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The Synthesis of Carbohydrates from Formaldehyde

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The problems of the synthesis of carbohydrates from formaldehyde are examined and the catalysts and conditions of the synthesis are described. The kinetics and current ideas concerning the mechanism of this process as well as different versions of its application in the regeneration of food products in manned spacevessels are discussed. The bibliography includes 141 references.

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I. INTRODUCTION

The rapid growth of the duration of space flights has given rise to new problems in the field of the construction of life support systems for the crews of space vessels. It is already insufficient merely to eliminate harmful substances from the atmosphere of the cabin in the space vessels and to provide stores of substances ready for consumption—water, oxygen and food. In the flights of manned spaceships and stations not less than 4–5 litres of water[1], approximately 1 kg of oxygen[2], and 1–1.3 kg of food[3] is the daily requirement per member of the crew. These figures show that space flights lasting several months require at least partial regeneration of water and oxygen, so that the starting weight of manned space vessels is not unduly large; for flights lasting more than a year the problem of the regeneration of food products becomes of urgent importance.

There is a possibility of two fundamentally different ways of constructing a life support system in space vessels: on physicochemical and biotechnical bases. Studies in both fields are in the initial stage.

Table 1. The compositions and caloric values of the diet of cosmonauts.

Spacevessel	Content of food products			Moisture, ml	Caloric value, kcal
	proteins, g	fats, g	carbohydrates, g		
Soyuz-3	120.9	118.5	267.1	521.5	2755.0
Soyuz-4, Soyuz-8	110.7	98.2	297.0	672.0	2586.0
Soyuz-9	109.7	100.3	339.2	756.3	2852.0
Soyuz-10, Soyuz-23	126.5	116.7	338.3	697.8	2992.3
Soyuz-19	129.2	135.1	289.5	747.6	2975.7
Salyut-3, Salyut-5	129.2	135.1	289.5	747.6	2975.7

Table 1 presents data[3] concerning the composition and caloric value of the food consumed by cosmonauts in Soviet spaceships and stations. Evidently the fraction of carbohydrates in the cosmonauts' food ration is more than 60% of the entire dry weight of the food, reaching in terms of weight 270–350 g per day. In view of the dominant carbohydrate content in the food, the attention of investigators should be devoted to the search for physicochemical or biotechnical methods of synthesis of carbohydrates from the main final products of the vital activity of the human organism—carbon dioxide and water.

At the present time only one suitable chemical synthesis of carbohydrates from simple molecules is know—the condensation of formaldehyde in aqueous solutions in the presence of a number of organic bases as process catalysts. This procedure was discovered by Butlerov as early as 1861.[4,5]

The synthesis of formaldehyde from CO_2 and H_2O under the conditions of the spaceship could be achieved in the following two ways[2]: by hydrogenating carbon dioxide to methane and by oxidising the latter to formaldehyde:

$$CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O \quad ,$$
$$CH_4 + O_2 \rightarrow HCHO + H_2O \quad ,$$

or by hydrogenating carbon dioxide to methanol, the oxidation of which can also yield formaldehyde:

$$CO_2 + 3H_2 \rightarrow CH_3OH + H_2O \quad ,$$
$$CH_3OH + {}^1/_2O_2 \rightarrow HCHO + H_2O \quad .$$

The first procedure can be achieved under atmospheric pressure, which is extremely important in relation to the conditions in space vessels. However, it is not so far been possible to overcome a number of significant disadvantages of this method of synthesis of formaldehyde—low selectivity in the oxidation of methane to formaldehyde and low yields of the latter under optimum process conditions. The second method is free from these disadvantages, but the need to use high pressures in order to obtain methanol at the present level of technology precludes its employment in space vessels.

Since the synthesis of formaldehyde by the above methods in space vessels is in principle feasible, the interest in the synthesis of carbohydrates from formaldehyde as an acceptable concluding stage in the conversion of the final products of the vital activity in a manned spaceship to food products is understandable. Hexoses, which are the most valuable carbohydrates as regards food, can be obtained by the condensation of six formaldehyde molecules:

$$6HCHO \rightarrow C_6H_{12}O_6 \quad .$$

However, a significant disadvantage of the synthesis of carbohydrates from formaldehyde, which has still not been overcome, is the low selectivity of this process. Apart from the small fraction of hexoses which can be assimilated by the human organism (D-modifications of glucose, fructose,

galactose, and mannose), the main bulk of the products of the synthesis consists of non-assimilable carbohydrates. This disadvantage of the method is aggravated by the formation of appreciable amounts of branched carbohydrates[6], which, according to some hypotheses, may exhibit a toxic activity when taken with food. Therefore, despite the fact that the synthesis of carbohydrates from formaldehyde takes place under readily realisable conditions—in aqueous solutions at atmospheric pressure and temperatures only a little above room temperature—it is not so far used in practice.

For the synthesis to be carried out in practice, it is necessary to increase greatly its selectivity, which requires detailed information about the kinetics and mechanism of the process. Particular attention has been devoted to these problems in studies during the last decade, in which the classical kinetic methods have been supplemented by an improved chromatographic technique for the analysis of products and by isotopic and spectroscopic methods. The use of a gradient-free reactor made it possible to obtain particularly valuable information about the kinetics of the synthesis. The search for optimum catalysts and conditions for the synthesis of carbohydrates is being vigorously prosecuted.

This review deals with the following problems: catalysts and conditions of the synthesis of carbohydrates from formaldehyde and the kinetics and mechanism of the process. In the concluding section of the review different versions of the application of this process in the regeneration of food products in manned space vessels are discussed.

II. CATALYSTS AND CONDITIONS FOR THE CONDENSATION OF FORMALDEHYDE TO CARBOHYDRATES

As already mentioned, sugars were obtained from formaldehyde for the first time by Butlerov[4,5]. The reaction took place in an aqueous solution at 100 °C using $Ca(OH)_2$, $Ba(OH)_2$, Na_2CO_3, and K_2CO_3 as catalysts. Subsequently a wide range of inorganic compounds were tested for catalytic activity in this process. Thus Loew[7-12] used in 1886 calcium hydroxide with added NaCl, KNO_3, and CH_3COONa as catalyst and observed that among these salts only NaCl has no inhibiting effect. According to Loew's data, sugars are formed when formaldehyde is acted upon by alkaline earth metal carbonates and lead oxide. In subsequent studies DL-fructose, DL-glucose, DL-sorbose, and DL-arabinose were isolated from syrups obtained by Loew's method[13-15].

The influence of calcium, barium, sodium, and iron hydroxides as well as $CaCO_3$ on the condensation of formaldehyde was investigated[16-18] and it was established that calcium hydroxide is the best catalyst. The use of potassium, sodium, and calcium phosphates[19] did not yield a positive result; when $MgSO_4$ was employed, it was possible to obtain a syrup in which fructose, sorbose, and arabinose were identified.

Schmalfuss[20-22] achieved for the first time the condensation of formaldehyde to carbohydrates at a high pressure and temperature (2 atm, 120 °C). MgO, Al_2O_3, CaO, $Ca(OH)_2$, NaOH, and $Al(OH)_3$ were used as catalysts. The carbohydrates were formed in all cases except when Al_2O_3 and $Al(OH)_3$ were used. In the presence of NaOH carbohydrates were formed 2 min after the start of the experiment but then began to decompose very rapidly. In the 1950's[23] a new highly active catalyst (TlOH) was introduced, the synthesis of carbohydrates in its presence being completed after 20 min at 60 °C. The activity of magnesium, calcium, zinc, cadmium, mercury, aluminium, lead, tin, antimony, bismuth, and manganese oxides has been investigated[24,25] in the condensation reaction. It was noted that only magnesium, calcium, and lead oxides exhibit a catalytic activity in the temperature range 75–100 °C.

Thus by the end of the 1960's it was established that the most active catalysts in the condensation of formaldehyde to carbohydrates are fairly strong bases—alkaline earth metal hydroxides and oxides, thallium hydroxide, and lead oxide. In subsequent years it was observed that certain tertiary amines[26], lanthanice hydroxides[27,28] and aluminosilicates[29,30] can function as condensation catalysts.

The catalytic activities of the following tertiary amines have been demonstrated[26]: triethanolamine, dimethylaminoethanol, pyridine, *N*-methylpiperidine, α-picoline, collidine, *N*-methylmorpholine, tetraethylammonium hydroxide, and a mixture consisting of β and γ-picolines. Their activities are appreciably lower than those of alkaline earth metal hydroxides. When the above organic bases are used as catalysts, the synthesis must be carried out at high temperatures (100 °C) and as a rule in the presence of a large excess of the base relative to formaldehyde. The catalytic activities of the organic bases have been confirmed[31]. Berlin and coworkers[27,28] observed a catalytic activity of lanthanide (La, Tb, Ho, Tm, Gd, Dy, Er, Sm, and Yb) hydroxides in the synthesis of carbohydrates at high temperatures (optimum process conditions 110 °C and 1.8 atm).

