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Formose Reactions. XXI. A Selective Formation of Dihydroxyacetone in the Formose Reaction in *N,N*-Dimethylformamide

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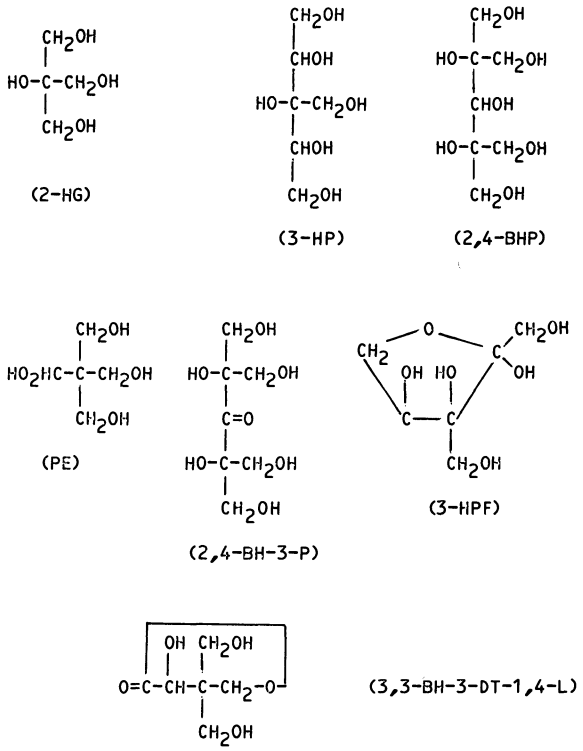
Dihydroxyacetone (DHA) was obtained in good yield from the selective formose reaction which was conducted with 2-(dimethylamino)ethanol and vitamin B_1 in *N,N*-dimethylformamide (DMF). The major products were isolated from the formose and identified as dihydroxyacetone and 2-(1,2-dihydroxyethyl)-5-(2-hydroxyethyl)-4-methylthiazole by spectral data. Vitamin B_1 suppressed the vaporization of formaldehyde from the reaction solution. Irrespective of the 2-(dimethylamino)ethanol concentration (above 0.1 M (1M=1 mol dm^{-3})), the maximum yield of DHA was 80—90 glc% at 1.0 M formaldehyde concentration, when the formaldehyde consumption was above 90%. Above 3.0 M formaldehyde concentration, selective formation of DHA (above 80 glc%) was obtained at the early stage of the reaction. The scheme for the formation of DHA in the formose reaction in the presence of vitamin B_1 was also proposed.

Dihydroxyacetone, a fermentation product of glycerol,[1] has been used as a building block for pharmaceuticals, dyes, foodgrade emulsifiers, plasticizers, fungicides, and alkyd-type resins. It is, furthermore, noted as a key intermediate in a novel pathway for formaldehyde fixation in methanol-utilizing yeasts.[2] Several methods of preparation of DHA by chemical means were studied.[3] It is also formed in the formose reaction catalyzed by aq-alc $Ca(OH)_2$.[4] Recently, Inoue *et al.*[5] reported that dihydroxyacetone was obtained in a good yield (80%) when the formose reaction was carried out in dioxane in the presence of 3-ethylbenzothiazolium bromide and triethylamine at 100 °C. The formose reaction[6] catalyzed by triethylamine and a derivative of thiazole in DMF solution at 100 °C was found to give no branched sugars such as glucose, galactose, xylose, and glyceraldehyde dimer. Furthermore at the early stage of the reaction glyceraldehyde dimer was the major products. It is important that three carbon carbohydrates such as dihydroxyacetone and glyceraldehyde are obtained in high selectivity.

We have studied the effects of various reaction conditions on the product distribution, such as catalysts, the concentration of formaldehyde and catalyst, the reaction temperature, the kind of solvent and so on. In our studies,[7-12] it has been found that some formose reactions in H_2O or methanol give selectively 2-(hydroxymethyl)glycerol (2-HG), 3-(hydroxymethyl)pentitol (3-HP), 2,4-bis(hydroxymethyl)pentitol (2,4-BHP), pentaerythritol (PE), 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P), 3-(hydroxymethyl)pentofuranose (3-HPF), or 3,3-bis(hydroxymethyl)-3-deoxy-tetrono-1,4-lactone (3,3-BH-3-DT-1,4-L), and these products have been isolated in a pure form. All of these products are branched sugars and sugar alcohols. It is interesting to study the formose reaction, using dipolar aprotic solvents such as DMF and dimethyl sulfoxide (DMSO) instead of protic solvents such as H_2O and methanol. We have searched for the catalysts which give the simple product-distribution in the gas chromatogram of trimethylsilyl derivatives, using DMF and DMSO as a solvent and have already reported that dihydroxyacetone (DHA) is formed selectively in the presence of 2-(dimethylamino)ethanol and vitamin B_1.[13] The role of vitamin B_1 was also observed: in the absence of vitamin B_1, formaldehyde vaporized and a self-condensation of



vaporized formaldehyde to paraformaldehyde took place very readily under the given reaction conditions; in the presence of vitamin B_1, however, such reactions were sufficiently suppressed for the formose reaction in DMF to occur smoothly. A product derived from vitamin B_1 was also isolated and assigned to be 2-(1,2-dihydroxyethyl)-5-(2-hydroxyethyl)-4-methylthiazole (**I**) on the basis of spectroscopic data.

