Formose Reactions. II. The Photochemical Formose Reaction

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Under UV irradiation in the presence of an inorganic base, aqueous formaldehyde was found to give pentaerythritol and 2-hydroxymethylglycerol as the main products, accompanied by the concomitant formation of a mixture of sugars and sugar alcohols. The results indicate that this photochemical formose reaction is considerably different in product distribution from the thermal formose reaction using the $Ca(OH)_2$ catalyst. The detailed examination of the photochemical formose reaction was carried out in the presence of Na_2CO_3, and a possible scheme for the formation of pentaerythritol and 2-hydroxymethylglycerol is proposed.

The formose reaction, which is essentially the autocondensation of formaldehyde by a base catalyst, resulting in the formation of a complex mixture of monosaccharides, has been studied by many investigators. Among various inorganic and organic bases, $Ca(OH)_2$ has been recognized as an excellent catalyst, for this reaction,[1–4] while the mechanism of the sugar formation has been discussed mainly in terms of the aldol condensation between formaldehyde and lower saccharide intermediates.[4–7] In the majority of the reports, the complexity of this reaction has been emphasized. The number of products amounts to more than 30,[8] and this complexity has made it difficult to utilize the method for common carbohydrate resources.

Formose can also be synthesized photochemically. The photochemical sugar formation from formaldehyde was found by Moore *et al.*,[9] who observed the sugar formation under sunlight or irradiation by a mercury lamp in the presence of $FeCl_3$ or uranium compounds as sensitizer. Since Baly *et al.*[10,11] reported that the irradiation of 40% formalin with ultraviolet light in the presence of $CaCO_3$ gives reducing sugars in *ca.* an 8% yield, no significant report on the photochemical formose reaction has appeared. The purpose of the present work is to obtain further information on the effect of additives on the product distribution in the photochemical formose reaction as well as to contribute to the elucidation of the mechanism.

Experimental

Materials. Aqueous formaldehyde solutions were prepared from paraformaldehyde (Merck Co.).[12] All of the inorganic bases used as catalysts were of an analytical grade.

Irradiation Procedure. An aqueous formaldehyde solution (230 ml) containing 15 g of a basic catalyst was irradiated internally with a 450-W high-pressure mercury lamp in a Pyrex tube equipped with a water jacket under stirring in air. The temperature of the solution was maintained at 28—30 °C. After irradiation, the reaction mixture was slightly acidified with 1 M HCl. The formaldehyde consumption and the sugar yield were determined by the methods described in an earlier paper.[12] The amount of the organic acids was determined for acidified 10 ml aliquots by back titration with 2 M KOH.

Thermal Formose Reaction. The reaction was carried out by the method previously described.[12] The sugar products were trimethylsilylated and analyzed by gas chromatography (Fig. 1).

Gas Chromatography. The reaction mixture was evaporated to dryness *in vacuo* at 40 °C by the repeated addition and concentration of water in order to remove formaldehyde as possible. The residue was trimethylsilylated in the usual manner[13] and extracted with chloroform. A Shimadzu GC-5A chromatograph, equipped with a hydrogen-flame ionization detector, was used under the following conditions: coiled glass column of 3 m by 0.3 in. o.d., adsorber, 5% silicon gum SE-30 on 60—80 mesh Chromosorb-W; nitrogen flow rate, 60 ml/min; temperature, 100—250 °C, rising at the rate of 4 °C/min.

Separation and Identification of Products. An aqueous solution (230 ml) containing formaldehyde (55.2 g) and Na_2CO_3 (15.0 g) was irradiated as above for 50 h. The consumption of formaldehyde, the sugar yield, and the yield of organic acid (as formic acid) were determined to be 42.8, 7.5, and 2.5% respectively, based on the starting formaldehyde. The reaction mixture was then passed through columns of Amberlite IR120(H) (120 ml) and Amberlite IRA400 (OH) (500 ml) successively, after which the columns were washed with water (200 and 500 ml respectively). The whole eluate was concentrated *in vacuo* to dryness by the repeated addition and concentration of water in order to remove the formaldehyde. The residue was dissolved in water (50 ml) and diluted with acetone (50 ml) to separate pentaerythritol(I), corresponding to the GLC peak 9 (Fig. 2) (8.8 g; 38% based on the consumed formaldehyde) as colorless crystals (mp 255—256 °C), which were identical with an authentic sample (IR).

