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Formose Reactions

VIII. Solvent Effects in the Formose Reaction[1]

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Effects of aqueous and nonaqueous alcoholic solvents and polar aprotic solvents on the CaO-catalyzed formose reaction were examined. The reaction occurs only in hydroxylic solvents. In alcohol–water solvent systems, the induction period of the reaction was found to correlate with their Z values and with the concentration of dissolved calcium ion. The formose reaction in 90 and 100% methanol was analyzed in some detail, suggesting that the formation of a formaldehyde hemiacetal was essential for the formose reaction in nonaqueous alcoholic solvents, and that competitions among the Cannizzaro, sugar formation, and sugar decomposition reactions are important factors affecting the sugar yield.

INTRODUCTION

The formose reaction, which produces a complex mixture of sugars and sugar alcohols by the base-catalyzed polycondensation of formaldehyde, has a complex nature. Extensive studies by many workers (*1*) and by us (*2–4, 12, 16, 18, 19*) have shown that the induction, formose-forming, and formose-decomposing steps are affected by various factors, such as the concentration of the substrate and catalyst, the kind of catalyst, and pH, and that in consequence the reaction rate in each step, the yield of formose, and the product distribution are altered. Among them, some attention has been drawn to the effects of organic solvent on the formose reaction (*3–10*). For example, the addition of methanol, 2-propanol, or tetrahydrofuran was reported to accelerate the formose reaction (*6–8*), particularly the induction period (*7*), whereas ethylene glycol and glycerol cause the delay of the reaction (*7*). We have shown that the amount of added methanol is an important factor; thus acceleration and retardation occur with the addition of a small and large amount of the solvent, respectively (*3*). The induction step in the formose reaction is more affected by methanol concentration than the formose-forming step. Thus at low methanol concentration, the latter step is scarcely influenced by methanol. This phenomenon agrees with the fact that there is no methanol effect at low methanol concentration on the formose reaction using a continuous stirring tank reactor which has the advantage that rates at the formose-forming step are measured directly (*5*). Moreover, methanol is known to increase the yield of formose by retarding

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the Cannizzaro reaction of formaldehyde (*3*, *7–10*). For the formose reaction in aqueous or pure organic solvents, there may be two principal factors affecting the reaction. In view of the involvement of the hydrated form of formaldehyde (dihydroxymethane) in its initial condensation into glycolaldehyde (*11*), the formation of the solvent adduct may be an important factor when an alcoholic solvent is employed:

$$\mathrm{H_2C{=}O} + \mathrm{ROH} \rightleftharpoons \mathrm{H_2C(OR)(OH)}$$

Our previous observation that the rate of formaldehyde consumption decreases with increased methanol (*3*), reflects the importance of solvent polarity. The rationale of this work has been to systematically study the effects of aqueous and nonaqueous solvents on the formose reaction, in particular focusing on their polarity and adduct-forming ability.

EXPERIMENTAL

Materials. Formaldehyde solution was prepared from paraformaldehyde by refluxing or stirring in each solvent at 60°C followed by filtration from the insolubles. The pH was adjusted by adding KOH dissolved in the same solvent used for each formose reaction. CaO used as catalyst was freshly calcined at 1000°C for 3 hr prior to use to avoid the poor reproducibility caused by the absorption of CO_2 and moisture from air as described in the previous paper (*3*). Other reagents were of an analytical grade.

Procedure. The apparatus and the experimental procedure were virtually the same as those described previously (*3*, *12*), except that the pH of the reaction mixture was adjusted to the initial value by adding a concentrated KOH solution to the solvent from time to time throughout the reaction. Because the pH value of the freshly prepared reaction mixture increased with a gradual increase of the concentration of the dissolved calcium ion species ([Ca]) (*3*), the initial pH was determined when it reached a maximum value at 10–20 min after the formaldehyde solution had been mixed with CaO. The reaction was followed by analyzing aliquots of the well-stirred reaction mixture at intervals. The aliquot taken up was cooled immediately by dry ice–acetone in order to prevent further reactions. The formaldehyde consumption, the sugar yield, the concentration of the dissolved calcium ion, oxidation–reduction potential of the reaction mixture (ORP), and pH were measured by the methods described in previous papers (*3*, *12*). The sugar yield was calculated as glucose based on the supplied formaldehyde.