The purpose of this paper is to report the effects of various inorganic and organic catalysts on the formose reaction in DMF and to reveal the effects of vitamin B_1, the reaction temperature, and the concentration of 2-(dimethylamino)ethanol and formaldehyde on the formation of DHA and (**I**).

Experimental

Materials. Two types of paraformaldehyde were used. Paraformaldehyde produced by Merck Co. (95%) had a smaller particle size and gave a faster HCHO consumption

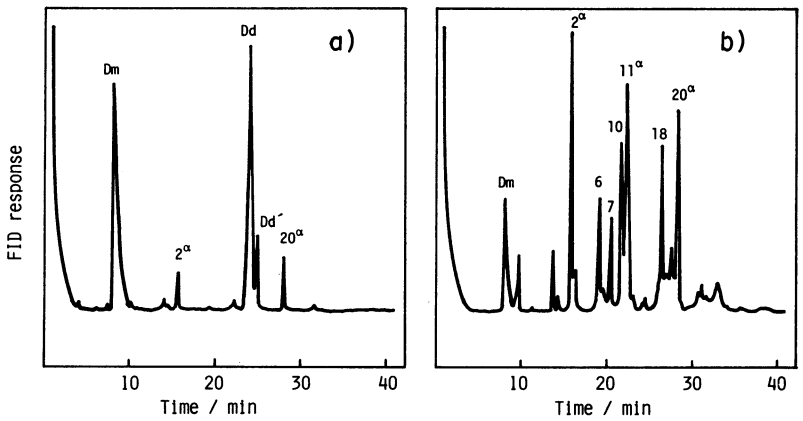


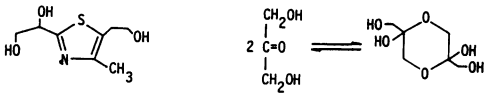
Fig. 1. The glc patterns of trimethylsilylated products from: (a) the selective formose reaction for 180 min starting from [HCHO]= 1.1 M, [2-(Dimethylamino)ethanol]=0.11 M, [Vitamin B_1-HCl]= 0.028 M and DMF=180 ml at 60°C, and (b) non-selective formose reaction for 5 min starting from [HCHO]=1.1 M, [$Ca(OH)_2$]=0.11 M, [Vitamin B_1-HCl]=0.028 M and DMF=180 ml at 100°C.

than that of Mitsubishi Gas Chem. (86%), but the differences in the product-distribution and the formose yield between the two were small. All the inorganic and organic bases used as catalysts were of analytical grade. DMF was purified in the usual way.[14]

Procedure. A representative example of the reaction is as follows. A five-necked flask (200 ml), which contained 180 ml of DMF, was preequilibrated at 60°C in a thermostat under nitrogen; the reaction was then initiated, followed by the addition of 2-(dimethylamino)ethanol (1.8 g, 0.11 M), paraformaldehyde (Merck Co., 6.3 g, 1.1 M), and vitamin B_1-HCl (1.7 g, 0.028 M) in this order. At suitable intervals, 5 ml aliquots were withdrawn into a 10 ml flask, and the reaction was quenched immediately by acidification with 9M HCl. The aliquots were analyzed for formaldehyde following the method of Bricker *et al.*,[15] except that the optical density was measured at 579 nm. Then, the reaction mixture was concentrated under reduced pressure (25—30°C/2 mmHg†) to yield a brownish syrup (6.5 g). The product yield and distribution were determined as the pertrimethylsilylated products by gas-liquid chromatography. The yield (mg/ml) was measured by the internal standard (pentaerythritol) method. The glc pattern (Fig. 1a) clearly indicates the selective formation (90%) of the product corresponding to the peaks Dm, Dd, and Dd', the retention times of which are the same as those of pertrimethylsilylated dihydroxyacetone. Furthermore, the glc analysis of peracetylated products indicated one major peak in the same manner as that of authentic DHA.

Separation and Identification of Products. The product corresponding to glc peaks Dm, Dd, and Dd' was isolated as follows: The formose syrup (6.5 g) obtained by the above reaction was acetylated with acetic anhydride in pyridine, and the reaction mixture was extracted with chloroform, the extract was concentrated to 4 ml and re-extracted with 400 ml of water. Then, the water layer was concentrated to 25 ml and 4 g of active carbon was added to the concentrated solution. Acetylated dihydroxyacetone (2.5 g, hydroscopic) was obtained as a yellow crystalline form by eluting the active carbon with methanol, followed by concentrating the methanol solution. ^{1}H NMR ($CDCl_3$) δ=2.15 (6H, s, 2×O-$COCH_3$) and 4.8 (4H, s, 2×C-CH_2). The molecular ion was observed at *m/z* 174 in the electron impact mass spectrum. IR (KBr) 1745 (C=O), 1418, 1373, 1239 (OAc), and 1052 cm^{-1}. The IR spectrum was in agreement with that of an authentic sample of acetylated dihydroxyacetone.