The mother liquor was evaporated to a sirup which was chromatographed in 2 g portions as follows. On the top of a column (20 cm by 2.8 cm o.d.) packed with dry cellulose powder, the sample, which had been mixed with a small amount of cellulose powder (Whatman CF-11) and dried in a desiccator, was placed; it was eluted successively with the following solvents: acetone, 500 ml; acetone–methanol (9: 1, v/v), 300 ml; acetone–methanol (8: 2, v/v), 300 ml; acetone–methanol (7:3, v/v), 200 ml; acetone–methanol (5: 5, v/v), 200 ml; methanol, 100 ml. The eluate was then collected in 50 ml portions and was analyzed by GLC and PPC. All the eluates were then divided into two fractions. Fraction A consisted of products corresponding to GLC peaks 1, 2, 3, 4, 5, 6, and 10 (Fig. 2) and amounted to 3.0 g (13%, based on the consumed formaldehyde); the second fraction consisted mainly of a product corresponding to the GLC peak 7 (2.8 g; 12%, based on the consumed formaldehyde). Part of the latter fraction was purified by paper chromatography as follows: Toyo filter paper No. 50; the upper layer of a mixture of 1-butanol–acetic acid–water (4: 1: 5) as the developing solvent; detection by an ammoniacal silver nitrate solution.[14] The chromatogram was extracted with methanol to give 2-hydroxymethylglycerol(II) (GLC peak 7) as a colorless sirup; it was identified from its spectral and analytical data: IR (KBr)

3400, 2950, 1460, 1120, 1040, 910 cm^{-1}; MS 122, 91, 73, 61, 45 *m/e*; Found: C, 39.43; H, 8.16%. Calcd for $C_4H_{10}O_4$: C, 39.34; H, 8.25%. The acetate of 2-hydroxymethylglycerol, NMR ($CDCl_3$) 2.07 (9H, s), 2.08 (3H, s), 4.13 (6H, s).

Amberlite IRA400 (OH) which had been treated with the total reaction mixture was washed with 0.2 M HCl (1 liter), and the washings was concentrated *in vacuo* (Fraction B), (8.5 g; 37%, based on the consumed formaldehyde). Fraction B consisted of products corresponding to GLC peaks (Fig. 2) 8, 14, 15, 20, 21, 23, 24, 27, 29, and organic acids.

Formation of 2-Hydroxymethylglycerol(II) from Glycolaldehyde and Formaldehyde. An aqueous formaldehyde solution (30 ml; 1.7 g) containing 0.75 g of glycolaldehyde and 0.48 g of Na_2CO_3 was stirred at 30 °C without irradiation. At intervals an aliquot was taken up and slightly acidified (pH, 5—6) with 1 M HCl to stop the reaction. The reaction mixture was evaporated to dryness as above, and the residue was trimethylsilylated and analyzed by gas chromatography. The results are shown in Fig. 6.

Photochemical Formation of Pentaerythritol (I). To 20 ml of an aqueous solution of 2-hydroxymethylglycerol (II), concd formalin, Na_2CO_3, and water were added so as to bring the concentrations of II, formaldehyde, and Na_2CO_3 to 0.1 M, 6M, and 0.62 M respectively, and the final volume to 25 ml. A quartz tube containing the solution was irradiated externally with a 450-W high-pressure mercury lamp at 30 °C. At intervals an aliquot was taken up and analyzed as above. The results are shown in Fig. 7.

Results and Discussion

The sugar yields in the photochemical formose reactions with various catalysts are summarized in Table 1.

TABLE 1. EFFECT OF INORGANIC BASE CATALYST ON THE PHOTOCHEMICAL FORMOSE REACTION[a)]

Inorganic base	Concentration of base (M)	Sugar yield as glucose (%)
$CaCO_3$	0.86	5.8
$Ca(OH)_2$	0.88	5.2
Na_2CO_3	0.62	8.7
$NaHCO_3$	0.78	4.5
NaOH	1.63	2.0
$Mg(OH)_2$	1.12	6.4

a) Light source, 450-W high-pressure mercury lamp (Pyrex); irradiation time, 72 h; [HCHO] = 12.3M; temperature, 30 °C.

