8.6 g, 0.10 mole) in chloroform (50 ml) was added during 4 min to a refluxing solution of trioxane (6.0 g, 0.067 mole) and boron trifluoride etherate (5.0 g, 0.035 mole). Water was removed continuously by a water trap. The reaction mixture was cooled 25 min after the addition of the ketone solution, washed with water and neutralized with sodium bicarbonate. The yield of the reaction product, 5, and the amount of unchanged 9 were found to be 11.8 g (82 %) and 8.0 g (95 %), respectively.

Reaction of 3-methyl-2-butanone (9) with trioxane. A solution of 9 (43 g, 0.50 mole) and trioxane (15 g, 0.17 mole) in chloroform (100 ml) was heated to reflux, and boron trifluoride etherate (7.0 g, 0.05 mole) was added. Water was removed by a water trap. After a reaction time of 90 min the solution was cooled, washed with water, neutralized with sodium bicarbonate, and dried over anhydrous calcium sulfate. The solvent as well as unchanged ketone 9 were distilled off under reduced pressure. The residue was distilled under vacuum through a Claisen head, and the main fraction (b.p._{0.3} 92–95°) crystallized on cooling. Recrystallization from petroleum ether yielded colourless plates, m.p. 33–34.5°. The product was characterized as the formal of 3,3-dimethyl-4-hydroxy-2-butanone (10) by IR and NMR spectra. Yield 11.2 g (28 %). Acid hydrolysis of 10 yielded 3,3-dimethyl-4-hydroxy-2-butanone, identified by VPC. An authentic sample of 3,3-dimethyl-4-hydroxy-2-butanone was prepared according to Dubois.²⁴

3-Methoxymethyl-2-butanone (12). Methyl isopropenyl ketone (8) (94 g, 1.1 moles) and sodium methoxide (2 g, 0.04 mole) were dissolved in methanol (1000 ml), and the solution was allowed to stand at room temperature for 3 days. Water (1500 ml) was added, and the solution was saturated with sodium chloride. The solution was extracted with chloroform, and after drying over sodium sulfate the extract was distilled through a packed column at atmospheric pressure to remove methanol and chloroform. The residue was distilled at reduced pressure through a Vigreux column. The main fraction, b.p.₃₈ 64–65°, after redistillation b.p.₁₃ 43°, was characterized as 3-methoxymethyl-2-butanone (12) by IR and NMR spectra and elemental analysis. (Found: C 62.29; H 10.52. Calc. for C₆H₁₂O₂: C 62.04; H 10.42). Yield 68 g (54 %).

Reaction of 3-acetoxymethyl-2-butanone (11) with trioxane. A solution of 11 (3.60 g, 0.026 mole), obtained from 2 with acetic anhydride-pyridine, b.p._{0.3} 43°, and trioxane (2.25 g, 0.025 mole) in chloroform (total volume 100 ml) was heated to reflux, and boron trifluoride etherate (3 ml) was added. After a reaction time of 20 min the amount of unconsumed 11 was found to be 2.9 g (80 %) by VPC.

Reaction of 3-methoxymethyl-2-butanone (12) with trioxane. If the methyl ether 12 was treated as described for 11, 79 % of the compound was unconsumed after a reaction time of 20 min.

Deuterium exchange experiments. 2-Butanone (0.10 g, 1.39 mmoles) and 3-hydroxymethyl-2-butanone (2) (0.141 g, 1.38 mmoles), respectively, were dissolved in a 5 M solution of deuterium chloride in deuterium oxide (0.5 ml). The solutions were kept in NMR test tubes in the NMR spectrometer (temp. 37°), and the rates of the exchange reactions were determined by integrating, at 10 min intervals during 1 h, the NMR signals from the protons in the 1- and 3-positions of the ketones as well as those from the protons of the hydration product from 2, *i.e.* methyl isopropenyl ketone (8). The non-exchangeable protons in the compounds served as internal standards.

Reaction of 2-butanone with aqueous formaldehyde. To a solution of 2-butanone (144 g, 2 moles) in 35 % aqueous formaldehyde (200 g, 2.3 moles of CH₂O) 30 ml of sulfuric acid was added, and the solution was refluxed for 3 h. The reflux condenser was exchanged for a take-off condenser and the reaction mixture was distilled, yielding a mixture of 2-butanone, water and methyl isopropenyl ketone (8). The yield of 8 was found to be 87.7 g (52 %) by VPC.

Dehydration of 3-hydroxymethyl-2-butanone (2). a) A solution of 2 (10.5 g, 0.10 mole) in chloroform (100 ml) was heated to reflux with stirring. Sulfuric acid (2 ml) was added. Water was removed continuously by a water trap. After a reaction time of 15 min the solution was cooled and neutralized with sodium bicarbonate. The yield of methyl isopropenyl ketone (8) was found to be 7.6 g (88 %) by VPC.

b) Boron trifluoride etherate (3 ml) as catalyst instead of sulfuric acid gave 2.4 g (28 %) of compound 8.