In contrast to early studies, Gable and Ponnamperuma[29] found that appreciable amounts of carbohydrates are obtained after a boiling solution of formaldehyde has been in contact with Al_2O_3 for 5 h. According to their data, the formation of hexoses in the presence of Al_2O_3 is favoured by the use of low formaldehyde concentrations (10^{-2} M). They also showed[29] that aluminosilicates such as kaolinite and illite are catalytically active in the synthesis of carbohydrates. Appreciable amounts of carbohydrates are formed in their presence after many hours of contact with a boiling solution of formaldehyde. It has been shown[30] that the NaX zeolite exhibits an appreciable catalytic activity in the synthesis of carbohydrates at 95 °C when the pH of the solution is sufficiently high (>10 at the outlet from the flow reactor).

Appreciable formation of carbohydrates has been observed[32] on prolonged refluxing of formaldehyde with a suspension of a carbonate-containing apatite.

III. GENERAL CHARACTERISTICS OF THE CONDENSATION REACTION

In the very earliest studies[8-12] it was already observed that the condensation of formaldehyde to carbohydrates is accompanied by the dismutation reaction

$$2CH_2O + H_2O \rightleftarrows CH_3OH + HCOOH$$

which leads to the formation of formic acid and methanol (the Cannizzaro reaction).

In 1895 Henry[33] identified glyceraldehyde and dihydroxyacetone in the formaldehyde condensation products and suggested that they are intermediates in the formation of hexoses. Neuberg[34] suggested in 1902 that glycolaldehyde is the first condensation product and is formed from formaldehyde at a low rate. According to Neuberg, the reaction is autocatalytic and heavier carbohydrates (starting from C_3) are formed at high rates.

In 1915 Franzen and Hauck[35] isolated salt-like compounds resulting from the combination of formaldehyde and calcium hydroxide and investigated the possibility of their presence as intermediates in the condensation reaction. They suggested

that in dilute solutions the first stage involves the interaction of methylene glycol (the main form of monomeric formaldehyde in aqueous solutions) with calcium hydroxide:

$$CH_2(OH)_2 + Ca(OH)_2 \rightarrow HOCH_2OCaOH + H_2O \quad .$$

In the next stage the interaction of two such molecules leads, in their view, to the formation of glycolaldehyde:

$$2HOCH_2OCaOH \rightarrow HOCH_2CHOHOCaOH + Ca(OH)_2.$$

However, Franzen and Hauck do not present any data in support of their ideas concerning the process mechanism apart from the possible composition of the salt-like products.

Schmalfuss[20-22] used for the first time as the catalyst the product of the condensation of formaldehyde carried out in the presence of MgO and observed its high catalytic activity. He also noted that the rate of condensation increases greatly following the addition of glucose to the reaction mixture. On the basis of these experiments, Schmalfuss arrived at the conclusion, reached previously by Neuberg, that the condensation is autocatalytic. This view was subsequently expressed by Trigerman et al. [36] Orther and Gerisch[37] analysed the composition of the products in the reaction carried out in the presence of lead hydroxide: after hydrogenation and subsequent fractionation of the condensate, it was possible to isolate glycerol, tetritols, pentitols, and hexitols. According to their reaction mechanism, carbohydrates ranging from C_3 to C_6 are formed via the self-condensation of formaldehyde, for example:

$$3CH_2O \rightarrow \text{trioses},$$

$$4CH_2O \rightarrow \text{tetroses, etc.}$$

Kuzin[38-44] continued Schmalfuss's experiments to elucidate the role of organic compounds added to the reaction mixture. He established that the addition of compounds such as polyhydric alcohols, acetone, penta-acetylfructose, and polysaccharides does not affect the rate of condensation when $Ca(OH)_2$ is used as for the catalyst. On the other hand, compounds such as hydroxyoxosuccinic acid, ethoxyacetaldehyde, benzoin, and acetoin eliminated or at least shortened the induction period on being added together with the hydroxide. Nowadays such compounds are regarded as cocatalysts. Kuzin attributed their catalytic activity to their ability to form enediols:

$$-\underset{\underset{OH}{|}}{CH}-\underset{\underset{O}{\|}}{C}- \rightleftarrows -\underset{\underset{OH}{|}}{C}=\underset{\underset{OH}{|}}{C}- \quad .$$

He regarded enolisation as a preliminary condition for the appearance of the activity of the cocatalyst.

Langenbeck[45-51] used as cocatalysts higher and lower monosaccharides, benzoylcarbinol, and a number of its derivatives. The kinetic measurements quoted by the authors show that the individual cocatalysts differ only by the induction period, and the corresponding kinetic curves are almost parallel. It was shown that glycolaldehyde and dihydroxyacetone are the most active cocatalysts. According to Langenbeck[47], the role of other cocatalysts, with a long induction period, reduces to the formation of glycolaldehyde or dihydroxyacetone with their participation. Langenbeck[51] suggested that the organic cocatalyst behaves as an activator of formaldehyde, which gives rise to glycolaldehyde on combining with a non-activated formaldehyde molecule:

$$R-CHOH-CO-R + CH_2O \rightarrow R-\underset{\underset{OH}{|}}{\overset{\overset{CH_2OH}{|}}{C}}-CO-R \rightarrow R-CHOH-CO-R + CH_2O^* \quad ;$$

$$CH_2O^* + CH_2O \rightarrow CH_2OHCHO \quad .$$

Here CH_2O^* is an activated formaldehyde molecule. Like, incidentally, Kuzin, Langenbeck assumed that the hydroxide plays only a secondary role. According to Kuzin's views, the hydroxide promotes the formation of enediol groups, ensuring the required pH and interacting with the hydrated forms of the carbohydrates and formaldehyde. However, this treatment conflicts with the specific catalytic action of a number of cations, which has now been demonstrated.

The formaldehyde condensation reaction has been thoroughly investigated in a series of studies[23,52-52] using alkali and alkaline earth metal hydroxides as catalysts. The kinetics and mechanisms of the Cannizzaro reaction were especially considered. The experimental results showed that the weaker the base the more effectively does it catalyse the Cannizzaro reaction:

$$Ca(OH)_2 \gg Tl(OH)_3 > Ba(OH)_2 > LiOH > NaOH,\ KOH.$$

It was also shown that low-molecular-weight alcohols, ethylene glycol, glycerol, dioxan, and tetrahydrofuran, added to the reaction mixtures, suppress the Cannizzaro reaction and increase thereby the yield of sugars. On the basis of paper chromatographic analyses of the products, the authors concluded that the primary reaction products is glycolaldehyde, which then condenses either with itself or with formaldehyde to give a wide range of reaction products—from trioses to hexoses. A stepwise mechanism of the formation of higher carbohydrates by the successive addition of a formaldehyde molecule to molecules of lower carbohydrates was put forward for the first time taking into account the keto–enol tautomerism and epimerisation[55]. Furthermore, the authors took into account in their scheme the fact that higher carbohydrates can be formed from lower carbohydrates as a result of the self-condensation of the latter:

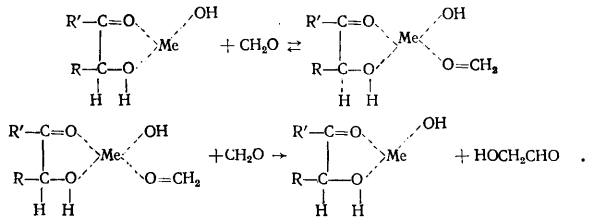
$$2CH_2OHCHO \rightarrow \text{tetroses},$$

$$2CH_2OHCHOHCHO \rightarrow \text{hexoses},$$

$$CH_2OHCHO + CH_2OHCHOHCHO \rightarrow \text{pentoses}.$$

It has been shown by a number of workers[56-62] that the carbohydrate self-condensation reactions proceed at a fairly high rate in alkaline solutions and should therefore play an important role in the mechanism of the formation of higher carbohydrates.

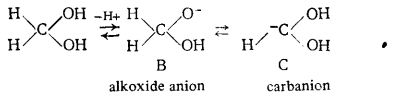
Pfeil and coworkers[56] suggested that the condensation proceeds at a complex of the undissociated metal hydroxide, the hydroxyoxo-compound, and formaldehyde:



Despite the fact that the existence of the complex of the hydroxyoxo-compound has not been demonstrated by any direct methods, one should note that Pfeil and coworkers were the first to draw attention to the possible decisive role of complexes of this kind in the synthesis of carbohydrates.