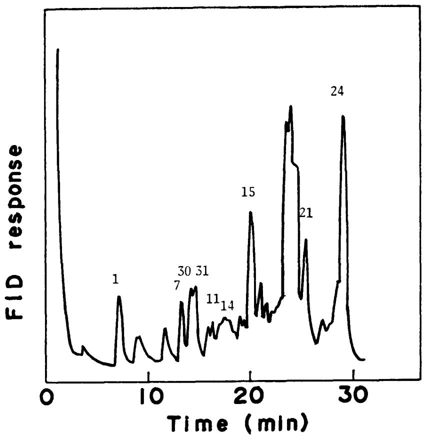


Fig. 1. Gas chromatogram of TMS derivatives of thermosynthesized formose.
[HCHO] = 2.0 M; [$Ca(OH)_2$] = 0.2 M; Temp, 60 °C; Total volume; 880 ml.[12)]

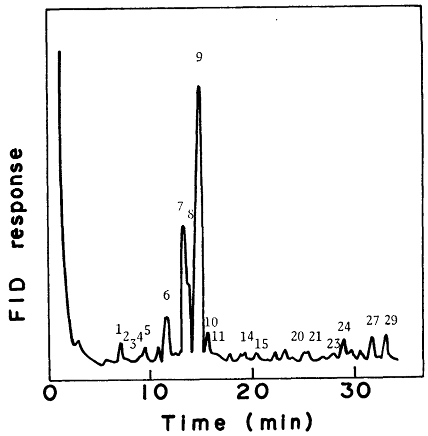


Fig. 2. Gas chromatogram of TMS derivatives of photochemically synthesized formose.
[HCHO] = 8.0 M; [Na_2CO_3] = 0.62 M; Temp, 30 °C; Light source, 450-W high-pressure mercury lamp; Irradiation time, 50 h; Total volume, 230 ml.

In the absence of a basic catalyst, the consumption of formaldehyde became negligible under UV irradiation for 50 h. When $CaCO_3$ was used as the catalyst, the sugar yield (5.8%) was lower than that (8%) reported by Baly.[11)] The discrepancy between these two experimental results might be attributed to differences in the irradiation conditions. The sugar yield was relatively high when Na_2CO_3 was used. The gas chromatogram of the trimethylsilylated products obtained by the use of the Na_2CO_3 catalyst is shown in Fig. 2. It is apparent that the product distribution of the photochemically synthesized formose is simpler than that of the formose prepared by the usual thermal method (Fig. 1). In experiments with the other catalysts listed in Table 1, the GLC patterns were similar to that of Fig. 2, but the product corresponding to peak 9 was obtained in the highest yield in case of the Na_2CO_3 catalyst. Therefore, the detailed studies of the photochemical formose reactions were made using the Na_2CO_3 catalyst.

The main products, corresponding to GLC peaks 7 and 9 of Fig. 2, were separated and identified as 2-hydroxymethylglycerol (II) and pentaerythritol (I) respectively. The compound I formed amounts to *ca.* 40% of the total products (by GLC), and the II, to 13%. Fractions A and B are most probably sugar alcohols and sugars respectively, judging from their behavior in the Benedict test (A: negative; B: positive) and the adsorption on the IRA400(OH) resin.

The formaldehyde consumption and the sugar yield in the photochemical formose reaction were found to depend on the formaldehyde concentration, which is shown in Fig. 3. At higher formaldehyde concentrations, both the formaldehyde consumption and the sugar yield increase. At concentrations less than 3 M, the reaction proceeded very slowly under a high-pressure mercury lamp (Pyrex), resulting in a formaldehyde consumption of less than 10% and a negligible formation of the sugars. However, when a 10-W low-pressure mercury

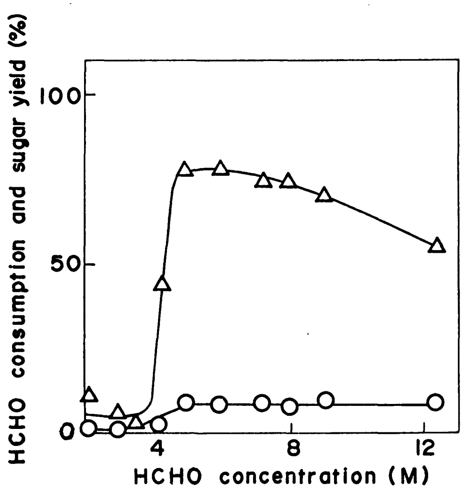


Fig. 3. Effect of HCHO concentrations on the HCHO consumption and the sugar yield.
$[Na_2CO_3]=0.62$ M; Temp, 30 °C; Light source, 450-W high-pressure mercury lamp; Irradiation time, 72 h; Total volume, 230 ml; △, HCHO consumption; ○, Sugar yield.

lamp (quartz tube) was used at a 2 M formaldehyde concentration, the consumption of formaldehyde and the sugar yield were raised to 70 and 5.4% respectively. The gas chromatogram of the products exhibited more than 30 peaks, and no selective formation of I and II was observed.

