

The Formaldehyde Species Reacting in Base-catalyzed Aldol Condensations

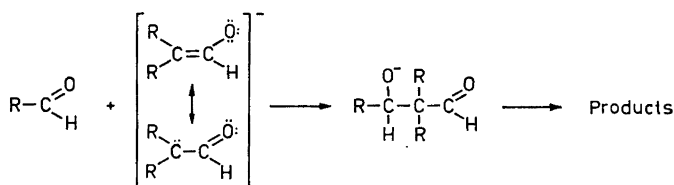
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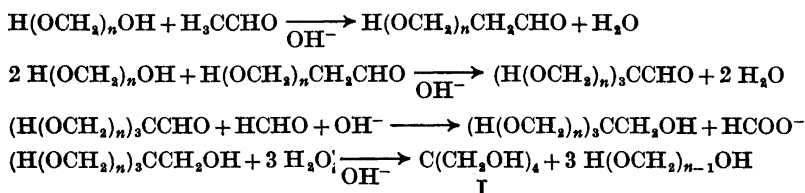
The mechanism of formation of by-products containing ether linkages in some base-catalyzed aldol condensations with formaldehyde is discussed. On the basis of experimental evidence it is concluded that these by-products are not formed *via* a condensation reaction with hydrates or hemiformals of formaldehyde. Therefore, formaldehyde must react in base-catalyzed aldol condensations exclusively in its free monomeric form even in hydroxylic solvents.

It is generally assumed that in base-catalyzed aldol type reactions between an aldehyde and an anion (such as an enolate ion in the normal aldol condensation), the aldehyde reacts in its free monomeric form¹ (Scheme 1).

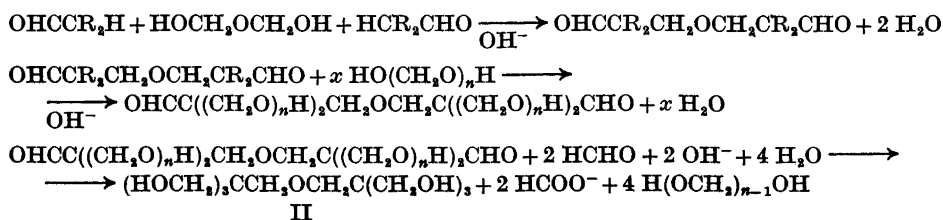
Scheme 1



The formation of pentaerythritol (I) from formaldehyde and acetaldehyde is generally looked upon as a series of aldol condensations, followed by a crossed Cannizzaro reaction. In order to explain the formation of dipentaerythritol (II) as a by-product of this reaction, Barth *et al.*² have proposed a reaction scheme for the aldol reactions, quite different from that shown in Scheme 1. These authors suggest that at least formaldehyde may react in the form of a monomeric or oligomeric hydrate, or as a hemiacetal rather than in its free monomeric aldehyde form. They give reaction schemes for the condensation between formaldehyde and acetaldehyde, leading ultimately to the formation of a mixture of I (Scheme 2) and II (Scheme 3).



Scheme 2



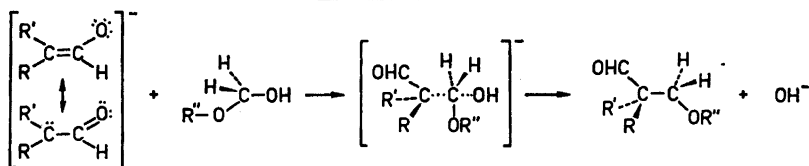
Scheme 3

In this scheme, any R can be either H or $(\text{CH}_2\text{O})_n\text{H}$.

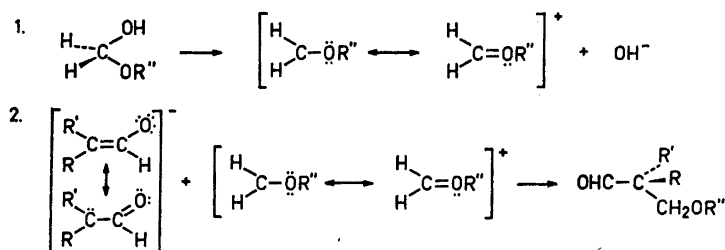
In the ultimate product II, the ether linkage present in the dimeric formaldehyde hydrate shown in the first line of Scheme 3 is still intact.

The actual mechanism of these reactions is not discussed by Barth and coworkers. Their proposal obviously would imply mechanistic steps analogous to an $\text{S}_{\text{N}}2$ (Scheme 4) or an $\text{S}_{\text{N}}1$ reaction (Scheme 5) (in these two schemes, R, R', and R'' can be H or any alkyl or aryl group). In this respect, the proposal is of more general interest, since it formally could be applied to other similar aldol reactions as well.