Deacetylation of the peracetylated products with barium hydroxide gave the original product, and the trimethylsilyl derivative showed exactly the same glc behaviour as that for the directly trimethylsilylated product. The product corresponding to peaks Dm, Dd, and Dd', therefore, was assigned as a mixture of dihydroxyacetone monomer and its diastereomeric dimers (**II**).



(I) (II)

The product (**I**) (40 mg, colorless syrup) corresponding to the glc peak 20$^\alpha$ was also isolated by chromatography on an active carbon column with water and methanol as eluent, followed by purification of the acetyl derivative of 20$^\alpha$ with thin-layer chromatography (benzene/EtOAc=1/1). IR (KBr) 1750 (C=0), 1640 (C=N-C), 1370, 1240 (OAc), and 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.07 (6H, s, 2×O-CO-CH_3), 2.16 (3H, s, O-CO-CH_3), 2.36 (3H, s, C-CH_3), 3.06, 4.23 (each 2H, t, -CH_2), 4.47 and 4.64 (each 1H, dd, J_{AX}=7.08 Hz, J_{BX}=3.62 Hz, **H**-A, B), and 6.24 (1H, dd, J_{AX}=7.08 Hz, J_{BX}=3.62 Hz, **H**-X). ^{13}C NMR ($CDCl_3$) δ=170.7 (s, **C**OCH_3), 170.4 (s, **C**OCH_3), 169.7 (s, **C**OCH_3), 161.6 (s, C-2), 149.6 (s, C-4), 128.2 (s, C-5), 70.6 (d, C-2'), 64.6 (s, C-2''), 63.9 (t, C-5''), 25.9 (t, C-5'), 20.9 (q, **C**OCH_3), 20.7 (q, **C**OCH_3), and 14.9 (q, CH_3). The chemical ionization mass spectra using *i*-C_4H_{10}, NH_3, or ND_3 as a reagent gas[16] showed a quasi-molecular ion at *m/z* 330 (MH^+), 347 ($M \cdot NH_4^+$), or 351 ($M \cdot ND_4^+$), respectively, which precisely indicated a molecular weight of 329. These results suggested that the acetate of the product (**I**) had no active hydrogen in the molecule. Deacetylation of the acetate with barium hydroxide gave product (**I**) as a colorless syrup. IR (KBr) 3350 (br., OH), 1630 (C=N-C), 1550, 1440, 1320, 1190, and 1050 cm^{-1}. ^{1}H NMR(CD_3OD) δ=2.29 (3H, s, C-CH_3), 2.90 and 3.69 (each 2H, t, -CH_2-), 3.74 (2H, d, -CH_2OH), and 3.83 (^{1}H, t, >CHOH). ^{13}C NMR (CD_3OD) δ=171.8 (s, C-2), 148.9 (s, C-4), 129.8 (s, C-5), 73.5 (d, C-2') 67.4 (t, C-2''), 63.1 (t, C-5''), 30.5 (t, C-5'), and 14.7 (q, CH_3). The chemical ionization mass spectra using *i*-C_4H_{10}, NH_3, or ND_3 as a reagent gas showed a quasi-molecular ion at *m/z* 204 (MH^+), 221 ($M \cdot NH_4^+$), or 228 ($d_3M \cdot ND_4^+$), respectively, which precisely indicated a molecular weight of 203 and the presence of three active hydrogens in the molecule. These results led us to assign 20$^\alpha$ to be 2-(1,2-dihydroxyethyl)-5-(2-hydroxyethyl)-

† 1 mmHg≈133.322 Pa.

4-methylthiazole as the product derived from vitamin B_1.

Results and Discussion

Formose Reactions in DMF in the Presence of Inorganic and Organic Bases. The formose reactions were carried out with various inorganic bases (Table 1). In the case of LiOH and $Pb(CH_3COO)_2 \cdot Pb(OH)_2$, formaldehyde was consumed smoothly, but after 2 h of reaction time, NaOH, $Mg(OH)_2$, $Ba(OH)_2$, and $Pb_2O(OH)_2$ gave little formose. LiOH, $Ca(OH)_2$, and $Sr(OH)_2$ were found to give the product of GP-11 selectively which had the same retention time as 3,3-BH-3-DT-1,4-L.[7] Under these reaction conditions, the formose yield was low and considerable paraformaldehyde adhered to the upper part of the reaction flask as described previously.[13]