The sugar yield (usually *ca.* 50%) in the $Ca(OH)_2$-catalyzed formose reaction, in which the Cannizzaro reaction competes with the sugar formation,[5,6] is known to improve upon the addition of methanol because of its inhibitory action on the Cannizzaro reaction.[15] The fact that the sugar yield was low regardless of the formaldehyde concentrations in the photochemical formose reaction (Fig. 3) may be ascribed to the accumulation of formic acid resulting from the Cannizzaro reaction, as may be seen in the decrease in the pH in the course of the reaction (Fig. 5). However, the addition of methanol to the photochemical reaction system resulted in a decrease in the formaldehyde consumption rate (Fig. 4), and the sugar yield became negligible. This shows that methanol has rather an inhibitory effect on the photochemical formose reaction.

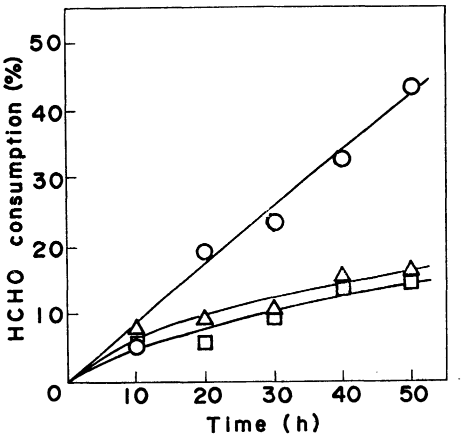


Fig. 4. Effect of methanol addition on the HCHO consumption.
$[HCHO]=8.0$ M; $[Na_2CO_3]=0.62$ M; Temp, 30 °C; Light source, 450-W high-pressure mercury lamp; [MeOH] (v/v): ○, 0%; △, 50%; □, 100%.

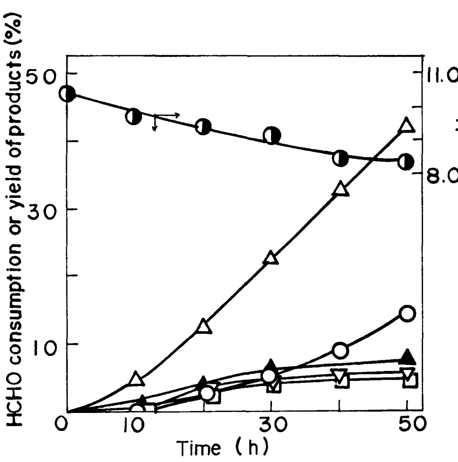


Fig. 5. Time course of the photochemical formose reaction.
$[HCHO]=8.0$ M; $[Na_2CO_3]=0.62$ M; Temp, 30 °C; Light source, 450-W high-pressure mercury lamp; Total volume, 230 ml; ◑, pH; △, HCHO consumption; ▽, Organic acid (as formic acid); ○, Pentaerythritol; □, 2-hydroxymethylglycerol; ▲, HCHO consumption by dark reaction.

The time course of a typical run of the photochemical formose reaction is shown in Fig. 5. In the earlier stages of the reaction, the yield of pentaerythritol (I) is equal to that of 2-hydroxymethylglycerol (II), but after 40 h the former appreciably exceeds the latter. A lowering of the pH due to the formation of organic acids was also observed. In a control experiment without UV irradiation, formaldehyde was consumed only to a small extent, and it was converted into organic acids nearly quantitatively by the Cannizzaro reaction.

Mechanistic Consideration. The compound I is usually prepared by treating acetaldehyde with about five equivalents of formaldehyde in an aqueous $Ca(OH)_2$ suspension. The reactions proceeds *via* the addition of three molecules of formaldehyde to acetaldehyde, followed by the Cannizzaro reaction of tris(hydroxymethyl)acetaldehyde, leading to I.[16] An attempt was made to detect acetaldehyde in the present photoreaction mixture with morpholine and sodium nitroprusside,[17] but acetaldehyde could not be detected in any stage of the reaction. The gaseous material evolved during the reaction was found by GLC analysis to be O_2 and CO_2 derived from the Na_2CO_3 catalyst.