Reaction of methyl isopropenyl ketone (8) with trioxane. a) A solution of 8 (16.2 g, 0.20 mole) and trioxane (12 g, 0.13 mole) in chloroform (100 ml) was heated to reflux with stirring, and sulfuric acid (4 ml) was added. After a reaction time of 60 min the solution was cooled and treated with water and sodium bicarbonate, and the yield of 5 was found to be 7.0 g (24 %) by VPC. In addition to unchanged ketone 8, only minor amounts of other products were present, as indicated by VPC and thin layer chromatography.

b) A solution of 8 (12 g, 0.14 mole) and trioxane (17 g, 0.19 mole) in chloroform (100 ml) was heated to reflux and boron trifluoride etherate (5.0 g, 0.035 mole) was added. After a reaction time of 2 h the solution was cooled and treated with water and sodium bicarbonate. The reaction mixture was found to contain 1.1 g (5 %) of compound 5 in addition to a large proportion of unchanged ketone 8.

Formation of 5-acetyl-5-methyl-1,3-dioxane (5) in various solvents. 2-Butanone (1.80 g, 0.025 mole) and trioxane (1.35 g, 0.015 mole) were dissolved in various solvents (see Table 1). The volume of each solution was 100 ml. The solutions were equilibrated for 20 min in a thermostat at 60° ± 0.05° with stirring. Boron trifluoride etherate (3.0 ml) was added, and samples were withdrawn 5, 10, 15, 20, and 30 min after the addition of the catalyst. The samples were cooled rapidly to 0° and neutralized with sodium bicarbonate. The yield of 5 was determined by VPC. The results are presented in Fig. 7.

Comparative experiments on the formation of 5-acetyl-5-methyl-1,3-dioxane (5) in nitromethane solution. a) *From 2-butanone.* A stirred solution of trioxane (2.25 g, 0.025 mole) in nitromethane (75 ml) was heated to 60° in a thermostat, and boron trifluoride etherate (2.0 ml) was added. After 2 min a solution of 2-butanone (1.08 g, 0.015 mole) in nitromethane (25 ml), preheated to 60°, was added during 3 min. The solution was cooled rapidly 6 min after the beginning of the addition of the ketone. The volume was measured and a sample neutralized with sodium bicarbonate. The yield of 5 was found to be 0.32 g (15 %) by VPC.

b) *From 3-hydroxymethyl-2-butanone (2).* In an experiment similar to a) a yield of 1.97 g (91 %) of 5 was found by VPC.

Effect of deuteration on the formation of 5-acetyl-5-methyl-1,3-dioxane (5) from 2-butanone in nitromethane solution. a) Reaction of 1,1,1,3,3-pentadeutero-2-butanone with trioxane. An azeotropic mixture of pentadeutero-2-butanone and deuterium oxide obtained from the deuteration of 2-butanone (see above) was dissolved in nitromethane, and the solution was dried overnight over anhydrous calcium sulfate. The concentration of deuterated ketone in the solution was determined by VPC. Samples of the solution were used to prepare nitromethane solutions (100 ml) containing trioxane (0.015 mole) and deuterated ketone (0.010, 0.015, 0.020, 0.025, and 0.035 mole, respectively). The solutions were heated with stirring to $60^{\circ} \pm 0.05^{\circ}$ in a thermostat. Boron trifluoride etherate (3.0 ml) was added, and samples were withdrawn 5, 10, 15, and 20 min after the addition of the catalyst. The samples were cooled rapidly to 0° and neutralized with sodium bicarbonate. The concentration of 5-acetyl- d_5 -5-methyl-1,3-dioxane in the samples was determined by VPC, and the initial rates of formation of the 1,3-dioxane obtained from the slopes of the time-concentration curves. The results are presented in Fig. 8.

b) Reaction of 2-butanone with trioxane. Solutions (100 ml) in nitromethane of trioxane (0.015 mole) and 2-butanone (0.010, 0.015, 0.025, and 0.035 mole, respectively) were treated as described under a). The concentration of 5-acetyl-5-methyl-1,3-dioxane (5) in the samples was determined by VPC, and the initial rates of formation of 5 obtained from the initial slopes of the time-concentration curves. The results are given in Fig. 8.

In a further series of experiments solutions in nitromethane (100 ml) of 2-butanone (0.025 mole) and trioxane (0.015, 0.025, and 0.035 mole, respectively) were treated as above. The results are given in Fig. 9.

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