The results of the formose reactions catalyzed by various inorganic bases and organic bases in the presence of vitamin B_1 are summarized in Tables 2 and 3, respectively. In Table 2, product (**I**) corresponding to glc peak 20$^{\alpha}$ which was derived from vitamin B_1 was

Table 1. Formose reactions catalyzed by various inorganic bases[a]

Base	Time	HCHOconsumption	Main products/glc%[b]						Total yield[f]
	min	%	2	10	11	18	19	26	mg·ml^{-1}
LiOH·H_2O	10	90	8.4 (0.06)	e)	37.2 (0.26)	10.9 (0.07)	9.4 (0.06)	e)	0.69
NaOH	180	c),d)	e)	e)	e)	e)	e)	e)	
KOH	120	67[d]	e)	e)	12.5 (0.27)	13.5 (0.30)	8.0 (0.17)	10.0 (0.22)	2.18
$Mg(OH)_2$	180	c),d)	e)	e)	e)	e)	e)	e)	
$Ca(OH)_2$	180	48[d]	e)	e)	25.8 (0.10)	e)	e)	e)	0.39
$Sr(OH)_2 \cdot 8H_2O$	180	48[d]	e)	e)	41.9 (0.30)	e)	e)	e)	0.71
$Ba(OH)_2 \cdot 8H_2O$	120	c),d)	e)	e)	e)	e)	e)	e)	
$Pb(CH_3COO)_2 \cdot Pb(OH)_2$	6	90	11.1 (0.41)	17.8 (0.65)	10.3 (0.38)	7.0 (0.26)	e)	e)	3.66
$Pb_2O(OH)_2$	180	39[d]	e)	e)	e)	e)	e)	e)	

a) DMF=180 ml, [HCHO]=1.1 M, [Base]=0.11 M, Temp=100 °C, pH: not adjusted, Stirring rate=240 min^{-1}. b) Parentheses indicate yield(mg/ml) measured by the internal standard(pentaerythritol) method. c) Solid paraformaldehyde remained in the reaction solution. d) A lot of paraformaldehyde adhered to the flask. e) GLC was below 1%. f) Total yield(mg/ml) is the summation of yield of each product measured by the internal standard(pentaerythritol) method.

Table 2. Formose reactions catalyzed by various inorganic bases in the presence of vitamin B_1[a]

Base	Time	HCHOconsumption[b]	Main products/glc%[c]							Total yield[h]
	min	%	DHA	1$^{\beta}$	2$^{\alpha}$	10	11$^{\alpha}$	18	20$^{\alpha}$	mg·ml^{-1}
LiOH·H_2O	8	93	54.1 (6.37)	e)	14.2 (1.68)	e)	5.4 (0.64)	e)	7.4 (0.87)	11.77
KOH	10	77[d]	42.1 (2.97)	e)	25.3 (1.78)	e)	7.7 (0.54)	e)	e)	7.05
	15	89	10.5 (1.45)	e)	22.4 (3.10)	8.3 (1.15)	15.1 (2.09)	13.3 (1.84)	7.4 (1.02)	13.82
$Ca(OH)_2$	3	97	9.3 (1.44)	e)	19.6 (3.02)	7.9 (1.22)	13.7 (2.11)	6.0 (0.93)	10.7 (1.65)	15.45
$Sr(OH)_2 \cdot 8H_2O$	5	98	6.3 (0.87)	e)	6.4 (0.88)	9.6 (1.33)	11.2 (1.55)	8.9 (1.23)	11.7 (1.62)	13.87
NaOH	120	34[d,g]	e)	22.6 (0.29)	e)	e)	e)	e)	14.4 (0.18)	1.29
$Ba(OH)_2 \cdot 8H_2O$	30	98	30.7 (4.96)	e)	16.8 (2.70)	e)	9.5 (1.54)	5.5 (0.88)	10.0 (1.61)	16.13
$Mg(OH)_2$	120	97	e)	e)	14.0 (1.84)	6.5 (0.85)	10.7 (1.41)	9.6 (1.26)	21.4 (2.81)	13.13
$Pb_2O(OH)_2$	60	90	e)	e)	24.6 (2.84)	14.0 (1.61)	10.3 (1.19)	e)	13.0 (1.50)	11.51
f)	120			46.7 (0.22)						0.41

a) DMF=180 ml, [HCHO]=1.1 M, [Base]=0.11 M, [Vitamin B_1-HCl]=0.028 M, Temp=100 °C, pH: not adjusted, Stirring rate=240 min^{-1}. b) The amount of paraformaldehyde adhering to the flask was small. c) Parentheses indicate yield(mg/ml) measured by internal standard(pentaerythritol) method. d) Solid paraformaldehyde remained in the reaction solution. e) GLC was below 1%. f) Paraformaldehyde and base were not added. g) A lot of paraformaldehyde adhered to the flask. h) Total yield(mg/ml) is the summation of yield of each product measured by the internal standard(pentaerythritol) method.