On the basis of the facts that glycolaldehyde is a product of the first step of the thermal formose synthesis using basic catalysts,[18] and that 2-hydroxymethylglycerol is detected in the final products by GC-MS,[19] the photochemical formose reaction must be: formaldehyde→glycolaldehyde (III)→2-hydroxymethylglycerol (II)→pentaerythritol (I). The following experiments support this sequence.

When an aqueous solution of glycolaldehyde (0.42 M), formaldehyde (1.9 M), and Na_2CO_3 (0.15 M) was allowed to stand at 30 °C, II was formed in *ca.* a 30%

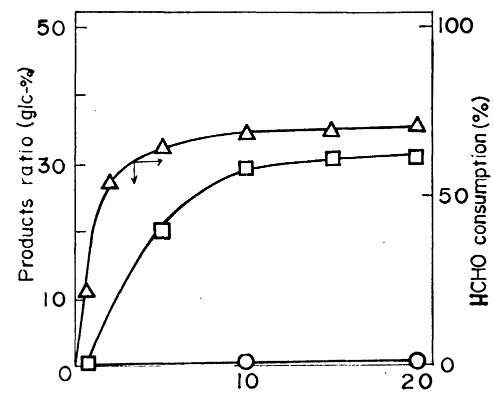


Fig. 6. Formation of 2-hydroxymethylglycerol from glycolaldehyde and formaldehyde.
[HCHO]=1.9 M; [Glycolaldehyde]=0.42 M; [Na_2CO_3]=0.15 M; Temp, 30 °C; Total volume, 30 ml; △, HCHO consumption; □, 2-hydroxymethylglycerol; ○, Pentaerythritol; Products analysis, GLC of TMS derivatives.

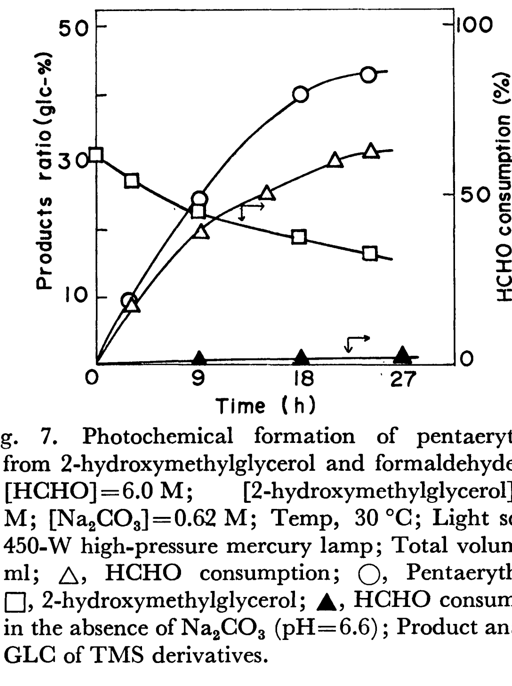
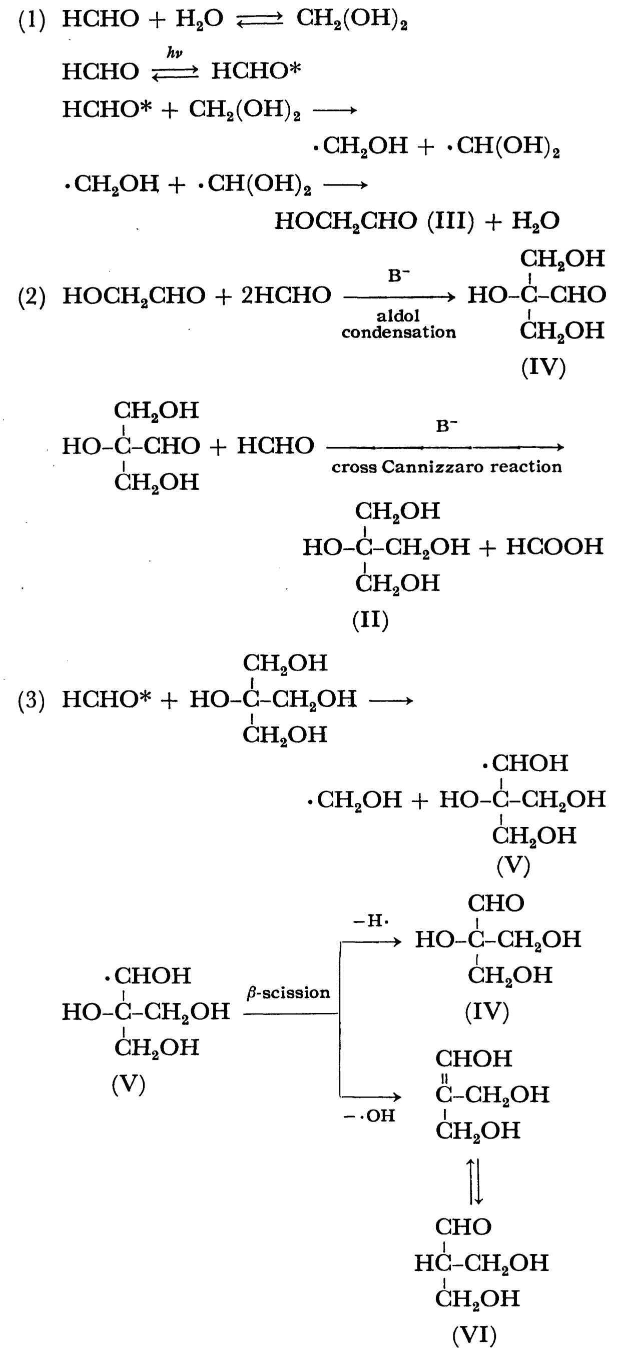