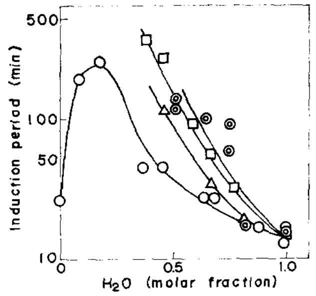


FIG. 1. Relationship between induction period and the H_2O content in various H_2O–alcohol solvent systems. [HCHO] = 1.0 *M*; [CaO] = 0.15 mol/liter; temp. = 60°C; pH was kept at the initial value [apparent pH (pH*), 10.5 to 11.8] by adding KOH; solvent system: ○, H_2O–methanol; △, H_2O–ethanol; □, H_2O–2-propanol; ◎, H_2O–t-butyl alcohol.

Under these reaction conditions, minimum ORP, which is usually observed at the end of the induction period of the formose reaction in an aqueous medium, was obscure in most organic solvents employed. In such cases the induction period (T_i) was determined by extrapolating the formaldehyde consumption curve at the maximum slope to the time-axis. The HCHO consumption rate, which approximately represents the formose-forming rate, was estimated from the maximum slope of the corresponding formaldehyde consumption curves.

Z values (the transition energies re-

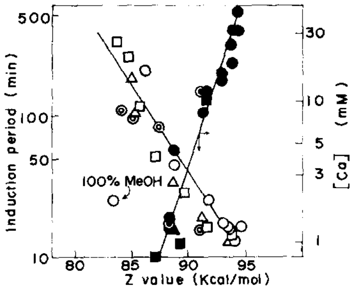


FIG. 2. Relationship between the Z value of various solvent systems and the induction period, and the initial concentration of the dissolved calcium ion in aqueous alcoholic solvents of various $[H_2O]/[ROH]$ ratios. [HCHO] = 1.0 M; [CaO] = 0.15 mol/liter; temp. = 60°C; total volume = 200 ml; pH was kept at the initial value (pH*, 10.5 to 11.8) by adding KOH; solvent system: ○ and ●, H_2O–methanol; △ and ▲, H_2O–ethanol; □ and ■, H_2O–2-propanol; ◎ and ◉, H_2O–t-butyl alcohol.

quired to excite 1-ethyl-4-carbomethoxypyridinium iodide) (*13*) in various solvents were determined at 13°C using a Shimadzu HPS-50L spectrophotometer.

RESULTS AND DISCUSSION

Polarity Effect of Various Alcohol–H_2O Solvent Systems on the Induction Period (T_i)

Figure 1 shows the effects of the alcohol–H_2O solvent systems on the induction period (T_i) of the formose reaction catalyzed by CaO. For a proper comparison, the pH of the reaction mixture was kept to the initial one in each case. There are two factors affecting T_i. T_i increases with decreased H_2O content, and the increase of T_i is dependent upon the kind of alcohol in the order: *t*-butyl alcohol > 2-propanol > ethanol > methanol. In pure ethanol, 2-propanol, and *t*-butyl alcohol, T_i was not observed even after 10 h and no formose reaction occurred, whereas in pure methanol, T_i is dramatically shortened compared with that in 90% methanol. From these results, it is obvious that the induction period (T_i) of the formose reaction is strongly affected by the nature of solvent.

