April, 1979] BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (4), 1091—1094 (1979) 1091

Formose Reactions. VI. Formose Synthesis in Methanol

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(Received January 6, 1978)

The formose reaction in methanol was compared with that in an aqueous solution. The reaction can occur in aqueous methanol even at a low [CaO]/[HCHO] ratio (0.05), at which the reaction does not take place in an aqueous solution, and the formaldehyde consumption rate decreases with an increase in the methanol concentration. Contrary to the formose reaction in an aqueous solution, the sugar yield in methanol becomes higher with an increase in the formaldehyde concentration. The rates of the sugar degradation and the formaldehyde consumption increase with an increase in the pH. The distribution of products is different from that in an aqueous solution, but both of them are very complex and essentially nonselective.

The formose reaction which forms a complex mixture of sugars from aqueous formaldehyde in the presence of a base, usually $Ca(OH)_2$, has been invesitigated by many workers. Among them, the effects of a nonaqueous solvent, especially methanol, on the reaction have received some attention, mainly in connection with attempts to improve the sugar yield and the selectivity in product formation.[1–4] One significant observation obtained in these studies has been that the sugar yield was found to increase upon the addition of methanol.[2–4] Concerning the effect of methanol on the rate of the formose reaction, two inconsistent experimental results have been reported. Pfeil *et al.*[2] carried out the formose reaction catalyzed by TlOH in aqueous media containing 7—40% of methanol, where the rate of the formaldehyde consumption increased with an increase in the concentration of methanol. Nakai *et al.*[4] reported that the addition of methanol slowed down the rate of the reaction catalyzed by $Ca(OH)_2$ and considered that the accelerating effect of methanol found by Pfeil might be due to impurities in the methanol.

As we have already reported,[5–7] in the formose reaction with $Ca(OH)_2$ in an aqueous solution, the sugar yield varies with the extent of the Cannizzaro reaction occurring, especially during the induction period, and when the ratio $[Ca(OH)_2]/[HCHO]$ is too small (0.05), the formose reaction does not take place. The latter phenomenon has been partly interpreted in terms of pH lowering due to the formation of formic acid by the Cannizzaro reaction. In view of the above results, it seemed interesting to see how the formose reaction is affected by the depression of the Cannizzaro reaction resulting from the addition of methanol. Another aim of the present work is to characterize the formose reaction in a methanol solvent, focussing on the effects of the formaldehyde concentration, the catalyst amount, and the pH on the sugar yield and on the rate of formaldehyde consumption.

Experimental

Materials. The formaldehyde solution in methanol was prepared as follows. After a suspension of 200 g of paraformaldehyde (Merck Co.) in 400 ml of methanol had been refluxed for 7 h, the mixture was filtered. The concentration of formaldehyde in the filtrate was *ca.* 12 M. When the formose reaction was carried out in a 1.0 M formaldehyde solution in methanol in the presence of 0.3 mol/l of a catalyst (CaO, $Ca(OH)_2$, or $CaCO_3$) at 60 °C, the consumption of formaldehyde after 2 h was 67, 41%, or negligible respectively. Thus, the most active CaO was used as the catalyst throughout this work; the catalyst was freshly calcined at 1000 °C for 3 h prior to use to avoid the poor reproducibility caused by the absorption of CO_2 and moisture from air. The methanol was distilled, and the other reagents were of an analytical grade.

Procedure. The reaction was carried out as has been described previously[5,7] and aliquots taken from the reaction mixture at intervals were cooled instantly in a Dry Ice–acetone bath to stop the reaction and were then immediately analyzed. The oxidation-reduction potential (ORP) and pH of the reaction mixture, the formaldehyde consumption, and the sugar yield were measured as has been reported previously.[5,7]

The amount of organic acids (as formic acid) (x M) formed by the Cannizzaro reaction was determined as follows. To a ml of the reaction solution, b ml of 0.05 M HCl was added; after the solution had been back-titrated with 0.05 M KOH (c ml), the amount of calcium ions was determined by titration with 0.01 M EDTA[9] (d ml):

$$x = (0.05c+2\times 0.01d-0.05b)/a.$$

The consumption rate of formaldehyde, $-d[HCHO]/dt$ (M/min), was determined from the maximum slope of the formaldehyde consumption curve. The products were trimethylsilylated by Sweeley's method[10] and the TMS derivatives were analyzed by gas chromatography as has been described previously.[8]