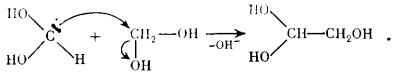
Other ideas about the mechanism of the action of bases on the condensation reaction were put forward by Runge and Mayer[26]. They established that in the presence of organic bases the Cannizzaro reaction does not take place. At the same time, under the influence of both inorganic and organic

bases (pyridine, dimethyl-aminoethanol, etc), the condensation reaction is characterised by an induction period and an autocatalytic period. The reaction time falls appreciably also after the addition of substances capable of forming enediol groups. The reaction mass, analysed by paper chromatography, does not differ in composition from the condensate obtained under the influence of an inorganic catalyst. On the basis of these extremely qualitative data, it was concluded that the mechanisms of the condensation reaction catalysed by organic and inorganic bases should be similar. Bearing in mind that organic catalysts such as tertiary amines cannot form complexes, Krylov et al.[27] proposed a mechanism in which a secondary role is assigned to the base. In the first stage a proton is abstracted in the presence of the base from the hydrated formaldehyde molecule with formation of structures corresponding to alkoxide and carbanionic forms:

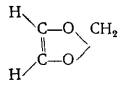


B alkoxide anion C carbanion

In such a system there is a possibility, albeit with a low probability, of the interaction of the carbanions of formaldehyde and its hydrated molecules to form a glycolaldehyde molecule:



The autocatalytic nature of the process is caused, according to the authors[27], by the intermediate formation of the five-membered ring



from the enediol form of glycolaldehyde and formaldehyde and by the ease of the successive interaction of this ring with two other formaldehyde molecules to form a new glycolaldehyde molecule with regeneration of the ring.

This mechanism suffers from the same significant disadvantage as those of Kuzin and Langenbeck. It cannot explain the dependence, observed by Pfeil as early as 1952, of the rate of reaction on the nature of the cation. The possibility of the formation of a ring of the above type is also doubtful.

IV. CURRENT STUDIES ON THE KINETICS AND MECHANISM OF THE SYNTHESIS OF CARBOHYDRATES

The kinetics of the synthesis of carbohydrates have been investigated by Krylov, Sinyak, and others[63–67] using alkaline earth metal hydroxides as catalysts. According to these workers, calcium and strontium hydroxides are much more active than $Ba(OH)_2$ and $Mg(OH)_2$; no catalytic activity has been found in $Be(OH)_2$. It has been discovered that only at a CH_2O concentration below 0.5% is there a linear relation between the rate of reaction and the CH_2O concentration; on the other hand, in the range 2.5–10% the rate is independent of the CH_2O concentration. Experiments carried out in the presence of various monosaccharides (C_3–C_6) showed that the variation of the rate of reaction with the cocatalyst concentration is also non-linear. At a monosaccharide concentration below $(3–4) \times 10^{-2}$ M and for degrees of conversion of formaldehyde up to 50%, the reaction kinetics in the presence of $Ca(OH)_2$ and $Sr(OH)_2$ can be described satisfactorily by the autocatalytic equation[64,65]

$$\frac{dx}{dt} = K(c_0 - x)(x_0 + x),$$

where c_0 and x_0 are the initial concentrations of formaldehyde and the monosaccharide and x is the current concentration of the reaction products. It was found[65] that the autocatalytic effect diminishes with increase of the number of carbon atoms in the monosaccharide and also that ketoses are more active than aldoses.

On the other hand, comparative experiments on the kinetics of the condensation of formaldehyde in the presence of a specific amount of $Ca(OH)_2$ in the form of a suspension and after filtering off the insoluble calcium hydroxide, carried out by the same workers[68], showed that the kinetic curves for the consumption of formaldehyde coincide. These experiments demonstrated the homogeneity of the reaction involving the condensation of formaldehyde to a sugar in the presence of $Ca(OH)_2$. Evidence for the homogeneous-catalytic nature of the process in the presence of $Ca(OH)_2$ was also obtained in other investigations[69–72].

The observed appreciable increase of the solubility of $Ca(OH)_2$ under the conditions of the synthesis has been explained[68] by the formation of a complex of the Ca^{2+} ion with formaldehyde and the reaction product—monosaccharides. The authors concluded that the elementary stages of the reaction take place in the coordination sphere of the catalytically active cation and put forward the following general kinetic equation for the reaction:

$$-\frac{d[CH_2O]}{dt} = k[Ca(OH)_2] \cdot \frac{b[CH_2O]}{1 + b[CH_2O]} \cdot \frac{b'[Pr]}{1 + b'[Pr]},$$

where b and b' are the complex formation equilibrium constants analogous to adsorption coefficients and Pr are reaction products. Different stages of the reaction are characterised by different reaction orders:

(1) For low conversions, when the concentration of CH_2O is low $\{b[CH_2O] \gg 1\}$ and

$$-\frac{d[CH_2O]}{dt} = k[Ca(OH)_2]\, b'[Pr]$$

the kinetics are described by the autocatalytic equation;

(2) For high conversions $\{b'[Pr] \gg 1\}$ and

$$-\frac{d[CH_2O]}{dt} = k[Ca(OH)_2]\, b[CH_2O]$$

the reaction is of first order with respect to formaldehyde:

(3) For moderate conversions $\{b[CH_2O] > 1;\ b'[Pr] > 1\}$, we have

$$-\frac{d[CH_2O]}{dt} \simeq k[Ca(OH)_2],$$

i.e. the reaction is of zero order with respect to formaldehyde.

Another important result of the investigations by the same workers was the discovery of a new class of catalysts—lanthanide hydroxides[27,28,73,74]. The authors suggested that new catalysts should be sought among the hydroxides of metals whose ionic radius is close to that of the metals in the catalysts already known. According to this hypothesis, the hydroxides of elements whose ionic radii is between 0.98 and 1.15 Å (Ca^{2+}–1.06 Å, Tl^{3+}–1.05 Å) should catalyse the condensation of formaldehyde to sugars. In this instance the groups of catalytically active cations includes those of lanthanide metals. Indeed, in the presence of La, Tb, Ho, Tm, Gd, Dy, Er, Sm, and Yb hydroxides, 100% conversion of formaldehyde was reached in the process after 5–6 h in an autoclave at 110 °C and a pressure of 1.8 atm. As for other catalytically active bases, the kinetics of the decrease

of the amount of formaldehyde were characterised by an induction period and auto-catalytic acceleration. The fact that the reaction proceeds wholly in an acid medium (the pH of the initial solutions at 110 °C in the presence of various catalysts varied in the range from 7 to 4) is of great interest. The conversion of formaldehyde via the Cannizzaro reaction takes place to an insignificant degree and the selectivity of the synthesis of carbohydrates in the presence of these catalysts is therefore greater than in the presence of $Ca(OH)_2$. These studies showed that the region where the condensation reaction can occur is not limited to an alkaline medium.

A kinetic equation analogous to that quoted by Krylov et al.[27] was obtained simultaneously and independently by Weiss et al.[75]. In a series of studies, carried out under Weiss's supervision, a detailed investigation was made of the kinetics of the condensation of formaldehyde in the presence of $Ca(OH)_2$ in a gradient-free reactor. At the same time a study was made of the Cannizzaro reaction[76]. The authors[75] began with the hypothesis that the following reactions take place in the formation of carbohydrates:

$$A_1 + Ca(OH)_2 \rightleftarrows A_1^* \quad , \qquad (1)$$

$$A_n + Ca(OH)_2 \rightleftarrows A_n^* \quad , \qquad (2)$$

$$A_n^* + A_1^* \rightleftarrows A_{n+1}^* + Ca(OH)_2 \quad , \qquad (3)$$

$$A_{n+1}^* \rightarrow A_{n+1} + Ca(OH)_2, \qquad (4)$$

where A_1 is formaldehyde, A_n a carbohydrate with n carbon atoms in the chain, and A_1^* and A_n^* are complexes of $Ca(OH)_2$ with formaldehyde and the carbohydrate respectively. In conformity with literature data[35,77], according to which formaldehyde and low-molecular-weight carbohydrates form complexes relatively readily, the authors[75] believe that stages (1) and (2) cannot be rate-limiting. The relatively low activation energy (16 kcal mol^{-1}) found by the authors made it possible to assume that stage (3) is likewise not rate-limiting. Assuming that stage (4) is rate-limiting, the authors derived the following equation:

$$r_F = k_4 K_1 K_2 K_3 S A_1 A_n / (1 + K_1 A_1 + K_2 A_n + K_1 K_2 K_3 A_1 A_n),$$

where r_F is the rate of reaction, K_1, K_2, and K_3 are the equilibrium constants of stages (1), (2), (3), k_4 is the rate constant for stage (4) in the forward direction, A_1 and A_n are the concentrations of formaldehyde and the carbohydrate respectively, and S is the concentration of $Ca(OH)_2$ equal to the sum of the concentrations of the hydroxide in a free state and in the form of a complex.

The equation obtained gives a formally satisfactory description of the observed kinetic relations for the reaction: autocatalysis for low conversions, zero order for intermediate conversions, and first order with respect to formaldehyde for high conversions. However, the above mechanism does not include the slowest stage, involving the dimerisation of formaldehyde, and cannot therefore explain the nature of the autocatalysis. In their purely kinetic study, Weiss and coworkers did not have as their aim a special investigation of the nature of the intermediate complexes. At the same time, the authors first complete analysis of the reaction products by a combination of gas chromatography and mass spectrometry[6,78,79] was a major step forward in this field. An important result of their investigation was the detection of a considerable content of branched carbohydrates in the reaction product.