Fig. 7. Photochemical formation of pentaerythritol from 2-hydroxymethylglycerol and formaldehyde.
[HCHO]=6.0 M; [2-hydroxymethylglycerol]=0.1 M; [Na_2CO_3]=0.62 M; Temp, 30 °C; Light source, 450-W high-pressure mercury lamp; Total volume, 25 ml; △, HCHO consumption; ○, Pentaerythritol; □, 2-hydroxymethylglycerol; ▲, HCHO consumption in the absence of Na_2CO_3 (pH=6.6); Product analysis, GLC of TMS derivatives.

yield (by GLC), while formaldehyde was consumed, but no formation of I was detected (Fig. 6). The compound III disappeared rapidly at an early stage of this reaction and was no longer detectable by GLC analysis after 30 min. On the other hand, when an aqueous solution of glycolaldehyde and formaldehyde at the same concentrations was irradiated for 20 h in the absence of Na_2CO_3, the consumption of formaldehyde was less than that in the thermal Na_2CO_3-catalyzed reaction (*ca.* 30%), and neither II nor I was formed. These results indicate that, in the presence of a base and formaldehyde, glycolaldehyde (III) smoothly gives rise to 2-hydroxymethylglycerol (II) by means of a reaction in the dark.

The lack of pentaerythritol formation in the experiment shown in Fig. 6 suggests that the step of pentaerythritol formation in the photochemical formose reaction might require UV irradiation. This was shown by a photochemical formation from II (0.1 M) in the presence of formaldehyde (6 M) and Na_2CO_3 (0.62 M) (Fig. 7). In the course of irradiation, pentaerythritol (I) increases with a decrease in the formaldehyde and II; when UV irradiation was omitted or when the reaction was carried out at pH 5, little formaldehyde was consumed and the formation of I was not observed. At a low concentration of formaldehyde (0.6 M), the yield of I decreases dramatically under a 20 h irradiation.

Now, the pathway of the formation of I and II from formaldehyde under UV irradiation in the presence of a base catalyst can be formulated as is shown in the following scheme:



(1) $HCHO + H_2O \rightleftarrows CH_2(OH)_2$

$HCHO \overset{h\nu}{\rightleftarrows} HCHO^*$

$HCHO^* + CH_2(OH)_2 \longrightarrow \cdot CH_2OH + \cdot CH(OH)_2$

$\cdot CH_2OH + \cdot CH(OH)_2 \longrightarrow HOCH_2CHO\ (III) + H_2O$

(2) $HOCH_2CHO + 2HCHO \xrightarrow[\text{aldol condensation}]{B^-} HO\text{-}\underset{CH_2OH}{\overset{CH_2OH}{C}}\text{-}CHO$ (IV)