TABLE 3. FORMOSE REACTIONS CATALYZED BY VARIOUS ORGANIC BASES IN THE PRESENCE OF VITAMIN B_1[a]

Base	Time	HCHOconsumption[b]	Main products/glc%[c]					Total yield[g]
	min	%	DHA	1β	2α	20α	24α	mg·ml^{-1}
dimethylamine (abt. 40% in water)	120	26[d]	f)	6.6 (0.04)	f)	f)	f)	0.55
morpholine	120	52[e]	f)	13.0 (0.13)	f)	f)	f)	0.97
N,N-dimethyl-aniline	120	40[e]	f)	17.1 (0.40)	f)	6.6 (0.15)	10.9 (0.25)	2.32
β-picoline	120	22[d),e]	f)	13.7 (0.21)	f)	14.0 (0.21)	f)	1.51
N-methyl-morpholine	120	38[d),e]	44.1 (1.93)	f)	f)	34.1 (1.49)	10.7 (0.47)	4.38
triethanolamine	60	75	f)	f)	f)	11.6 (1.49)	f)	2.09
trimethylamine (30% in water)	60	93	75.2 (10.49)	f)	6.2 (0.87)	9.7 (1.35)	f)	13.95
2-(dimethyl-amino)ethanol	30	91	82.0 (11.79)	f)	f)	8.5 (1.22)	f)	14.35
triethylamine	30	91	81.7 (8.64)	f)	5.1 (0.54)	8.0 (0.84)	f)	10.58
N-methyl-piperidine	30	93	81.4 (10.16)	f)	5.6 (0.70)	7.3 (0.92)	f)	12.49

a) DMF=180 ml, [HCHO]=1.1 M, [Base]=0.11 M, [Vitamin B_1-HCl]=0.028 M, Stirring rate=240 min^{-1}., pH: not adjusted, Temp=100°C. b) The amount of paraformaldehyde adhering to the flask was small. c) Parentheses indicate yield(mg/ml) measured by the internal standard(pentaerythritol) method. d) A lot of paraformaldehyde adhered to the flask. e) Solid paraformaldehyde remained in the reaction solution. f) GLC was below 1%. g) Total yield(mg/ml) is the summation of the yield of each product measured by the internal standard(pentaerythritol) method.

formed. LiOH, KOH, and $Ba(OH)_2$ were found to give DHA selectively. Compared with the cases in the absence of vitamin B_1, formaldehyde was consumed smoothly, the yield of formose increased, and the amount of formaldehyde adhering to the reaction vessel was small. In the absence of base, the formose reaction did not proceed and the added formaldehyde was recovered entirely over 120 min. Hence, it can be concluded that by itself vitamin B_1 has no catalytic action for the formose reaction in DMF. As shown in Table 3, (**I**) was also formed except in the case of dimethylamine and morpholine. Dimethylamine, morpholine, *N,N*-dimethylaniline, and β-picoline were found to give gas chromatogram peak number 1β (GP-1β) as a major product which was formed easily when vitamin B_1 was heated in DMF; 2-(dimethylamino)ethanol, trimethylamine, *N*-methylpiperidine, and triethylamine were found to give the good yield of DHA.

Effects of Vitamin B_1. As described above, the formose reactions in the presence of vitamin B_1 gave smoother formaldehyde consumption, better yield of formose, and less formaldehyde adhering to the reaction vessel. The solubility of formaldehyde in DMF at 60 or 100°C was measured in the presence or absence of vitamin B_1 with the results shown in Fig. 2. The amount of dissolved formaldehyde in DMF and the solution rate increased with an increase in temperature. At 60°C, formaldehyde scarcely vaporized and remained in the solution, but at 100°C, the vaporization of formaldehyde proceeded smoothly and the formaldehyde concentration in the solution decreased rapidly. In the presence of vitamin B_1, however, the vaporization of formaldehyde was suppressed. Furthermore, solid paraformaldehyde remained in the solution.

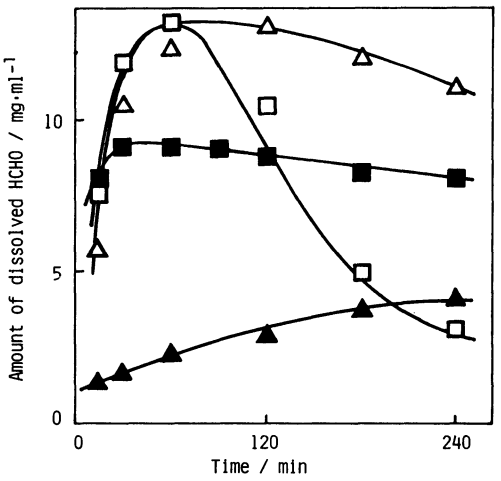


Fig. 2. Solubility of HCHO in DMF.
DMF=180 ml, [HCHO]=1.1 M, Stirring rate=240 min^{-1}. □, Temp=100°C; ▲, Temp=60°C; ■, Temp=100°C; up to 15 min and 60°C after 15 min; △, Temp=100°C; [Vitamin B_1-HCl]=0.028 M.