Solvent polarity is generally expressed by various kinds of parameters, such as dielectric constant (D), Z value, and E_T value (*13, 14*). A semilogarithmic plot of T_i vs the Z value of the solvents used in the experiment of Fig. 1 gave an approximately linear relationship (Fig. 2). However, a semilogarithmic plot of T_i vs $D-1/2D+1$, which is another measure of solvent polarity (*15*), did not give a straight line. It has been reported that, for the reaction between ions or between an ion and a neutral molecule, a linear relationship exists between $\log k$ (k, the rate constant of reaction) and $1/D$, and for the reaction among polar molecules a linear relationship also exists between $\log k$ and $D - 1/2D + 1$ (*15*). These predictions suggest that the interaction between a calcium ion (or a calcium ion complex) and formaldehyde may be an important factor determining the induction rate of the formose reaction in aqueous alcoholic solvents.

As has been already reported (*11, 16*), the dissolved calcium ion species, especially $CaOH^+$, is an effective catalytic species in both induction and formose-forming steps of the formose reaction catalyzed by $Ca(OH)_2$ in aqueous solution. The import-

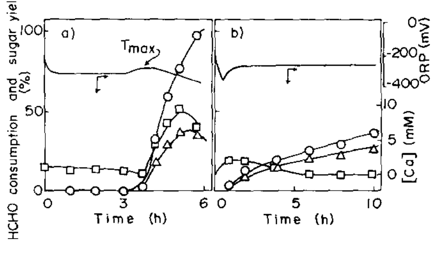


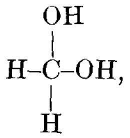
FIG. 3. Time courses of the formose reaction in 90% (a) and 100% (b) methanol. The pH was kept at the initial value (pH*, 11.0 and 11.1, respectively) by adding KOH. [HCHO] = 1.0 M; [CaO] = 0.15 mol/liter; temp. = 60°C; total volume = 200 ml; ○, HCHO consumption; △, sugar yield; □, concentration of the dissolved calcium ion species ([Ca]).

ance of the dissolved calcium is exemplified by Fig. 2, which shows an approximately linear relationship between log [Ca] and Z value. It is now obvious from Fig. 2 that the concentration of the dissolved calcium ion ([Ca]) increases and T_i decreases with increased Z value. In summary, it can be said that [Ca] is the most important factor controlling the induction period in protic solvents as well as in aqueous media (*16*, *18*) and that the Z value of solvents is a good parameter for estimating the easiness for the occurrence of the induction.

The Formose Reaction in 90% Aqueous Methanol and 100% Methanol

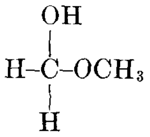
As shown in Fig. 1, a dramatic shortening of T_i is observed when the methanol content is increased from 90 to 100 mole%. In order to evaluate this phenomenon, the formose reactions carried out in 90 and 100% methanol were compared by analyzing the progress of reaction as shown in Fig. 3. The apparent pH (pH*) of the reaction mixture was kept to the initial pH by adding KOH from time to time throughout the reaction. For the reaction in 90% methanol, the time courses (Fig. 3) of the HCHO consumption, the sugar yield, and [Ca] were similar to those for the reaction carried out in an aqueous solution (*12*, *19*). It has been shown in a previous paper (*3*) that the induction period becomes longer with increased methanol content, that the consumption of formaldehyde is small during the induction period, indicating the inhibitory effect of methanol to the Cannizzaro reaction of formaldehyde, that T_{max} obtained from the oxidation–reduction potential (ORP) of the reaction mixture and the yellowing point, at which the sugar yield becomes maximum in an aqueous solution (*12*), can be seen when the methanol content is below 30 to 40%, and that at low methanol contents, T_{min}, which is an ORP minimum appearing at the end of the induction period (*12*, *19*), can also be observed. When the methanol content was raised to above 50%, T_{min} was obscure and T_{max} did not agree with the time showing the highest sugar yield, as seen in Fig. 3 (90% methanol).