Following Breslow[80,81], Weiss et al.[75] attribute an important role in the process to the Lobry de Bruyn–van Ekenstein rearrangement, the occurrence of which determined the ratio of the aldoses and ketoses in the reaction products. The rearrangement is based on the formation of the enediol form from the carbonyl form. As a result of the reversibility of this process, there is a possibility of the reformation of the carbonyl form together with its epimer and the ketose. The reaction is catalysed by both acids and bases. This rearrangement therefore always accompanies the condensation reaction, complicating the composition of the final products.

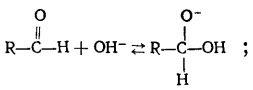
Weiss and coworkers[75,76] also investigated the ratio of the rates of the condensation and Cannizzaro reactions. The rate of the latter passes through a maximum near 50% conversion.

A single mechanism has been proposed for the Cannizzaro reaction and the reaction involving condensation to sugars[82]. On the grounds that the reaction does not require high concentrations of calcium cations, the authors conclude that the entire process is catalysed by the singly dissociated form of the calcium hydroxide formed on dissolution of $Ca(OH)_2$:

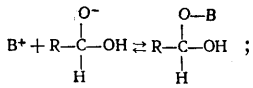
$$Ca(OH)_2 \rightleftarrows CaOH^+ + OH^- \quad ,$$
$$CaOH^+ \rightleftarrows Ca^{2+} + OH^- \quad .$$

The overall mechanism is based on the hypothesis of the decisive role of the interaction of the carbonion and the carbonium ion formed from formaldehyde molecules via the following mechanism:

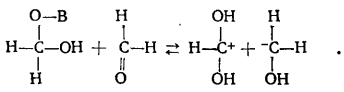
(a) the aldose or formaldehyde interacts with a hydroxide ion to form the anionic form:



(b) the anionic form interaction with the hydroxide cation (in the present instance, with $CaOH^+$), giving rise to a salt-like complex:

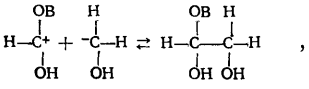


(c) the initiation of the condensation begins with the transfer of a hydride ion from the salt-like formaldehyde complex to a free formaldehyde molecule:

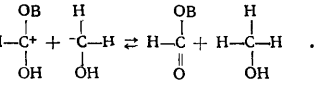


After this, two reactions pathways are possible:

(d) either recombination of the ions with formation of carbohydrate molecules—condensation (in the simplest case a salt-like complex of glycolaldehyde is produced):



(e) or proton transfer from the carbonium ion with formation of methanol (or a polyol) and a formate (the Cannizzaro or cross-Cannizzaro reactions):



It is believed[82] that the nature of the base affects the ratio of the rates of the last two stages and is therefore responsible for the process selectivity. The authors think that stage (d) is highly reversible on the grounds that, for low conversions, small amounts of glycolaldehyde are formed, while stage (e) is almost irreversible. Stage (d) explains the formation of the first condensation products. Further formation of carbohydrates proceeds mainly as a result of the aldol condensation, which the authors believe is also based on stage (d). However, the transfer of a hydride ion is inconsistent with modern ideas concerning the mechanism of the aldol condensation and requires at least special demonstration.

In the same study[82] the authors observed instances of instability of the rate of reaction for slight changes in the concentrations of the hydroxide and the components of the reaction, the pH, or temperature. The authors attribute this instability to the specific features of the autocatalytic reaction in a gradient-free reactor. The possibility of concentration instabilities in autocatalytic processes has been accounted for theoretically[83].

An interesting phenomenon—the inhibiting effect of transition metal hydroxides on the condensation of formaldehyde in the presence of calcium hydroxide—has been observed by Morozov and Levanevskii[84]. In their experiments $\sim 10^{-4}$ M transition metal hydroxide was introduced into the reaction mixture in the presence of a $Ca(OH)_2$ concentration of $\sim 10^{-2}$ M. As a rule, an appreciable increase of the induction period was observed. The induction period was longest in the presence of Fe^{2+} and Mn^{2+}. Under these conditions, the Cannizzaro reaction was not inhibited. It was established that the nature of the kinetic curves depends on the instant when the inhibitor is introduced and on the nature of the cocatalyst. The introduction of monosaccharides, such as C_2 and C_3, into the reaction mixture reduces the inhibition.

It was later established[85] that the inhibiting effect on the synthesis in the presence of $Ca(OH)_2$ can also be shown by lanthanide hydroxide. The experiments were performed at 60 °C and a concentration of hydroxides of $\sim 10^{-4}$ M. Praseodymium(III), gadolinium(III), terbium(III), and ytterbium(III) hydroxides have the strongest inhibiting effect. Lanthanum(III), europium(III), dysprosium(III), and erbium(III) hydroxides are weak inhibitors. Cerium(III), neodymium(III), samarium(III), holmium(III), and thulium(III) hydroxides exhibit an intermediate inhibiting activity. The composition of the condensation products is in all cases almost the same as in the presence of pure calcium hydroxide. The main reaction products are pentoses and hexoses. The addition of glyceraldehyde to the initial mixture reduced the inhibiting effect of lanthanide hydroxides. On the basis of these results, the authors conclude that the inhibiting effect of transition metal and lanthanide hydroxides is associated with the inhibition of the slowest stage—involving the formation of a molecule of glycolaldehyde from two formaldehyde molecules. The authors do not discuss the reasons why lanthanide cations, which are catalytically active in the synthesis of carbohydrates in the absence of calcium hydroxide, exhibit an inhibiting effect when the latter is introduced. In the same study[85] inhibitors of another type, inhibiting the condensation proper, were investigated. They include nitrobenzene and copper hydroxide. The inhibition at this stage is associated with the oxidative breakdown of the organic cocatalyst—the carbohydrate formed during the induction period. Such inhibition was first discovered by Langenbeck[47].

The condensation of formaldehyde to carbohydrates has been investigated in the presence of lead oxide[72,86–90]. The authors found that, in the presence of PbO, the rate of conversion of CH_2O into carbohydrates is independent of the surface area of the catalyst. As in the experiments with alkaline earth metal hydroxides, sugars greatly accelerate the reaction. The authors believe that these findings indicate a homogeneous autocatalytic mechanism of the condensation of CH_2O in the presence of PbO, which forms a soluble catalytically active complex with carbohydrates.

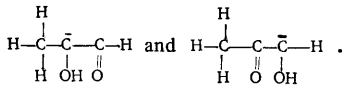
The influence of added alkaline earth and lanthanide oxides [MgO, CaO, BaO, Dy_2O_3, Sm_2O_3, and $Eu(OH)_3$] as well as the oxides of variable-valence metals tending to form complexes (Fe_2O_3, Co_2O_3, ZnO, and CuO) on the rate of condensation under the influence of the lead catalyst has been investigated[87]. The oxides were introduced at concentrations of 10 wt.% relative to the weight of PbO and 1 wt.% relative to the weight of CH_2O. It was found that BaO, CaO, and MgO intensify the effect of lead oxide, a synergistic and not an additive effect being produced. Lanthanide oxides have an inhibiting effect, while the oxides of effective complex-forming metals, cobalt(III) and copper(II), are still more powerful inhibitors. The addition of Fe_2O_3, and NiO, and ZnO has almost no influence on the condensation reaction.

One should also note that the condensation in the presence of both pure PbO and a mixture of oxides proceeds at comparatively low pH values. Thus, for conversions α not exceeding 25% in an experiment with pure PbO, the pH is 6.8 ($\alpha = 16\%$), while in the presence of added MgO ($\alpha = 7\%$), CaO ($\alpha = 25\%$) and BaO ($\alpha = 20\%$) the pH values are 8.9, 7.5, and 6.7 respectively. The condensation does not begin at pH values below 5 and is appreciably accelerated when the initial pH is raised to 8.0, while in the presence of $Ca(OH)_2$[71,72] at 50 °C the synthesis no longer occurs even at pH less than 9.5. According to the authors[87], the action of metal oxide added to PbO consists both in altering the pH and in the involvement of the dissolving metal ions in complex formation, which promotes or hinders the formation and subsequent reactions of complexes capable of propagating the condensation process. It has been suggested that the synergism may be associated with the formation of polynuclear complexes with a higher catalytic activity than the complexes of lead alone. The inhibiting effect of a number of oxides is attributed to the possibility of the decomposition of catalytically active complexes on the surface of these oxides.