In all cases studied, the total amount of adhering, dissolved, and residual formaldehyde at 240 min was nearly equal to the amount of formaldehyde added. These results suggest that the interaction between vitamin B_1 and formaldehyde yields the Lapworth intermediate (**III**)[6,17] which is well known as "active aldehyde" in the transketolase reaction.[18]

Figure 3 shows the relationship between the vitamin B_1 concentration and the yield of DHA in the presence of 2-(dimethylamino)ethanol at 100°C. As the reaction proceeded, the yield of DHA increased and reached a constant value. The yield of DHA increased with increasing vitamin B_1 concentration up to a concentration

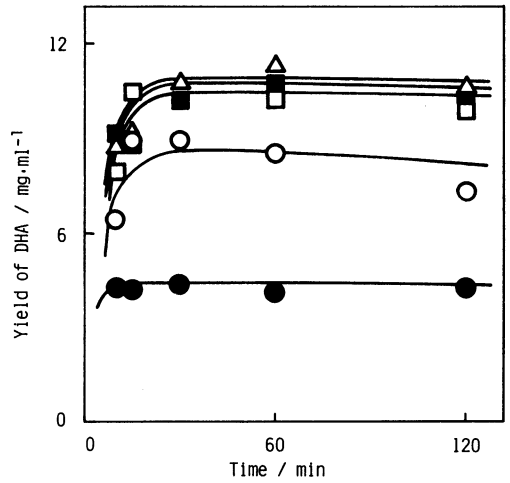


Fig. 3. Effect of vitamin B_1 concentration on the yield of DHA.
DMF=180 ml, [2-(Dimethylamino)ethanol]=0.11 M, [HCHO]=1.1 M, Stirring rate=240 min^{-1}, Temp=100 °C.
[Vitamin B_1-HCl] (M): ●, 0.007; ○, 0.014; □, 0.028; ■, 0.042; △, 0.056.

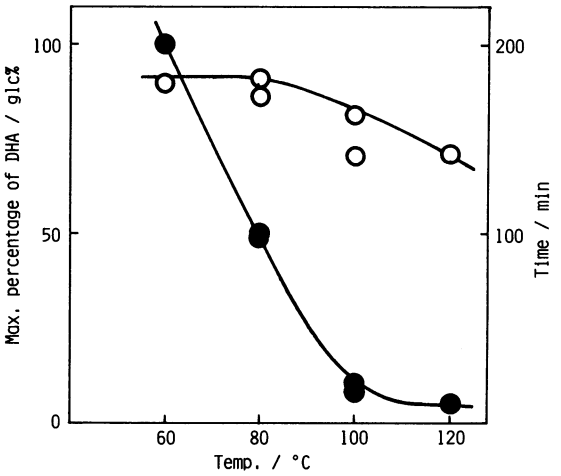


Fig. 4. Effect of temperature on the reaction time when DHA shows maximum percentage in glc and the value of its maximum percentage.
DMF=180 ml, [2-(Dimethylamino)ethanol]=0.11 M, [HCHO]=1.1 M, [Vitamin B_1-HCl]=0.028 M, Stirring rate=240 min^{-1}.
○, Max. percentage of DHA (glc%); ●, The time(min) when DHA showed max. percentage.

of 0.028 M. In the absence of vitamin B_1, 4.4 g of paraformaldehyde adhered to the upper part of the reaction vessel after 120 min of reaction time, when the formaldehyde consumption was 11% and DHA no longer formed. GP-2$^{\alpha}$ formed in *ca.* 20 glc% yield at 0.007 M of vitamin B_1 and, with an increase in vitamin B_1 concentration, decreased to less than 1 glc% at 0.028 M. The yield of product (**I**), furthermore, increased with increasing concentration of vitamin B_1.

Effects of the Reaction Temperature. The influence of the reaction temperature on the formose reaction was studied. This included the yield of DHA, the product distribution, the formaldehyde consumption *etc.* The results are shown in Fig. 4. By raising the reaction temperature, the formaldehyde consumption

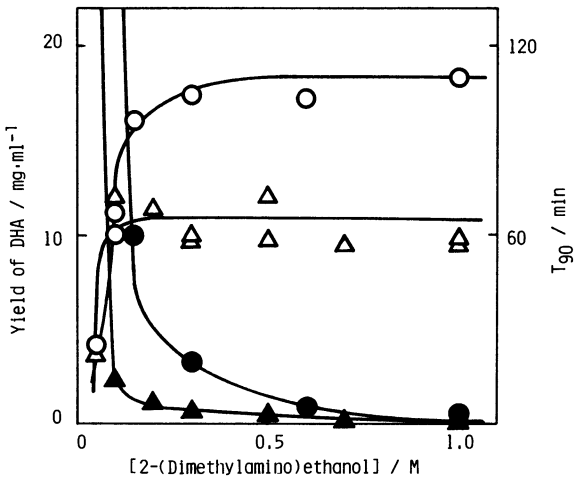


Fig. 5. Effect of the concentration of 2-(dimethylamino)ethanol on the yield of DHA and T_{90}.
DMF=180 ml, [Vitamin B_1-HCl]=0.028 M, Temp.=100 °C, Stirring rate=240 min^{-1}. Yield of DHA, [HCHO] (M): △, 1.1; ○, 3.0. T_{90}, [HCHO] (M): ▲, 1.1; ●, 3.0.