Scheme 4

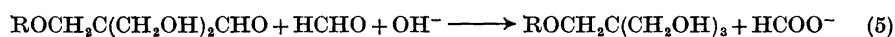
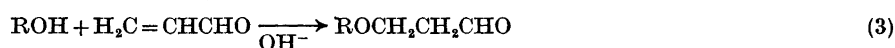
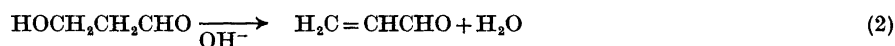


Scheme 5



If such reactions actually occur, one might expect that acetals or at least formals could be formed or hydrolyzed in alkaline media. The formation of acetals could formally be written either as a nucleophilic attack by an alkoxide anion on a hemiacetal carbon atom in analogy with Scheme 4, giving an acetal and a hydroxide ion, or as an attack by an alkoxide ion on the intermediate carbonium ion shown in Scheme 5. The hydrolysis could then simply be pictured as the reversal of one or the other of these mechanisms. Since it is well known that such reactions do not take place under alkaline conditions, the mechanisms for aldol ether formation shown in Schemes 4 and 5 are unlikely.

A mechanism for the formation of the ether linkage in dipentaerythritol, which differs from that proposed by Barth *et al.*, has been suggested by Wawzonek and Rees.³ According to these authors, β -hydroxyaldehydes formed in reactions between formaldehyde and other aldehydes, such as acetaldehyde (Scheme 6, Eqn. 1), undergo dehydration (Eqn. 2) in the alkaline medium. Base-catalyzed addition of an alcohol to the α,β -unsaturated aldehyde thus formed will give a β -alkoxyaldehyde (Eqn. 3). Additional aldol condensation steps (Eqn. 4), followed by a crossed Cannizzaro reaction (Eqn. 5), give a product containing an ether linkage.

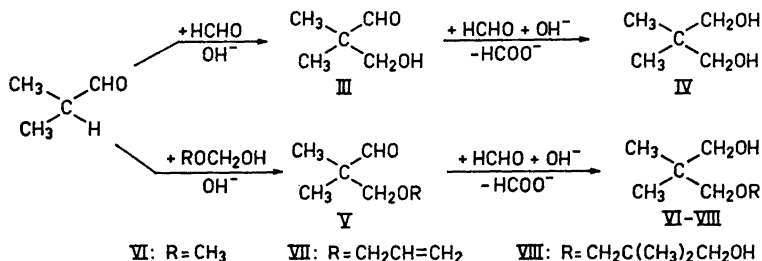


Scheme 6

It is evident that only aldehydes with at least two α -hydrogens can give rise to ethers, if this reaction path is followed. Otherwise, the β -hydroxyaldehyde formed in the first step cannot be dehydrated.

In order to test the correctness of the hypothesis advanced by Barth *et al.*, we have examined the base-catalyzed reaction between isobutyraldehyde and formaldehyde (Scheme 7). In this case, dehydration of the aldol primarily

Scheme 7



formed, 2,2-dimethyl-3-hydroxypropanal (III, pentaldol), cannot take place, and therefore, ether formation according to the reaction scheme proposed by Wawzonek and Rees is excluded. Such ether formation, however, would be possible if the idea of Barth *et al.* is correct (*cf.* Scheme 7, reaction *via* V).

Thus, if the reaction is carried out in concentrated aqueous solution, at least partial formation of 2,2,6,6-tetramethyl-4-oxa-1,7-heptanediol (VIII, see Scheme 7) could be expected, since, under these conditions, the isobutyraldehyde could react with the hemiformal of III or IV. Compound VIII is closely related to dipentaerythritol (II, 2,2,6,6-tetrakis(hydroxymethyl)-4-oxa-1,7-heptanediol). Similarly, if the reaction is carried out in alcoholic rather than in aqueous solution, the formation of ethers of IV, corresponding to the alcohol used, would be expected to take place. Experiments have been carried out using water, methanol, and allyl alcohol, respectively, as solvents.

The ethers VI,⁴ VII, and VIII have been synthesized. When the reaction between formaldehyde and isobutyraldehyde was carried out under the different reaction conditions mentioned, these ethers were shown not to be products in amounts detectable by VPC. It is therefore concluded that the reaction path suggested by Barth *et al.* is not even followed in hydroxylic solvents, where the conditions should be most favourable because of the extensive formation of hemiformals in such media. This supports the view that in base-catalyzed aldol condensations with formaldehyde, this latter reacts exclusively in its free monomeric form.

EXPERIMENTAL

Commercial purum grade organic chemicals were generally tested by vapour phase chromatography (VPC) before use, and in most cases redistilled. The methanol was of Merck's *p.a.* quality. NMR-spectra (in CDCl_3 , with TMS as internal reference) were recorded on a Varian A-60 spectrometer. VPC was performed, using a Perkin-Elmer 800 instrument.