The attempt to demonstrate with the aid of ultraviolet spectroscopy the formation of complexes of glucose and the products of condensation with PbO did not yield clearcut results[88,89]. In a study over a comparatively narrow spectral range (40000–54000 cm^{-1}), adjoining the far ultraviolet, the authors observed in the spectra of solutions of PbO containing glucose and the condensate an intense band having a maximum at ~ 48000 cm^{-1}, corresponding to the Pb^{2+} ion. The appearance of this band, which is absent from the spectra of aqueous solutions of PbO owing to the low solubility of the latter, was attributed to the formation of lead complexes with glucose and other carbohydrates. The absence of other specific bands in this part of the spectrum did not allow the authors to put forward a hypothesis concerning the possible structure of the complexes.

Other ideas about the mechanism of the condensation of formaldehyde have been put forward[91–97]. The mechanism proposed by the above workers is based on the hypothesis that the active intermediate compounds are the carbanionic forms of formaldehyde and the carbohydrates. For glyceraldehyde and dihydroxyacetone, this form is, according to the authors, the carbanion R^-, having the following limiting

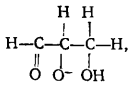
structural formalae:



The mechanism of the condensation of formaldehyde in the absence of an organic cocatalyst is not considered by the investigators. The following pathways leading to the formation of carbanions R^- are postulated: (a) via the interaction with hydroxide ions ($C_{3A} + OH^- \rightarrow R^- + H_2O$) and (b) as a result of the interaction with formaldehyde or glyceraldehyde alkoxide anions:

$$C_{3A} + C_{3A}^- \rightarrow R^- + C_{3A} \ , \quad C_{3A} + F^- \rightarrow R^- + F \ ,$$

where C_3A is a molecule of glyceraldehyde and C_{3A}^- is its alkoxide anion having the structure



F^- is the alkoxide anion derived from formaldehyde, and R′ is the glyceraldehyde carbanion.

The carbanion is consumed in the condensation reaction, in isomerisation to a dihydroxyacetone molecule, and in the formation of alkoxide anions derived from formaldehyde and trioses. The proposed overall mechanism consists of eleven stages, taking into account the processes enumerated above, and of four possible processes involving the formation of alkoxide anions:

$$OH^- + F \rightleftarrows F^- + H_2O, \quad OH^- + C_{3A} \rightleftarrows C_{3A}^- + H_2O \ ,$$
$$OH^- + C_6 \rightleftarrows C_6^- + H_2O \ , \quad OH^- + C_4 \rightleftarrows C_4^- + H_2O \ .$$

The authors were the first to take into account the equilibrium between the monomeric formaldehyde and its polymeric forms[94]. Applying the principle of steadystate values in relation to R^-, the authors determined the ratio of the rate constants for the following stages:

$$R^- + C_{3A} \xrightarrow{k_1} C_{3K} + C_{3A}^- \ , \quad R^- + H_2O \xrightarrow{k_2} C_{3K} + OH^- \ ,$$
$$R^- + F \xrightarrow{k_3} C_4^- \ , \quad R^- + C_{3A} \xrightarrow{k_4} C_6^- \ .$$

where C_3K is a dihydroxyacetone molecule. The following values were obtained: $k_3/k_4 = 0.6$, $k_2/k_4 = 0.15$ mol litre^{-1}, and $k_1/k_4 = 0.03$.

Salt-like compounds of formaldehyde and hydrocarbons with calcium hydroxide, analogous to the compounds isolated by Franzen and Hauck[35], were isolated in two investigations[95,96]. However, the authors[95,96] believe that these compounds do not play a significant role in the condensation mechanism. The possible causes of the specific action of the cations derived from the hydroxides on the rate and selectivity of the synthesis have not been considered[91-97].

Towards the end of the 1960's and the beginning of the 1970's, studies on the reaction mechanism as well as those designed to elucidate the possible practical applications of the carbohydrates obtained were initiated by Japanese investigators. Nakai et al.[98] investigated the condensation in the presence of $Ca(OH)_2$ at 50 °C and found that the yield of sugars per gram of formaldehyde is a maximum when solutions with formaldehyde concentrations in the range of 0.81–4.05% are used. The employment of small amounts of monosaccharides as cocatalysts tends to increase the yield of sugars and decrease the reaction time. As in an earlier study[65], it was found that ketoses are more effective as cocatalysts than aldoses.

Mizuno et al.[31] investigated the catalytic activity of a number of inorganic and organic bases in the condensation reaction: $Ca(OH)_2$, $Ba(OH)_2$, $Sr(OH)_2$, $Mg(OH)_2$, $Pb(OH)_2$, KOH, TlOH, pyridine, picoline, collidine, *N*-methylpiperidine, *N*-methyl-morpholine, 2-(dimethylamino)ethanol, triethanolamine, and tetraethylammonium hydroxide. According to their data[31], the best catalyst at 50 °C is $Ca(OH)_2$ (the yield of carbohydrates is 55%). The sugars were analysed by all possible chromatographic methods: paper, thin-layer, gas–liquid, and liquid adsorption chromatography[99,100]. The authors were able to identify 33 carbohydrates ranging from C_2 to C_7, the main components being hexoses and pentoses. Methods for the isolation of various carbohydrates for subsequent toxicological tests have been developed[101,102].

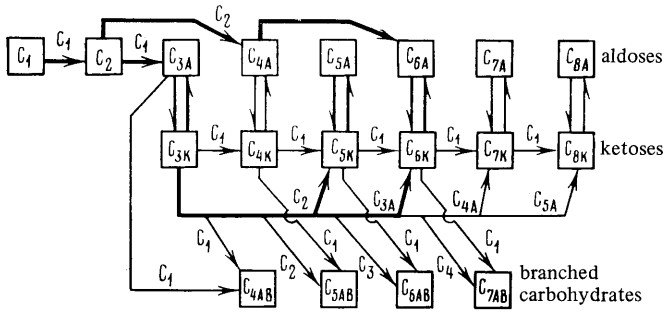


Figure 1. Schematic illustration of the formation of carbohydrate products in the formaldehye condensation reaction (according to Mizuno[103]); C_iA = aldoses with i carbon atoms; C_iK = ketoses with i carbon atoms; C_iAB = branched carbohydrates with i carbon atoms.

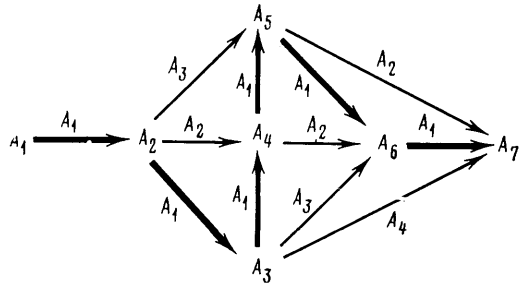
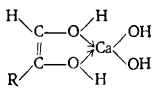


Figure 2. Schematic illustration of the formation of carbohydrate products in the formaldehyde condensation reaction (according to Weiss et al.[75]); A_i = carbohydrate with i carbon atoms. Thick arrows—tentative pathway leading to the formation of carbohydrates.

On the basis of gas-chromatographic and mass-spectrometric analyses of the reaction products, a new condensation mechanism (Fig.1), differing appreciably from Weiss's scheme[75] (Fig.2), has been proposed[103]. The controversial hypothesis has been put forward that, among all the carbohydrates, starting from C_3, only ketoses undergo cocondensation with formaldehyde. However, according to Mizuno, this is not

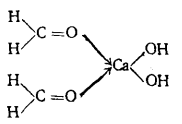
the main reaction pathway. According to the scheme in Fig.1, C_4 aldoses are formed mainly as a result of the self-condensation of glycolaldehyde, while C_6 aldoses are produced by its cocondensation with tetroses. Among ketoses, the highest reactivity is attributed to dihydroxyacetone. Its cocondensation with glycolaldehyde is regarded as the main pathway leading to the formation of pentoses and its cocondensation with glyceraldehyde is believed to be the main pathway to the ketohexoses. In the transformations of tetroses the Lobry de Bruyn–van Ekenstein equilibrium is not considered (without adequate justification). The controversial nature of a number of postulates of the above mechanism is evidently due to the limited amount of experimental data on which it is based.

Fujino and Kobayashi[69,70] were the first to draw attention to the structure of the intermediate compounds of carbohydrates with hydroxides, which apparently play the role of condensation catalysts. The existence of these compounds has been postulated but has been in no way demonstrated in the series of the above studies. Fujino and Kobayashi[69,70] investigated the physicochemical properties of homogeneous systems such as CaO–glucose and CaO–xylose obtained after prolonged mixing of CaO with the carbohydrates at 10 °C and after filtering off the undissolved CaO. The study was carried out by NMR and infrared spectroscopy. On the basis of the results, the authors concluded that complexes of the calcium hydroxide with carbohydrates, having the structure

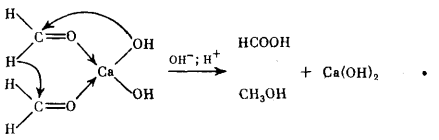

(I)

are formed.