Results and Discussion

Effect of Methanol Concentration. Figure 1 shows the effects of the methanol content on the formose reaction which was carried out at [CaO]/[HCHO] = 0.05 in aqueous methanol. As has been reported previously,[5–7] the formose reaction did not proceed at this [CaO]/[HCHO] ratio unless methanol was added, but the Cannizzaro reaction occurred preferentially. Under these conditions, the formaldehyde consumption was found to be approximately equal to the amount of formaldehyde consumed by the Cannizzaro reaction. The addition of methanol brought about the consumption of the formaldehyde resulting from the formation of sugars. When the methanol content varied in the range from 25 to 100%, the amount of formaldehyde consumed by the Cannizzaro reaction became smaller,

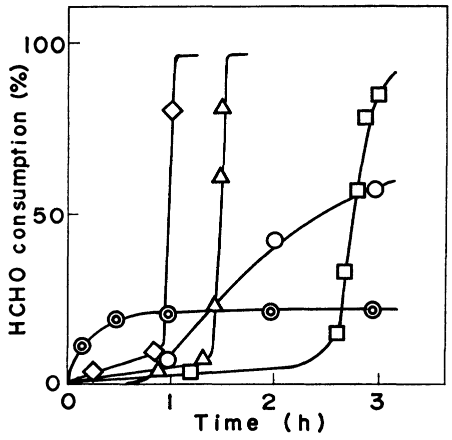

Fig. 1. Effect of methanol concentration on the formose reaction.
[HCHO] = 1.0 M; [CaO] = 0.05 mol/l; temp, 60 °C; total volume = 200 ml. HCHO consumption, [MeOH] (vol %): ◎, 0; ◇, 25; △, 50; □, 75; ○, 100.

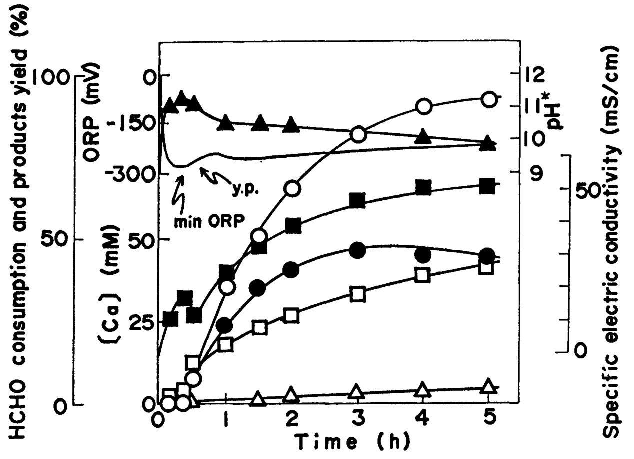

Fig. 2. Potentiometric and products analyses of the formose reaction in methanol.
[HCHO] = 1.0 M; [CaO] = 0.3 mol/l; temp, 60 °C; total volume = 880 ml; ○, formaldehyde; ●, total sugars; △, organic acids; □, [Ca]; ■, electric conductivity; ▲, pH* (apparent pH in methanol); —, ORP.

that is, from *ca.* 12 to 5% for the total formaldehyde consumption. Since methanol obviously prevents the formation of formic acid, the addition of methanol will not appreciably change the pH of the reaction mixture, so the reaction mixture can keep the necessary concentration of CaOH$^+$, which has previously been shown to be the effective catalytic species during the induction period.[6] Figure 1 reveals further that, with an increase in the methanol content, the induction period is prolonged and the formaldehyde consumption rate becomes slower. In 100% methanol, however, the induction period is much more shortened than that in 75% aqueous methanol. This kinetic difference between the reactions in 75 and 100% methanol led us to assume that not only the pH, but also the solvent polarity, may influence the progress of the formose reaction. The solvent-polarity effect on the formose reaction will be reported elsewhere.

The Formose Reaction in 100% Methanol. A typical time-course of the reaction in 100% methanol with respect to physical measures, such as the pH, the oxidation-reduction potential (ORP), and the electric conductivity, and chemical measures, such as the formaldehyde consumption, the sugar yield, the organic acid formation, and the amount of dissolved calcium, is shown in Fig. 2. It has been previously shown that the ORP minimum and maximum indicate the end of the induction period and that of the sugar-forming step respectively in the formose reaction using a Ca(OH)$_2$–H$_2$O system.[7] The method was found to be applicable to the CaO–MeOH system only for determining the end of the induction period. In an aqueous solution, the yellowing point is observable at the end of the sugar-forming step, where the sugar yield reaches its maximum,[5,7] whereas, in methanol, the end of the sugar-forming step is in accord with neither the yellowing point nor the ORP maximum. As the sugar formation proceeds, the pH of the reaction mixture decreases and the amount of dissolved calcium increases, as was observed in the formose reaction in an aqueous solution.[6] A characteristic change was observed in the electric conductivity with a small drop between the ORP minimum and the yellowing point. Since the electric conductivity increases in parallel with the amount of dissolved calcium ion, it is assumed that the observed drop is due to a change in the dissolved calcium-ion species, such as the formation of a complex between calcium and a product which may be a catalytic species in the formose reaction.[12] This assumption is supported by the fact that the electric conductivity of a 0.1 M methanol solution of calcium chloride decreased from 38 to 23 mS/cm upon the addition of fructose (0.5 M).

