The Mechanism of Acetal Formation by Aldehydes or Ketones with Orthoformates

By J. W. SCHEEREN,* J. E. W. VAN MELICK, and R. J. F. NIVARD
(*Department of Organic Chemistry, R.C. University, Nijmegen, The Netherlands*)

Summary The formation of acetals from aldehydes and orthoformates does not proceed *via* an intermediate addition product; an alternative for the function of the orthoformate is given.

ALTHOUGH the use of an orthoformate in the synthesis of acetals[1] is now general,[2] especially in the acetalisation of ketones, its function has not been fully explained. The orthoformate might participate in a reaction[2–4] according to

$$R^1R^2CO + HC(OR^3)_3 \xrightarrow{H^+} \underset{(I)}{R^1R^2C(OR^3)OCH(OR^3)_2} \xrightarrow{H^+} R^1R^2C(OR^3)_2 + HCO_2R^3 \qquad (1)$$

However, the strong acceleration of the reaction by addition of alcohol has been ascribed to an irreversible water-binding role of orthoformate[2]:

$$\begin{aligned} R^1R^2CO + R^3OH &\xrightarrow{H^+} R^1R^2C(OR^3)_2 + H_2O \\ HC(OR^3)_3 + H_2O &\rightarrow 2R^3OH + HCO_2R^3 \qquad (2) \end{aligned}$$

While investigating the synthesis and stability of mixed orthoformates[6] we were able to synthesize compounds like (I; $R^1 = H$, $R^2 = H$ or Me, $R^3 = $ Me or Et) from dialkoxymethyl acetate[7] (II) and hemiacetals (III), using an excess of triethylamine to prevent acid-catalysed decomposition of (I).

$$\underset{(III)}{R^1R^2C(OR^3)OH} + \underset{(II)}{HC(OR^3)_2OCOMe} \rightarrow \underset{(I)}{R^1R^2C(OR^3)OCH(OR^3)_2} + MeCO_2H \qquad (3)$$

Since the hemiacetal of acetaldehyde is in rapid equilibrium with alcohol and aldehyde, the main product in that case was trialkyl orthoformate formed from (II) and the alcohol.[6] Compound (I) with $R^1 = H$, $R^2 = $ Me, $R^3 = $ Me or Et could only be obtained in 15—20% yields; for $R^1 = R^2 = H$, $R^3 = $ Et, however, the yield was about 50%.

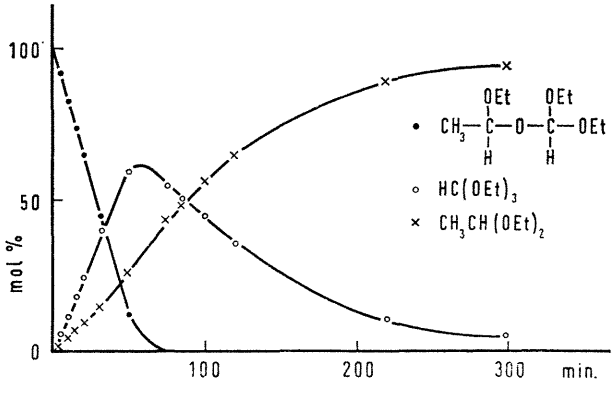


FIGURE. *Decomposition of* (I; $R^1 = $ Me, $R^2 = H$, $R^3 = $ Et) *with time, under the influence of* $F_3C{\cdot}CO_2H$.

The decomposition of (I) was studied by n.m.r. spectroscopy. After addition of a drop of trifluoroacetic acid to 1 ml. of the pure compound the n.m.r. spectrum of the reaction mixture was traced at regular time intervals. The concentrations of (I) and alkyl orthoformate were measured by integration of the $H–C(–O–)_3$ proton absorptions and that of the acetal by integrating the α-proton quartet.

In the Figure the concentrations of (I; $R^1 = $ Me, $R^2 = H$, $R^3 = $ Et), ethyl orthoformate and acetaldehyde diethyl acetal are plotted against time. The concentration of acetaldehyde has not been given because it was practically the same as that of ethyl orthoformate during the whole course of the reaction. The data reveal that formation of acetal must be preceded by decomposition of (I) into orthoformate and aldehyde. The velocity of acetal formation appears to depend not on the concentration of (I) but on the concentrations of orthoformate and acetaldehyde; it reaches a maximum value when decomposition of (I) is nearly complete (after 80 min.), and concentrations of ethyl orthoformate and acetaldehyde are at their maximum. To reveal more accurately the course in the first stage of the reaction measurements were repeated at very low acid concentration. Decomposition of (I) is then strongly slowed down (32% in 2 hours). It appeared that the presence of acetal could not be detected until 10 minutes after zero time. At that time 6% of compound (I) had already decomposed and appeared to be present as orthoformate and acetaldehyde. In compounds (I) with $R^1 = H$, $R^2 = R^3 = Me$ and $R^1 = R^2 = H$, $R^3 = Et$ acid-catalysed decomposition and acetalisation appear to be much slower (5% decomposition in 30 min. and 10% in 24 hr., respectively) but similar curves were obtained. In all cases addition of R^3OH accelerates both decomposition and acetal formation to the same degree.