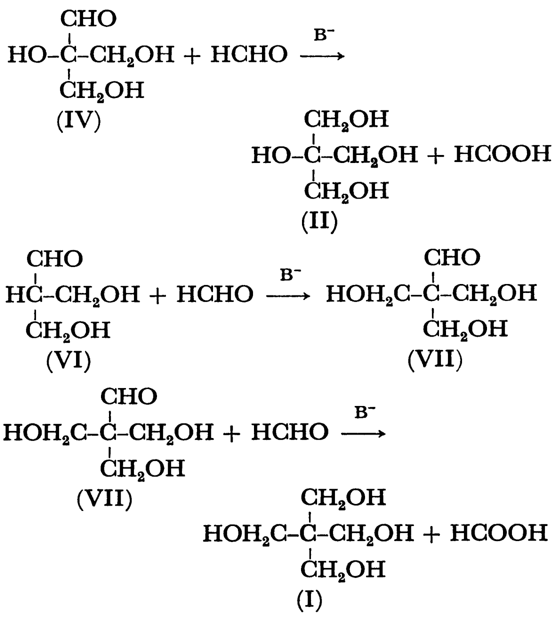
$HO\text{-}\underset{CH_2OH}{\overset{CH_2OH}{C}}\text{-}CHO + HCHO \xrightarrow[\text{cross Cannizzaro reaction}]{B^-} HO\text{-}\underset{CH_2OH}{\overset{CH_2OH}{C}}\text{-}CH_2OH + HCOOH$ (II)

(3) $HCHO^* + HO\text{-}\underset{CH_2OH}{\overset{CH_2OH}{C}}\text{-}CH_2OH \longrightarrow \cdot CH_2OH + HO\text{-}\underset{CH_2OH}{\overset{\cdot CHOH}{C}}\text{-}CH_2OH$ (V)

$HO\text{-}\underset{CH_2OH}{\overset{\cdot CHOH}{C}}\text{-}CH_2OH$ (V) $\xrightarrow{\beta\text{-scission}}$

$\xrightarrow{-H\cdot} HO\text{-}\underset{CH_2OH}{\overset{CHO}{C}}\text{-}CH_2OH$ (IV)

$\xrightarrow{-\cdot OH} \underset{CH_2OH}{\overset{CHOH}{\overset{\|}{C}}}\text{-}CH_2OH \rightleftarrows H\underset{CH_2OH}{\overset{CHO}{C}}\text{-}CH_2OH$ (VI)



$$\mathrm{HO{-}\overset{CHO}{\underset{CH_2OH}{C}}{-}CH_2OH + HCHO \xrightarrow{B^-} HO{-}\overset{CH_2OH}{\underset{CH_2OH}{C}}{-}CH_2OH + HCOOH}$$

(IV) (II)

$$\mathrm{H\overset{CHO}{\underset{CH_2OH}{C}}{-}CH_2OH + HCHO \xrightarrow{B^-} HOH_2C{-}\overset{CHO}{\underset{CH_2OH}{C}}{-}CH_2OH}$$

(VI) (VII)

$$\mathrm{HOH_2C{-}\overset{CHO}{\underset{CH_2OH}{C}}{-}CH_2OH + HCHO \xrightarrow{B^-} HOH_2C{-}\overset{CH_2OH}{\underset{CH_2OH}{C}}{-}CH_2OH + HCOOH}$$

(VII) (I)

(1) The first step is the formation of glycolaldehyde (III) from formaldehyde with light, as has already been reported by Pribram.[20] An n-π^* excited state of formaldehyde [$\lambda_{\max}^{H_2O}$ 288 nm (log ε 1.13)[21]] abstracts hydrogen from its hydrated form,[22] methanediol; this is followed by the coupling of the two radical species.

(2) The second step may consist of thermal processes. In the presence of a base, glycolaldehyde (III) smoothly undergoes aldol condensation with formaldehyde, followed by a cross-Cannizzaro reaction between 2-formylglycerol (IV) and formaldehyde to yield 2-hydroxymethylglycerol (II).

(3) The final step probably involves a photochemical process. An excited state of formaldehyde may abstract hydrogen from a methylene group of II, giving a substituted hydroxymethyl radical (V). The radical may then undergo β-scission to yield either 2-formylglycerol (IV) or bis(hydroxymethyl)acetaldehyde (VI). The oxygen evolved during the reaction may come from the hydroxyl radicals. In the presence of a base and formaldehyde, the former (IV) undergoes a cross-Cannizzaro reaction to revert back to II. The latter (VI) undergoes an aldol condensation with formaldehyde, followed by a cross-Cannizzaro reaction of the tris(hydroxymethyl)-acetaldehyde (VII) thus formed, to yield, finally, pentaerythritol (I).

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