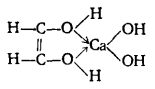
Fujino and Kobayashi[69,70] performed experiments on the condensation of formaldehyde at 50 °C in the presence of complexes of calcium hydroxide with glucose and xyloses and also with formaldehyde, prepared beforehand by the method indicated above. The results of these experiments led to the conclusion that, under the formaldehyde condensation conditions, two types of calcium hydroxide complexes are formed: (1) with the carbohydrate in the enediol form, having the structure given above and (2) with formaldehyde. having the structure



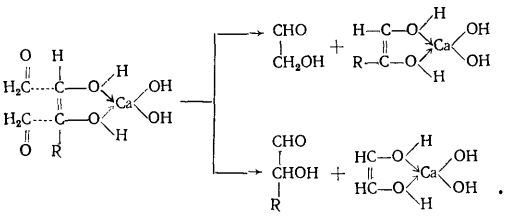
The complexes of the first type catalyse the condensation to carbohydrates and those of the second type catalyse the Cannizzaro reaction via the mechanism



In the absence of an organic cocatalyst, there is, however, a possibility of the formation of the complex


(II)

This complex of glycolaldehyde and the hydroxide has an enediol group and, like complex (I), is the catalyst of subsequent condensation, which proceeds via the following mechanism according to the authors:



The rate constants for the synthesis of carbohydrates and the Cannizzaro reaction in the presence of alkaline earth metal hydroxides have also been determined[70]. When glucose was used as the cocatalyst, their activity in the synthesis of carbohydrates fell in the sequence

$$Ca(OH)_2 > Sr(OH)_2 > Ba(OH)_2.$$

An analogous activity series had been established earlier[64]. The activity series of the above hydroxides for the Cannizzaro reaction in the presence of glucose is the opposite to that found for the synthesis of carbohydrates, while in the absence of glucose it is identical. The authors[70] also found the ratios of the zero-order rate constants for the synthesis of carbohydrates and the Cannizzaro reaction at 50 °C:

$Ca(OH)_2$	$Sr(OH)_2$	$Ba(OH)_2$
4.1	2.1	0.73

These ratios virtually agreed with the ratios of the degrees of involvement, determined previously[26], of CH_2O in the synthesis of carbohydrates and in the Cannizzaro reaction (4.0 : 2.3 : 0.8).

In recently published studies[104–106] an attempt was made to use the potentiometric method for the investigation of the kinetics of the synthesis of carbohydrates in the presence of $Ca(OH)_2$. The authors determined the end of the induction period from the time required for the attainment of a minimum in the oxidation-reduction potential of the reaction system, while the time required to reach its maximum corresponded, according to their data, to the complete conversion of formaldehyde. Using this relatively insensitive method, the authors found that, after the end of the induction period, the kinetics of the syntheses correspond to first order with respect to CH_2O and zero order with respect to $Ca(OH)_2$. Like Weiss and coworkers[82], they concluded that the true process catalyst is $CaOH^+$. Despite the contradictory nature of the kinetic relations found by these workers and by Weiss et al.[75], the former[104–106] believe that their investigation confirmed the mechanism of the synthesis of carbohydrates proposed by Weiss[82].

The result obtained[107] on precipitation of Ca^{2+} ions by oxalic acid at the end of the induction period is of interest. It was observed that, following the subsequent addition of KOH and the adjustment of pH to 12, the synthesis at 60 °C can be carried out selectively in the direction of the formation of a few branched carbohydrates and the corresponding alcohols (the alcohols 2-hydroxymethylglycerol, 2,4-hydroxymethylpentitol, and 3-hydroxymethylpentitol are formed preferentially).

Harsch et al.[108] used for the first time high-pressure liquid chromatography to obtain kinetic data for the change in the content of products during the synthesis of carbohydrates from formaldehyde. They studied model reactions

involving the cocondensation of formaldehyde with glycolaldehyde, glyceraldehyde, and dihydroxyacetone in the presence of $Ca(OH)_2$. The results confirmed the stepwise mechanism of this synthesis of carbohydrates[55]. In view of the absence of even traces of octoses in experiments with glyceraldehyde, the authors[108] regard as unlikely the mechanism proposed by Mayer and Jaschke[59], according to which the reactions involving the dimerisation of tetroses to octoses and their subsequent cleavage to dihydroxyacetone and aldopentose play and important role in the formation of the final products. They also criticise Breslow's mechanism of autocatalysis[81] which is based on the hypothesis of the ready cleavage of tetroses under the conditions of the synthesis. Such cleavage leads to a rapid increase of the content of glycolaldehyde in the reaction system. The secondary role of this mechanism follows from the evidence obtained by the authors[108] for the high rates of cocondensation of tetroses with formaldehyde and the extremely low rates of cleavage of tetroses.

Guillot et al.[109] investigated the kinetics of the synthesis of carbohydrates in the presence of TlOH using a number of aromatic α-ketols (benzoyl-carbinol, 1-phenyl-2-hydroxy-1-butanone, and 1-phenyl-1-hydroxy-2-butanone) as cocatalysts. It was found that, for degrees of conversion of formaldehyde of 5–95%, the kinetics are described satisfactorily by the autocatalytic equation

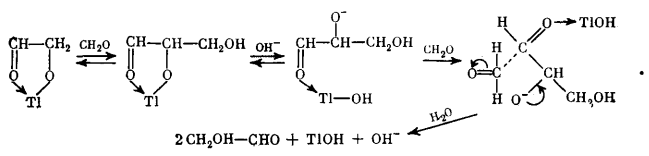
$$\lg\left[\frac{x}{a-x}\right]_{x_1}^{x_2} = k(t_2 - t_1),$$

where a is the initial concentration of formaldehyde, x_1 and x_2 are the amounts of formaldehyde in mol litre^{-1} which have reacted at times t_1 and t_2, and $k = k_0\,[Tl^+][OH^-]$. Benzoylcarbinol proved to be the most active cocatalyst (more active than glycolaldehyde) and phenylhydroxybutanones proved to be the least active. The induction period increased with increasing formaldehyde concentration.

In their explanation of the experimental results the authors[109] began with the hypothesis that a complex of formaldehyde with Tl^+ having the following structure can be formed in an alkaline medium:



The interaction of this complex with a second formaldehyde molecule leads in their view to the slow formation glycolaldehyde. They explain the autocatalysis by the much faster formation of glycolaldehyde on interaction of two formaldehyde molecules with the alkoxide anion derived from glycolaldehyde (or α-ketol) and coordinated to Tl^+, via the following mechanism:



The literature data considered above show that, despite much attention devoted to the study of the kinetics of the synthesis of carbohydrates and the considerable progress achieved in the analysis of the composition of the products of the synthesis during the last decade, many aspects of the mechanisms of this process remain obscure. There has been no lack of attempts to put forward new mechanisms. Such mechanisms, developed on the basis of only kinetic data and the results of the analysis of the composition, cannot be regarded as sufficiently well founded and it is not surprising that several mutually exclusive mechanisms have been proposed recently. The mechanism of the first stage of the synthesis—the dimerisation of formaldehyde to glycolaldehyde—remains completely obscure. There is no satisfactory explanation of the autocatalytic nature of the process. An important theoretical and practical task is the elucidation of the conditions for the complete suppression of the formation of branched carbohydrates. Weiss's studies in this field constitute only the first steps. Evidently success in the solution of the above problems in the synthesis of carbohydrates will be possible only by combining kinetic research techniques with modern physicochemical and physical methods.

A combined study of the mechanism of the synthesis was therefore undertaken at the Institute of Chemical Physics of the USSR Academy of Sciences in 1969[111–116] in which ultraviolet and NMR spectroscopy as well as radioactive tracers were used in addition to kinetic methods. The kinetics were studied in a static reactor in the presence of alkaline earth metal hydroxides (calcium, strontium, and barium). Gas-chromatography[6] made it possible to carry out a complete group analysis of the carbohydrates with separate determination of the linear and branched components in each carbohydrate fraction with the given number of carbon atoms in their molecules.

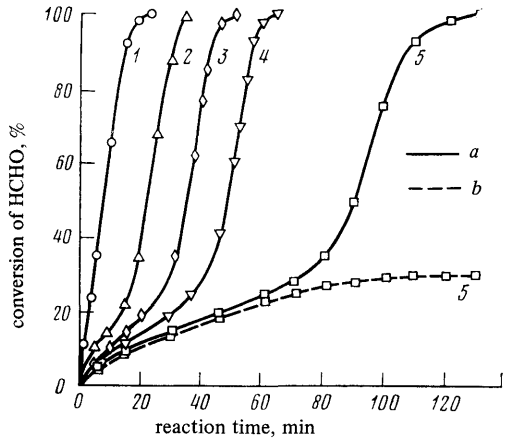


Figure 3. Kinetic curves for the overall conversion of formaldehyde (a) and the conversion via the Cannizzaro reaction[12] (b) for different molar concentrations of glycolaldehyde: 1) 0.042; 2) 0.008; 3) 0.0017; 4) 0.0008; 5) 0.0; $c_{H_2CO} = 1.53$ M; $c_{Ca(OH)_2} = 0.19$ M; $t = 40$ °C.