On the other hand, the formose reaction in 100% methanol was quite different from that in aqueous methanol (Fig. 3). Despite the fact that the concentration of the dissolved calcium ion species ([Ca]) in 100% methanol was almost same as that in 90% methanol, the induction period (T_i) was much shortened compared with that in 90% methanol solvent. However, the formaldehyde consumption rate at the formose-forming step in 100% methanol was slower than that in 90% methanol. In 95% methanol, T_i and the formaldehyde consumption rate became an intermediate value between those in 90 and 100% methanol. The different behavior of the formose reactions in 90 and 100% methanol may be ascribed not only to [Ca] but also possibly to the solvation of formaldehyde. In the mixture of methanol and H_2O, even 90% aqueous methanol, formaldehyde may be strongly hydrated (*20*) to exist in the form of



$$\mathrm{H{-}\overset{OH}{\underset{H}{C}}{-}OH},$$

whereas in 100% methanol it may be solvated to form the hemiacetal



$$\mathrm{H{-}\overset{OH}{\underset{H}{C}}{-}OCH_3}$$

(*21*). The anomalous deviation of the length of the induction period in 100% methanol seen in Fig. 1 is now explained in terms of such solvation.

The Formose Reaction in Various Organic Solvents

The features of the CaO-catalyzed formose reaction (T_i, the HCHO consumption

TABLE 1

Formose Reaction in Various Solvents[a]

Solvent	Dielectric constant[b] (at 25°C)	Z value[b] (kcal/mol at 25°C)	E_{T} value[b] (kcal/mol at 25°C)	T_i (min)	HCHO consumption rate (mol/liter · min × 10^2)	Sugar yield (%)
Water	78.5	94.6	63.1	18	23.3	44
Ethylene glycol	38.7	85.1	56.3	15.5	17.4	46
Glycerol	42.5	82.6[c]	—	22.5	2.0	
Methanol	31.2	83.6	55.5	22	0.85	43
Propylene glycol	32.0	82.2[c]	—	47	9.8	
Methyl cellosolve	16.0	78.5[c]	52.3	100	0.19	13
1,3-Butanediol	—	80.8[c]	—	120	0.12	
Ethylene chlorohydrin	25.8	81.1[c]	—	184	0.77	37
1,4-Butanediol	32.9	81.0[c]	—	240	0.68	
Ethanol	25.7	79.6	51.9	[d]		
1-Propanol	21.8	78.3	50.7	[d]		
Benzyl alcohol	13.0	78.3[c]	50.8	[d]		
2-Propanol	18.6	76.3	48.6	[d]		
1-Butanol	17.1	77.7	50.2	[d]		
t-Butyl alcohol	11.4	71.3	43.9	[d]		
Dimethyl sulfoxide	48.9	71.1	45.0	[d]		
Ethylene carbonate	73.0	80.5[c]	—	[d]		
Formamide	109.5	83.3	56.6	[d]		
N-Methyl formamide	182	79.6[c]	54.1	[d]		
Propylene chlorohydrin	—	79.8[c]	—	[d]		

[a] [HCHO] = 1.0 M; [CaO] = 0.3 mol/liter; temp. = 60°C; total volume = 300 ml.

[b] Taken from Refs. (*14*, *15*, *22*).

[c] Determined in this work.

[d] The formose reaction did not occur in 10 hr.

rate, and the sugar yield) in various organic solvents were compared with their polarity parameters (D, Z, and E_{T} values) as summarized in Table 1. Apparently, more polar solvents are favorable for the occurrence of the formose reaction, with a few exceptions. The Z and E_{T} values of solvent appear to correlate better with the reaction rate than the dielectric constants. The most characteristic property of solvents, in which the formose reaction can take place, is no doubt that they have an alcoholic hydroxy group capable of forming a hemiacetal with formaldehyde. Supporting this conclusion, methylal was found to undergo no formose reaction in aqueous solution, but the reaction could occur when the solution was once acidified with hydrochloric acid which is known to hydrolyze methylal into a hemiacetal (*17*).