rate increased, the yield of DHA decreased, and the side-products (**I**) and GP-2$^{\alpha}$ formed appreciably. The time at which DHA showed maximum percentage in the gas chromatogram decreased rapidly with an increase in the reaction temperature and at that time the formaldehyde consumption was above 90%. Irrespective of the reaction temperature, the amount of DHA hardly changed after reaching the maximum value. It can therefore be presumed from these results that even at the high reaction temperature of 100 or 120 °C, DHA is stable under these reaction conditions.

Effects of the 2-(Dimethylamino)ethanol Concentration. Figure 5 shows the relationship between the yield of DHA, the formaldehyde consumption, and the 2-(dimethylamino)ethanol concentration. With an increase in the 2-(dimethylamino)ethanol concentration, the yield of DHA and the decreasing rates of the total sugar and DHA increased, however, above 0.1 and 0.15 M of the base concentration at the formaldehyde concentration of 1.0 and 3.0 M, respectively, the maximum yield of DHA had a constant value regardless of the base concentration. The maximum total sugar yield were 10—13 and 30—35 mg/ml, respectively. The maximum percentage of DHA, furthermore, was 80—90 and 60—80 glc% at 1.0 and 3.0 M of the formaldehyde concentration, when the formaldehyde consumption was above 90 and 60—80%, respectively. At a formaldehyde concentration of 3.0 M the formation of other products which might be derived from DHA reduced the selectively for DHA formation. The time (T_{90}) when the formaldehyde consumption reached 90% shortened with increasing base concentration. This suggests that 2-(dimethylamino)-ethanol not only catalyzes the formose reaction, but also decomposes the products formed. It is also considered that DHA is the principal in the formose reaction. Product (**I**) was detected only below 0.1 M of the base concentration at 1.0 M of the formaldehyde concentration, however, at 3.0 M of formaldehyde, the yield of product (**I**) was 1—2 mg/ml, regardless of the base concentration.

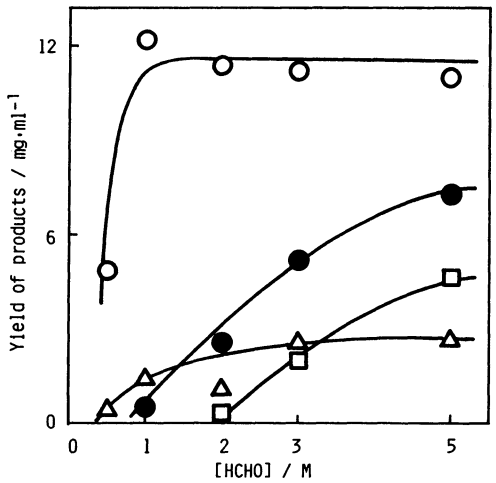


Fig. 6. Effect of HCHO concentration on the yield of products.
DMF=180 ml, [2-(Dimethylamino)ethanol]=0.11 M, [Vitamin B_1-HCl]=0.028 M, Stirring rate=240 min^{-1}, Temp=100°C.
○, DHA; ●, 2α; □, 10; △, 20α.

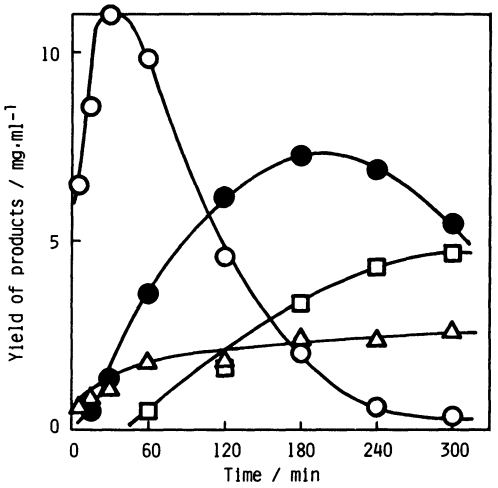
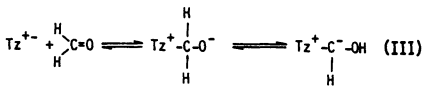
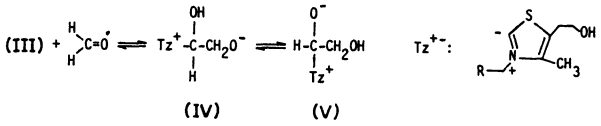


Fig. 7. Time-courses of the yield of products.
DMF=180 ml, [HCHO]=5.0 M, [2-(Dimethylamino)-ethanol]=0.11 M, [Vitamin B_1-HCl]=0.028 M, Stirring rate=240 min^{-1}, Temp=100°C.
○, DHA; ●, 2α; □, 10; △, 20α.