2,2-Dimethyl-3-methoxypropanol (VI). The method reported by Brown and van Gulick⁴ was used. The product boiling between 154–155° was collected, and by means of VPC and TLC (thin layer chromatography) was found to contain at least two minor impurities. Compound VI was purified by means of chromatography on a silica gel column with benzene-diisopropyl ether (4:1) as eluent, followed by distillation. (Found: C 60.95; H 12.19. Calc. for $\text{C}_6\text{H}_{14}\text{O}_2$: C 60.98; H 11.94.) The NMR-spectrum showed five peaks, all singlets (δ in ppm): 0.90 (6H, $\text{C}(\text{CH}_3)_2$); 3.02 (1H, OH); 3.22 (2H, CCH_2OCH_3); 3.33 (3H, OCH_3) and 3.40 (2H, CCH_2OH).

2,2-Dimethyl-3-allyloxypropanol (VII). The synthesis was analogous to that reported for the production of allyl ethers of pentaerythritol.⁵ To a solution of 0.5 mol of IV in 0.5 mol of DMSO, 0.6 mol of NaOH was added under vigorous stirring. The reaction mixture was heated to 95°, at which temperature 0.6 mol of allyl bromide was added dropwise under continued stirring. After 5 h, the mixture was cooled and filtered. The filtrate was diluted with CHCl_3 to 250 ml, and extracted twice with 50 ml of water to remove most of the DMSO. The chloroform layer was dried, filtered and distilled through a Vigreux column. The product was collected at 80–85°/15 mmHg, and traces of DMSO were removed by chromatography on a silica gel column. With ethyl acetate as eluent, compound VII was obtained in pure form after redistillation. (Found: C 66.21; H 11.15; O 22.68. Calc. for $\text{C}_9\text{H}_{16}\text{O}_2$: C 66.63; H 11.19; O 22.18.) The NMR-spectrum showed, in addition to the multiplets from the allyloxy group, four singlets (δ in ppm): 0.90 (6H, $\text{C}(\text{CH}_3)_2$); 2.98 (1H, OH); 3.26 (2H, $\text{CCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$) and 3.39 (2H, CH_2OH).

2,2,6,6-Tetramethyl-4-oxa-1,7-heptanediol (VIII). Initial experiments were made to synthesize the diol VIII with variations of the Williamson ether synthesis in different

solvents. However, attempts to react the dry monosodium salt of IV with 3-bromo-2,2-dimethylpropanol in DMSO gave unreacted IV only. This failure is probably due to the strong steric hindrance in the neopentyl-type halide. Synthesis of VIII was finally achieved by alcoholysis of 3,3-dimethyloxetane by IV, using CH_2Cl_2 as solvent. The crude oxetane fraction (30 g) obtained by the method of Searles *et al.*⁸ was added dropwise during a 4 h period to a vigorously stirred and refluxing solution of 32 g of IV in 700 ml of CH_2Cl_2 in the presence of 2 ml of conc. sulfuric acid. After further refluxing overnight, the reaction mixture was washed once with saturated aqueous NaHCO_3 and once with water, and then dried. Removal of the solvent gave 38.5 g of an oil which was found by VPC to contain about 40 % of VIII. Acetylation of the oil with acetic anhydride gave 45 g of an oil which was distilled through a short Vigreux column. At 91–94°/0.3 mmHg, 9 g of almost pure diacetate of VIII was collected. Preparative VPC, followed by preparative TLC, removed two persistent impurities, and a final microdistillation gave the diacetate of VIII in analytically pure form. (Found: C 61.16; H 9.49. Calc. for $\text{C}_{14}\text{H}_{20}\text{O}_5$: C 61.29; H 9.55.) The NMR-spectrum showed four singlets (δ in ppm): 0.93 (12H, $\text{C}(\text{CH}_3)_2$); 2.06 (6H, OCOCH_3); 3.15 (4H, $\text{CCH}_2\text{OCH}_2\text{C}$) and 3.89 (4H, $\text{CCH}_2\text{OCOCH}_3$).