The results are in agreement with the following decomposition scheme:

$$R^1R^2C(OR^3)OCH(OR^3)_2 \overset{H^+}{\rightleftarrows} R^1R^2C(OH)OR^3 + [R^3O\overset{\cdots}{-}CH\overset{\cdots}{-}OR^3]^+ \quad (4)$$

$$R^1R^2C(OH)OR^3 \rightleftarrows R^1R^2C{=}O + R^3OH \quad (5)$$

$$R^3OH + [R^3O\overset{\cdots}{-}CH\overset{\cdots}{-}OR^3]^+ \rightleftarrows (R^3O)_3CH + H^+ \quad (6)$$

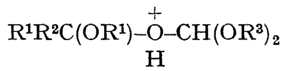
Acetal formation will arise in the same way as in the absence of orthoformates but the water formed will be removed by the dialkoxymethyl carboxonium ion:

$$H_2O + [R^3O\overset{\cdots}{-}CH\overset{\cdots}{-}OR^3]^+ \rightarrow HC(OR^3)_2OH \rightarrow R^3OH + HCO_2R^3 \quad (7)$$

The alternative, direct interaction of (III) with the carboxonium ion as suggested by MacKenzie:[5]

$$R^1R^2C(OH)OR^3 + [R^3O\overset{\cdots}{-}CH\overset{\cdots}{-}OR^3]^+ \rightarrow [R^1R^2C\overset{\cdots}{-}OR^1]^+ + HC(OR^3)_2OH \quad (8)$$

etc., seems less probable. The transition state for this reaction will resemble (I) in one of its protonated forms:



$$R^1R^2C(OR^1){-}\overset{+}{\underset{H}{O}}{-}CH(OR^3)_2$$

and thus acetal formation should be faster at first when (I) is at a maximum.

The scheme (reactions 4—7) has been corroborated by the fact that compounds like (I) from which relatively stable hemiacetals result decompose very slowly at room temperature, *e.g.* $H_2C(OEt)OCH(OEt)_2$.

$CCl_3CH(OEt)OCH(OEt)_2$ does not decompose at all at room temperature; at 100° chloral and orthoformate are formed but of course no acetal.[8] In agreement with the stability of cyanohydrins, compounds like $R^1R^2C(CN)OCH(OR^3)_2$ with $R^1 = Me$, $R^2 = H$ or Me, $R^3 = Me$ or Et show only disproportionation[6] but no decomposition upon addition of acid at room temperature; at 100° a carbonyl compound (R^1R^2CO) and dialkoxymethyl cyanide are formed.

We are studying whether compounds $R^1R^2CXOCH(OR^3)_2$, in which X represents other leaving groups, also decompose according to

$$R^1R^2CXOCH(OR^3)_2 \rightarrow R^1R^2C{=}O + HCX(OR^3)_2.$$

Preliminary experiments with X = AcO revealed that in this case decomposition according to

$$R^1R^2C(OAc)OCH(OR^3)_2 \rightarrow R^1R^2C(OR^3)(OAc) + HCO_2R^3$$

could not be excluded.

(*Received, June 11th*, 1969; *Com.* 834.)

---

[1] L. Claisen, *Ber.*, 1896, **29**, 1005; 1907, **40**, 3903.
[2] Houben-Weyl, "Methoden der organischen Chemie", Georg Thieme Verlag, Stuttgart, 1965, Band VI/3, p. 221.
[3] J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," Benjamin, New York–Amsterdam, 1965, p. 448.
[4] H. W. Post, *J. Org. Chem.*, 1940, **5**, 244.
[5] C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, 1955, **20**, 1695.
[6] J. W. Scheeren and W. Stevens, *Rec. Trav. chim.*, 1969, **88**, 897.
[7] J. W. Scheeren, A. P. M. v.d. Veek, and W. Stevens, *Rec. Trav. chim.*, 1969, **88**, 195.
[8] H. W. Post, *J. Org. Chem.*, 1941, **6**, 830.