As is to be expected from the inhibitory role of methanol on the Cannizzaro reaction, the formation of organic acids (mainly formic acid) is depressed, but the sugar yield does not increase so much as expected. This fact indicates that the sugar yield in methanol would be influenced also by factors other than the Cannizzaro reaction. One such possible factor is a competition between the formation and the degradation of formose sugars. This is supported by the facts that the formaldehyde consumption rate (possibly the formose-forming rate) in methanol is much slower than that in aqueous solution, and that the yellowing point, which implies the degradation of products, appears at an early stage of the total formose reaction in methanol, as is shown in Fig. 2.

In order to obtain further information on the formose-degradation process, the reaction was followed by measuring the ultraviolet spectrum of aliquots. Although no ultraviolet absorption was observed until the yellowing point, a broad absorption maximum at *ca.* 300 nm became observable thereafter and gradually increased. The absorption maximum is shifted from *ca.* 300 to *ca.* 260 nm when the apparent pH (pH*) of the solution is changed from 13.0 to 1.0. The Tilman reagent is reduced strongly by the reaction mixture. On the basis

TABLE 1. EFFECTS OF [HCHO] AND [CaO] ON THE FORMOSE REACTION IN METHANOL[a)]

[CaO] (mol/l)	[HCHO] (M)	T_{min} (min)	T_{max}[b)] (min)	Sugar yield at T_{max} (%)	r_c (M/min)
0.15	0.2	60	$(17)_{300}$[c)]	13	0.01×10^{-2}
0.15	0.4	20	$(72)_{240}$[c)]	32	0.19×10^{-2}
0.15	1.0	12	240	44	0.55×10^{-2}
0.15	2.0	14	180	52	2.23×10^{-2}
0.15	3.0	22	150	56	2.51×10^{-2}
0.15	5.0	60	$(67)_{300}$[c)]	57	3.16×10^{-2}
0.05	0.5	30	$(59)_{290}$[c)]	36	0.14×10^{-2}
0.2	0.5	20	$(72)_{180}$[c)]	32	0.20×10^{-2}
0.5	0.5	24	180	32	0.79×10^{-2}
0.5	1.0	14	120	40	1.00×10^{-2}
0.5	2.0	12	150	45	2.82×10^{-2}
0.5	3.0	140	220	42	2.41×10^{-2}
0.5	5.0	150	240	50	7.93×10^{-2}

a) Temp, 60 °C; total volume, 200 ml. b) The time when the sugar yield became highest and the HCHO consumption was above 95%. c) The number in parentheses is the HCHO consumption (%) at the time (min) shown by the subscript.

of these results, one of the degradation products is assumed to be a reductone (Triose reductone: λ_{max}, 266 nm (pH, 1.8); 314 (13.5)).[11)] Formose reactions in methanol were carried out with various CaO amounts and formaldehyde concentrations; the results obtained are summarized in Table 1. At a constant formaldehyde concentration ([CaO]/[HCHO]>0.1), the sugar yields are virtually independent of the CaO amount. At a constant CaO amount, the sugar yield increases with an increase in the formaldehyde concentration, but the sugar yield is independent of the formaldehyde concentration when the concentration is high (>2.0 M). These features are significantly different from those in an aqueous solution. The sugar yield in an aqueous solution is known to decrease with an increase in the formaldehyde concentration.[5)] These differences are mainly attributable to an inhibitory effect of methanol on the Cannizzaro reaction.

Since the formaldehyde consumption rate (r_c) in methanol is relatively slow, as has been noted above (Table 1), the product degradation rate (r_d) may appreciably influence the sugar yield. (Because of the complex nature of formose decomposition, the quantitative evaluation of r_d was difficult. Therefore, the decrease in the sugar content analyzed by the known method[13)] was regarded as a rough measure of r_d.) Considering that the observed pH decreases as the formation of sugars progresses (Fig. 2), the high sugar yield at a high level of formaldehyde might be attributable to a slower r_d resulting from the pH lowering, accompanied by the progress of the sugar formation. On the other hand, the sugar yield is rather independent of r_d in an aqueous solution, because the r_c in the formose-forming step is very fast. For example, $r_c=37.5\times10^{-2}$ M/min at [HCHO]=1.0 M and [Ca(OH)$_2$]=0.13 mol/l.[7)] It seems likely that the sugar yield in methanol is also largely dependent on r_c. This idea is supported by the fact that the sugar yield increases with an increase in r_c (Table 1).