Sugar Yield

The sugar yield in H_2O–alcohol solvent systems is plotted as a function of the H_2O content (Fig. 4a) and of the Z value (Fig. 4b). The sugar yield is largely affected by the kind of alcohol and increases in the order: methanol > ethanol > 2-propanol > t-butyl alcohol. Regardless of the kind of alcohol, the sugar yield shows a maximum value at a H_2O molar fraction of 0.85–0.95 or at a Z value of 92–93. This may be attributed to the existence of competitions among the Cannizzaro, sugar formation, and sugar decomposition reactions as discussed in previous papers (*3*, *12*, *16*, *18*). In particular, when the fraction of H_2O is above 0.90, the sugar yield is considerably lowered as the amount of formaldehyde consumed by the Cannizzaro reaction increases, even though the sugar-formation rate remains constant. On the other hand, below 0.85 of the H_2O fraction, the Cannizzaro reaction is depressed while the sugar-formation rate becomes slower. Consequently, the sugar yield is dependent mainly on the decomposition rate of the sugar formed. Furthermore, in the aqueous formose reaction catalyzed by $Ca(OH)_2$, the relationships between the Cannizzaro and formose reactions at various conversion levels have also been studied in detail by Weiss *et al.* (*5*, *23*). At conversion levels below 4%, the formaldehyde disappearance rate by the Cannizzaro reaction is triple that by the formose condensation. Near 50% conversion, which is where the stoichiometry of the Cannizzaro reaction requires that its absolute rate passes through a maximum, the formaldehyde disappearance by the Cannizzaro reaction is only 5% of that by the formose condensation.

Figure 5 shows a plot of the sugar yields in aqueous methanol as a function of the H_2O fractions at various formaldehyde and CaO concentrations. While the sugar yield increased with decreased formaldehyde concentration at higher H_2O fractions in agreement with the finding obtained previously in the formose reaction in aqueous solution (*18*), the sugar yield at lower H_2O fraction increased with increased formaldehyde concentration. Thus, in order to obtain formose in better yields in aqueous methanol with relatively higher fractions of methanol, higher formaldehyde concentrations are necessary. This result has the practical advantage of yielding a large amount of sugar at once compared to that in aqueous or dilute aqueous methanol.

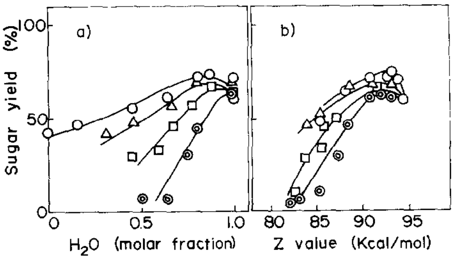


FIG. 4. Effect of the content of H_2O in various H_2O–alcohol solvent systems on the sugar yield (a) and the sugar yield in these systems as a function of their Z values (b). [HCHO] = 1.0 M; [CaO] = 0.15 mol/liter; temp. = 60°C; total volume = 200 ml; pH was kept at the initial value (pH*, 10.5–11.8) by adding KOH; solvent system: ○, H_2O–methanol; △, H_2O–ethanol; □, H_2O–2-propanol; ◎, H_2O–t-butyl alcohol.

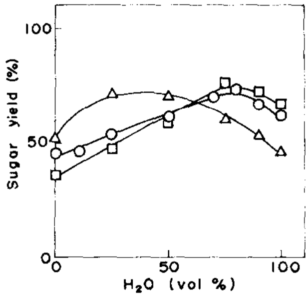


FIG. 5. Effect of water content on the sugar yield in H_2O–methanol solvents. Temp. = 60°C; total volume = 200 ml; pH was kept at the initial value (pH*, 10.8 to 11.8) by adding KOH; △, [HCHO] = 5.0 M and [CaO] = 0.5 mol/liter; ○, [HCHO] = 1.0 M and [CaO] = 0.15 mol/liter; □, [HCHO] = 0.5 M and [CaO] = 0.15 mol/liter.

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