Fig. 3 presents the kientic curves obtained[112] for the condensation of formaldehyde (1.53 M) at 40 °C in the presence of $Ca(OH)_2$ (0.18 M) and variable amounts of glycolaldehyde used as the cocatalyst. Evidently a decrease of the induction period corresponds to an increase of the concentration of glycolaldehyde. At a concentration of this cocatalyst of 4.2×10^{-2} M the induction period disappeared altogether and, up to almost complete conversion of formaldehyde (~90%), the condensation proceeded as a zero-order reaction with respect to formaldehyde. Analogous kinetics were observed when glucose was used as the catalyst, but the induction period did not disappear completely even at a glucose concentration of 1×10^{-1} M. When $Ca(OH)_2$ was used as the catalyst

and glucose as a cocatalyst, it was established[113,115] that the induction period passes through a minimum with increasing NaOH content (from 0.1 to 1.0 M). In the range of conversions α from 20–30 to 80–90% the rate of condensation of formaldehyde was found to be constant but increases linearly with increasing concentration of OH^- ions. This is consistent with the zero order with respect to formaldehyde and the first order with respect to $Ca(OH)_2$ found in earlier studies[27,75] for moderate conversions.

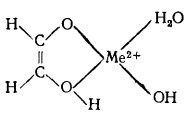
The observed minimum in the induction period with increasing NaOH concentration in solution must be regarded as confirmation of the earlier conclusion[82] that the catalytically active form of $Ca(OH)_2$ is the cation $CaOH^+$.

It has been observed[116] by means of the radioactive tracer method, using glucose labelled with ^{14}C, that, under the conditions of the synthesis, the carbohydrates undergo the disproportionation reactions

$$C_mH_{2m}O_m + C_nH_{2n}O_n \rightarrow C_{m-k}H_{2(m-k)}O_{m-k} + C_{n+k}H_{2(n+k)}O_{n+k},$$

known previously solely as biocatalytic reactions[117]. At the same time radioisotope data show that the rates of these reactions, as well as secondary reactions in the synthesis of carbohydrates such as retroaldol cleavage, are much lower than the rate of growth of carbohydrate molecules.

Analysis of the ultraviolet spectra of alkaline solutions of carbohydrates in the presence and absence of alkaline earth metal ions[111] as well as ultraviolet spectra of samples of the solution removed from the reactor during the synthesis of carbohydrates[113–118] made it possible to attribute the appearance of the band in the range 300–340 nm in these spectra to the formation of complexes of the enediol forms of carbohydrates and hydroxides of the type



.

It was found that the position of the absorption maximum depends on the nature of the cation forming the complex. When glucose was used as the ligand, the absorption maximum was found at 342 nm for $Ca(OH)_2$, 332 nm for $Sr(OH)_2$, and 322 nm for $Ba(OH)_2$.

An important result of the ultraviolet spectroscopic study was the observation that the kinetics of the increase of the optical density of this band for different carbohydrates (glycolaldehyde, dihydroxyacetone, glyceraldehyde, arabinose, glucose, and fructorse) are similar to the initial kinetics of the synthesis using the same carbohydrates as cocatalysts. This suggested that the complexes of the above type are capable of manifesting autocatalytic activity.

In view of this conclusion, the results of the chromatographic analysis (carried out immediately after preparing the solution) of the complex of α-D-glucose and $Ca(OH)_2$ are of interest[71,72,119]. Analysis demonstrated the presence in solution of a number of other hexoses (fructose, mannose, etc.) together with glucose. This enabled Weiss[119] to conclude that the catalytically active complex is a dynamic mixture of carbohydrate complexes of different structures and not the complex of an individual carbohydrate. The application of photoelectron X-ray spectroscopy to obtain information about the structure of the catalytically active complexes of calcium hydroxide with glucose and dihydroxyacetone, isolated from solution by the method of Roy and Mitra[121], showed[120] that the corresponding complexes consist of adducts with weakly polarised bonds between Ca^{2+} and the carbohydrate molecule.

The results of this study justified the conclusion that the autocatalytic nature of the synthesis of carbohydrates is due to the possibility of the formation of glycolaldehyde via two pathways having sharply different rates: (a) via the slow dimerisation of the formaldehyde in the coordination sphere of the calcium cation and (b) via the much faster dimerisation in the coordination sphere of the calcium cation where two coordination sites are occupied by the enediol form of glycolaldehyde formed previously.

The multistage mechanism of the synthesis of glycolaldehyde from formaldehyde, which accounts for the autocatalytic nature of its formation, can be formulated as follows in accordance with the evidence presented above:

$$A + K \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} AK \quad , \tag{1}$$

$$AK + A \xrightarrow{k_2} EK \quad , \tag{2}$$

$$EK \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} K + C_2 \quad , \tag{3}$$

$$EK + A \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} EKA \quad , \tag{4}$$

$$EKA + A \xrightarrow{k_5} EK + C_2 \quad , \tag{5}$$

where A is formaldehyde, K the catalyst [the $CaOH^+$ cation for $Ca(OH)_2$], C_2 glycolaldehyde (in the non-hydrated form), EK the complex of the catalyst with the enediol form of glycolaldehyde, and EKA the complex EK whose coordination sphere contains formaldehyde A.

^1H and ^{13}C NMR showed[113,122] that, under the conditions of the synthesis, formaldehyde exists mainly in the form of unionised and singly ionised methyleneglycol. However, these data do not rule out the possibility of the involvement of formaldehyde in the proposed stages in the non-hydrated form. One should bear in mind that the concentration of this form under the conditions of the synthesis cannot exceed several hundredth per cent of the overall formaldehyde concentration[123].

The elucidation of the problem of the form in which formaldehyde participates in the proposed stages is difficult and requires additional studies.

The equation derived on the basis of the above mechanism for the rate of the initial stage of the reaction [until the attainment of a degree of conversion of formaldehyde of ~20% when part of $Ca(OH)_2$ still remains in the precipitate] has the following form[113,118]:

$$w = (k_2K_I[A]^2 + k_5K_{III}K_{IV}[A]^2[C_2])[Ca(OH)_2]_0 \times \\ \times (1 + K_w/K_I'[H^+] + K_{II}'[H^+]/K_w)^{-1} \quad ,$$

where k_2 and k_5 are the rate constants for stages (2) and (5), K_I, K_{III}, and K_{IV} are the rate constants for the formation of complexes in stages (1), (3), and (4), K_W is the ionic product of water, and K_I' and K_{II} are the first and second dissociation constants of $Ca(OH)_2$. Since $k_5 \gg k_2$, the term $k_2K_I[A]^2$ in the expression for the rate of reaction can be neglected, whereupon the above expression reduces to the form typical for autocatalytic reactions:

$$w = k_5K_{III}K_{IV}[A]^2[C_2][Ca(OH)_2]_0(1 + K_w/K_I'[H^+] + K_{II}'[H^+]/K_w)^{-1} \quad .$$

At a constant pH and in the presence of $Ca(OH)_2$ in the precipitant, we obtain

$$w = k[A]^2[C_2] \quad .$$

The constancy of the rate of reaction in the range of values of α from 20–30% to 80–90% has been attributed[113] to the fact that, starting from $\alpha = 20$–30%, the main pathway followed in the consumption of formaldehyde is its aldol condensation with C_2–C_4 carbohydrates. According to Ingold[124], the rate-limiting stage in this process is the formation of carbanions from C_2–C_4 carbohydrates, which sould lead to the first reaction order with respect to OH^-. The rate of formation of carbanions from glycolaldehyde has been estimated by NMR[125]. The observed overall zero order of the synthetic reaction for a slight change in pH in the range of values of α from 20–30% to 80–90% shows that the rate constants for the formation of carbanions from the C_2–C_4 carbohydrates differ little and that the overall C_2–C_4 concentration hardly changes in the above range of values of α.

The first information about the significant influence of the nature of the catalyst cation on the ratio of the linear and branched carbohydrates formed has been obtained in a number of studies[112–115]. Table 2 presents the corresponding data for 100% conversion of formaldehyde using glycolaldehyde (4.2×10^{-2} M) as the cocatalyst. The data for the C_4 fraction, whose composition should be closer to that for the primary products than the composition of the C_5 and C_6 fractions, are particularly instructive. The proportion of linear carbohydrates in this fraction is 81% for $Ca(OH)_2$, 37% for $Sr(OH)_2$, and 21% for $Ba(OH)_2$. It follows from the data in Table 2 that $Ca(OH)_2$ is most selective in relation to the synthesis of linear carbohydrates but even for this hydroxide the proportion of branched carbohydrate is high.