TABLE 2. EFFECT OF THE pH ON THE FORMOSE REACTION IN METHANOL

[HCHO]=1.0 M; temp, 60 °C

[Ca] (M)	pH*[a)]	T_{min} (min)	T_{max} (min)	Sugar yield at T_{max} (%)	r_c (M/min)
0.05	9.0	84	300	58	0.95×10^{-2}
0.05	9.5	22	150	57	1.58×10^{-2}
0.05	10.0	10	150	50	1.70×10^{-2}
0.05	10.5	8	70	44	2.70×10^{-2}
0.1	8.5	200	600	61	0.34×10^{-2}
0.1[b)]	9.0	52	210	59	1.51×10^{-2}
0.1[b)]	9.5	16	80	56	2.51×10^{-2}
0.1[b)]	10.0	7	60	49	3.98×10^{-2}

a) The apparent pH in methanol measured by electrodes adjusted with aqueous buffers. b) The reaction mixture became heterogeneous near the yellowing point.

In order to examine the effect of the pH on the formose reaction, CaCl$_2$ was used instead of CaO and the pH of the solution was adjusted by methanolic KOH. The results obtained are shown in Table 2. Under the conditions at low calcium concentrations (<0.1 M), the reaction mixture is homogeneous. The sugar yield increases with a decrease in the pH, though r_c slows down at a lower pH. Both r_c and r_d will vary with a change in the pH, and, at a very low pH (pH*=8.5), r_d is assumed to be extremely slow compared with r_c.

The pH and the catalyst concentration were found to affect the induction period in a homogeneous system. As is shown in Table 2, the induction period, T_{min} (the time up to the ORP minimum), becomes shorter with increases in the pH and the calcium concentration. This indicates that the induction step of the formose reaction in methanol may also be catalyzed mainly by CaOH$^+$, as in aqueous media.[6)] Although the sugar yield in an aqueous solution increases as the induction

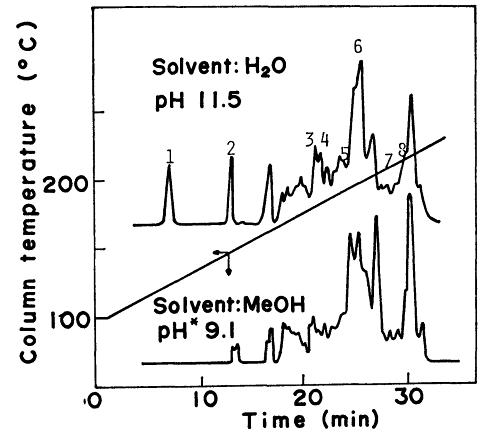

Fig. 3. Gas chromatograms of TMS derivatives of products. Column, SE-30 on Chromosorb W (60—80 mesh); N$_2$ flow rate, 60 ml/min; [HCHO]=1.0 M; [CaCl$_2$]=0.1 M; temp, 60 °C.

1, Glycerol; 2, 2-hydroxymethylglycerol; 3, xylose; 4, xylitol; 5, fructose; 6, 3-hydroxymethyl-1,2,3,4,5-pentanepentol; 7, solbitol, mannitol; 8, glucose.

period becomes shorter,[5,6] there was no relationship between the sugar yield and the length of the induction step in methanol. Although in an aqueous solution, the sugar yield is greatly affected by the amount of formaldehyde consumed by the Cannizzaro reaction occurring in the induction period, in methanol it is mostly influenced by the difference between r_c and r_d.

In summary, in order to obtain formose in a good yield in methanol, the formose reaction should be carried out under conditions in which the concentrations of formaldehyde and calcium ion are as high as possible and the pH is maintained at low values, such as pH*=8.5 (apparent pH).

Product Distribution. Figure 3 shows gas chromatograms of the TMS derivatives of the products obtained in aqueous and methanol solutions. The identities of some of the peaks were assigned by comparison with the retention times for authentic samples. The formation of sugar alcohols in methanol suggests that methanol strongly depresses the Cannizzaro reaction of formaldehyde, but not the cross-Cannizzaro reaction involving the aldoses formed. A comparison of these gas chromatograms indicates that the reaction in methanol produces a smaller amount of sugar alcohols than those in water, and that the product distribution is quite different, although both cases are essentially nonselective.

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