Effects of the Formaldehyde Concentration on the Product Distribution. The relationship between the formaldehyde concentration and the product distribution is shown in Fig. 6. Irrespective of the formaldehyde concentration (above 1.0 M), the maximum amounts of DHA and product (**I**) showed constant values of *ca.* 12 and 2 mg/ml, respectively. However, by raising the formaldehyde concentration, the yields of GP-2α and GP-10 increased; the isolation and structure elucidation of these products are now under investigation. The proportion of DHA in the total products decreased. Above 3.0 M formaldehyde concentration, the selective formation of DHA (above 80 glc%) occurs during the early stage of the reaction. Concerning the formation of glyceraldehyde, the same phenomenon was observed by J. Castells *et al.*[6]: Paraformaldehyde (1.33 mol) was added, with continuous stirring, to a solution of triethylamine (186 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (185 mmol) in DMF (250 ml) at 100°C. The amount of DHA formed, furthermore, decreased rapidly with in increase in the formaldehyde concentration. Figure 7 shows the typical time-courses of the products. In these experiments, the formaldehyde consumption at 300 min was 85%. GP-2α and GP-10 increased instead of DHA decreasing. These results suggest that DHA is a precursor of GP-2α and GP-10 and play an important role in the formose reaction.

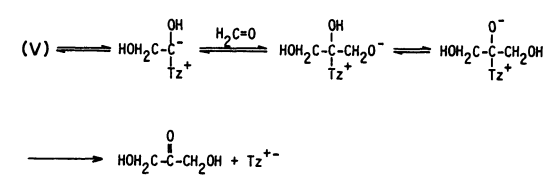
Scheme for DHA Formation. J. Castells *et al.*[6] suggested the following scheme concerning the formation of glycolaldehyde, glyceraldehyde, and DHA in the formose reaction carried out under the similar reaction conditions to ours. In the scheme they made two assumptions: (1) The Lapworth intermediate (**III**) did not attack ketone carbonyl groups. This assumption was based on the fact that no branched-chain products were isolated in any benzoin condensation.; (2) The Lapworth intermediate (**III**) did not react, or reacted slowly, with aldohexoses, due to the predominance of hemiacetal forms (masked aldehyde carbonyl groups).



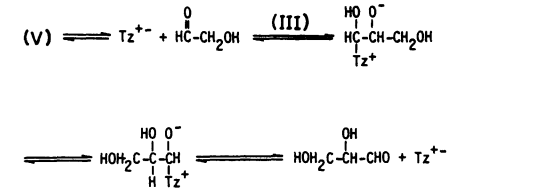


In penetrating studies on benzoin and acetoin formation in the presence of thiamine and other thiazolium compounds pursued by Breslow and others,[18,19] the hydrogen atoms at position 2 of the thiazolium ring was found to exchange rapidly in a deuterated solvent. The product (**I**), furthermore, was detected in the products of the formose reaction in the presence of vitamin B_1. These results suggest the presence of the intermediate (**IV**) which would give the intermediate (**V**). Then, the two following paths may be considered: Further addition of formaldehyde and formation of DHA (Path 1); formation of glycolaldehyde and glyceraldehyde (Path 2).

Path 1



Path 2



The formation of glycolaldehyde and glyceraldehyde as minor products and of dihydroxyacetone (DHA) as a major product suggests that Path 1 would be predominant under the reaction conditions investigated in this report. The above formulation of the reaction mechanism, however, can not explain why Path 1 proceeds in preference to Path 2, and how the substituent group on the nitrogen atom of the thiazolium ring affects the formation of DHA.

Conclusions. From these observations, one can draw the following conclusions. First, vitamin B_1 has no catalytic action for the formose reaction in DMF by itself, but gives more smooth formaldehyde consumption, better yield of formose, and the formation of 2-(1,2-dihydroxyethyl)-5-(2-hydroxyethyl)-4-methylthiazole and some complexes with formaldehyde. Second, by raising the reaction temperature, the side-reactions also proceed easily, however, even at such high reaction temperatures as 100 or 120°C, DHA is stable under these reaction conditions. Third, DHA is the principal intermediate in the formose reaction and is decomposed by the excess of base.

Finally, the present investigation provides the following guide-lines for obtaining high DHA yield in batch-reaction systems. Further addition of formaldehyde to DHA and the decomposition of DHA must be minimized. This may be done at low formaldehyde concentrations, at relatively low reaction temperature (60°C), and at high [base]/[HCHO] ratios with low base concentrations, or by stopping the reaction at an early stage in the case of high formaldehyde concentrations.

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