Condensations of isobutyraldehyde with formaldehyde. A. In water. A mixture of 78.2 g of paraformaldehyde (96 %, 2.50 mol of formaldehyde), 250 ml of water and 100 mg of NaOH was stirred, until all solid material had disappeared (30 min/75°). A solution of 50 g of NaOH (1.25 mol) in 250 ml of water was added. After adjustment of the temperature to 25°, 72.2 g (1.0 mol) of isobutyraldehyde was added dropwise under stirring during a 25 min period. Stirring was continued for 1 h at 28° and then for 16 h at 44°. The reaction mixture was cooled and neutralized to pH 7 with 12.8 ml of 0.25 M H_2SO_4 . After being saturated with NaCl, the reaction mixture was extracted with 4 × 400 ml of EtOAc. After drying of the extract and removal of the solvent, 99.3 g of a crystalline residue was obtained. After drying for 5 h at 25°/0.5 mmHg, the weight of this material was 98.2 g (94.4 % crude yield) and its melting range 121–129°. VPC of the acetylated product (0.5 g of product, 0.5 ml of pyridine and 5 ml of AcOAc; 30 min at 70°) showed the presence of at least 4 minor impurities, but none of them had the same retention time as the diacetate of VIII. Two different columns were used, namely 1.20 m × 1/8", 10 % XF 1150 on Chromosorb W and 1.80 m × 1/8", 5 % Carbowax 20M on Chromosorb G. The chromatograms were compared with those of authentic material, and as little as 0.02 % of VIII should have been detected.

B. In methanol. (a) With NaOCH_3 as the condensing agent: 11.5 g of Na (0.5 mol) in pieces was stirred under N_2 in 1 l of absolute CH_3OH , until the metal had reacted. After a temperature adjustment to 25°, 32 g (1.05 mol) of paraformaldehyde (99.0 %) was added, and stirring was continued until all solid material had disappeared. To the resulting clear, colourless solution, 36.1 g of isobutyraldehyde (0.5 mol) was added dropwise at 25–28° during a period of 1.5 h. During the following 3 h, the temperature was gradually raised to 65°, and the mixture was then left at this temperature under stirring for 4.5 days. A slow stream of N_2 was passed over the mixture throughout the reaction time, but the mixture gradually became dark brown. After cooling, the mixture was neutralized with 23 g of AcOH (0.38 mol), which caused a considerable decrease in colour. The bulk of the methanol was distilled off at 30°/60 mmHg, and the residue was treated with 500 ml of CHCl_3 and 100 ml of water. The aqueous phase, which contained most of the coloured matter, was removed, and the organic phase was washed with 50 ml of water. The water extracts were combined and washed with 100 ml of CHCl_3 , and then discarded. The combined chloroform extracts were dried over Na_2SO_4 and filtered. The solvent was distilled off, leaving an oily residue. The distillate was combined with the methanol distilled off previously. The solvents were removed by distillation at atmospheric pressure with the use of an efficient column, until the volume of the residue was about 10 ml. This residue was acetylated and examined in the same way as the oily residue obtained from the chloroform phase. The same columns were used as under A. As indicated by the large amount of AcOH needed for neutralization, the Cannizzaro reaction is extremely slow under the conditions used in this experiment. As indicated by the chromatogram, several condensation products were formed. At least with one of the columns, however, no compound with the retention time of the acetate of VI was observed.

(b) With KOH. A mixture of 18.5 g of paraformaldehyde (99.0 %, 0.6 mol) and 250 ml of abs. methanol was shaken in the presence of 100 mg of KOH. After brief warming to 50°, all solid material had disappeared, and the solution was cooled and neutralized

with a few drops of formic acid. After addition of 14.55 g (0.2 mol) of isobutyraldehyde, the resulting solution was added dropwise under stirring to a solution of 2 g of KOH in 250 ml of abs. methanol. Additional portions of about 1.7 g of KOH were added to the reaction mixture with about 30 min intervals, until a total of 14.1 g (0.25 mol) of KOH had been added. The aldehyde mixture was added over a 4 h period, after which stirring and warming were continued an additional 17 h. After this period, the clear colourless solution was cooled and neutralized with 2.4 g of AcOH (0.04 mol), and the solvent was removed under reduced pressure. The residue was extracted with 500 ml of CHCl_3 , and the resulting solution was shaken first with 100, and then with 50 ml of saturated brine. The combined water extracts were shaken with 100 ml of CHCl_3 , and then discarded. The combined chloroform extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was acetylated and tested by VPC. The combined solvents were examined as in the preceding experiment. Neither in the main product, nor in the solvent mixture could any acetate of VI be detected.

C. In allyl alcohol. The same conditions were used as in the second experiment under B, with the following exceptions. Allyl alcohol replaced methanol. The aldehyde mixture was added over a 4 h period, and the reaction mixture was neutralized after one additional hour. The solvent was removed by azeotropic distillation with water, and the residual crystalline mass was extracted repeatedly with CHCl_3 . The latter solvent was removed from the combined extracts under reduced pressure, and the residue was acetylated and tested by VPC. No acetate of VII could be detected. In a similar experiment with butyraldehyde instead of isobutyraldehyde, an optimum yield of 58 % of 2-ethyl-2-allyloxymethyl-1,3-propanediol was obtained.⁷

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