Table 2. Fractional composition (%) of the carbohydrates[112] formed in the condensation of formaldehyde (1.53 M) in the presence of calcium, strontium, and barium hydroxides (0.19 M); cocatalyst—glycolaldehyde (4.2×10^{-2} M).

Carbohydrates	Condensation conditions*			
	$Ca(OH)_2$; 40°; 20 min; 7.2%	$Ca(OH)_2$; without cocat., 40°; 135 min; 35.5%	$Sr(OH)_2$; 40° 23 min; 6.0%	$Ba(OH)_2$; 50°; 50 min; 18%
C_3	6.6	11.1	4.5	3.6
C_4 (branched)	1.3	6.2	4.6	9.1
C_4 (lin.)	5.6	9.9	2.7	2.4
ΣC_4	6.9	16.1	7.3	11.5
C_5 (branched)	5.1	5.6	4.2	2.4
C_5 (lin.)	15.2	21.6	9.7	5.2
ΣC_5	20.3	27.2	13.9	7.6
C_6 (branched)	31.5	19.7	21.8	22.8
C_6 (lin.)	16.6	15.4	16.7	10.1
ΣC_6	48.1	35.1	35.8	32.9
C_7	18.1	10.5	35.4	44.5
Σ branched without C_7	38	35.5	31	34
Σ lin. without C_7	44	58	34	21

* The catalyst, temperature, reaction time, and the degree of conversion via the Cannizzaro reaction are quoted.

The results obtained can be regarded as promising in the sense that they indicate the possibility of a considerable alteration of the proportion of linear carbohydrates when one catalyst is replaced by another or when the temperature is altered, i.e. they give rise to the hope that it may be possible to select optimum catalysts and conditions whereby the content of branched carbohydrates in the products of synthesis can be reduced to an acceptable minimum or fully eliminated. The latest results[126] show that, in principle, one can achieve a very high selectivity of the synthesis in favour of linear hexoses, provided that the synthesis is carried out at sufficiently high temperatures. Thus, at 98 °C and using $Ca(OH)_2$ as the catalyst, the proportion of hexoses reaches 84% of all the products (by weight) for a degree of conversion of 18%; 90% of the hexoses then consist of a mixture of approximately equal amounts of glucose and idose.

The data discussed above show that, despite certain advances in the elucidation of the mechanism of the synthesis of carbohydrates from formaldehyde and promising indications of a possibility of achieving a highly selective process, it is necessary to continue research into the mechanism and to develop ways of increasing the process selectivity. In particular, it is necessary to refine the structure of catalytically active complexes of carbohydrates and formaldehyde with hydroxides. As already mentioned, the problem of the form (hydrated or non-hydrated, ionised or unionised) in which formaldehyde is involved in the formation of glycolaldehyde remains unelucidated. Exhaustive kinetic information (the reaction order with respect to formaldehyde, the concentration of calcium hydroxide ions and OH^- ions, and the activation energy) for the induction period is so far lacking. The problem of the extent to which branched carbohydrates can be involved in secondary disproportionation and retroaldol cleavage reactions remains completely obscure. This evidently does not complete the list of the obscure problems of the mechanism. It is no less important to continue the search for optimum catalysts and conditions for a highly selective synthesis of assimilable carbohydrates. The results obtained hitherto in attempts to increase the process selectivity constitute only the first steps in this practically important field of study.

V. THE POSSIBLE VERSIONS OF THE CONDENSATION OF FORMALDEHYDE OF CARBOHYDRATES IN LIFE SUPPORT SYSTEMS IN SPACE VESSELS

It follows from the foregoing that the selectivity of the synthesis of carbohydrates from formaldehyde is as yet insufficient for this process to be used without significant improvement in life support systems at the concluding stage of the conversion of the final products of the vital activity of the human organism into food products. When formaldehyde is fully converted into carbohydrates in the presence of $Ca(OH)_2$, one of the most effective catalysts of this process, the proportion of hexoses in the carbohydrate products is only ~50%.[76] On the other hand, the proportion of assimilable hexoses must be less than 25% since, in view of the characteristics of the process examined above, half of all the carbohydrates should apparently be formed in the non-assimilable L-form. Furthermore, the non-assimilable carbohydrates include also all the branched and certain linear D-hexoses produced.

The low process selectivity is apparently the main cause of the negative results of toxicological assessments of the carbohydrates synthesised. After a most careful purification of the carbohydrates [precipitation of $Ca(OH)_2$, treatment of the filtered solution with a cation exchanger, an anion exchanger, and activated charcoal], prolonged feeding of rats with the product led to weight loss by the animals accompanied by a number of pathological phenomena and terminating in their death[127]. Therefore, together with the search for ways of improving significantly the selectivity of the synthesis of assimilable hexoses from formaldehyde,

it is desirable to carry out also studies designed to elucidate the possibility of employing this process in other more promising versions.

A 50 day experiment[128], showing that human diet can contain considerable amounts of glycerol (110 g per day) without any harmful consequences of health, was carried out recently. Later studies[129] showed that glycerol in the diet can constitute more than half, by weight, of the entire daily ration for man (up to 300 g per day).

On the other hand, it is known[130] that hydrogenolysis can yield glycerol as the main reaction product. At the beginning of the 1940's the first patents were taken out[131–133] for the synthesis of glycerol by the hydrogenolysis of a mixture of carbohydrates synthesised from formaldehyde.

Bearing in mind these data, Weiss et al.[134] suggested that at the end of the synthesis of carbohydrates the reaction mixture be hydrogenated and hydrogenolysed under conditions ensuring the preferential formation of glycerol. This application of the formaldehyde condensation process can ensure the recycling under the conditions of the space vessel of at most between 20 and 50% of carbon dioxide in the form of glycerol which is assimilable by the human organism.

In view of the low selectivity of the condensation of formaldehyde to assimilable carbohydrates, this verion of the process makes it possible to obviate difficulties associated with the toxic effect of complex mixtures of the carbohydrates synthesised. However, at present one can only speak of the possibility, in principle, of using this version of the formaldehyde condensation process. Comparatively few studies have been made on these lines and the selectivity achieved in the synthesis of glycerol is insufficient. Thus it can be shown[135,136] that the selectivity of the hydrogenolysis of sucrose (200–225 °C, 200 atm) in relation to the formation of glycerol is only 31%. A disadvantage of this version of the process is also the necessity to employ severe conditions—high temperatures and pressures.

Another way of obtaining glycerol from formaldehyde may therefore be more promising for the conditions in space vessels: preliminary synthesis of carbohydrates from formaldehyde under conditions ensuring the preferential formation of trioses and subsequent hydrogenation of the latter to glycerol. Studies by Weiss and coworkers[137] showed that the selective synthesis of trioses is in principle possible if the process is terminated at low degrees of conversion of formaldehyde. Thus, at 40 °C in the presence of $Ca(OH)_2$ for degrees of conversion of ~10%, the content of trioses in the carbohydrate products can be close to 80% according to the above authors' data. We obtained similar results[112]. Direct data indicating the possibility of the selective synthesis of trioses from formaldehyde have also been obtained. According to Shapira[138], in the presence of the $CaO-Al_2O_3$ catalyst and after the addition of 5% of glyceraldehyde as the cocatalyst, it is possible to obtain trioses with a selectivity of 73% for an overall conversion of formaldehyde of 71%.

The hydrogenation of trioses in the presence of fairly active catalysts (for example, ruthenium catalysts) could be carried out at a much lower temperature and pressure compared with those indicated above for hydrogenolysis; a very high hydrogenation selectivity is then achieved[138].

The above advantages of this version of the synthesis of glycerol evidently make it desirable to carry out special studies in order to elucidate the possibility of its practical application.

The selective synthesis of trioses from formaldehyde may be of particularly great interest in view of the fact that trioses can be converted with the aid of an immobilised enzyme (aldolase) into D-glucose, nutritionally the most valuable carbohydrate, with a selectivity close to 100%.[117] However, despite the known advantages of this version of the synthesis of D-glucose (not only under conditions of space vessels but also for terrestrial purposes), there have been almost no studies designed to elucidate the possibility of the practical realisation of this synthesis.

The difficulties associated with the low selectivity of the synthesis of carbohydrates and the possible toxicity of individual products can also be avoided by employing solutions of synthetic carbohydrates as the nutrient medium for the growing of yeast. This method of using synthetic carbohydrates has been proposed by Soviet and American investigators[68,139]. The yeast grown in this way can evidently serve under the conditions of prolonged space flights as a valuable additional source of food protein and vitamins. The protein content in yeast is 45% and yeast is capable of synthesising also other valuable food components: lipids, glycolipids, and sugars[140].

Yeast (or at any rate some of their species) have less stringent requirements as regards the composition of carbohydrates than the human and animal organism and the extent to which they can utilise synthetic carbohydrates can be fairly high. Thus the degree of utilisation of carbohydrates reached 30–40% in a study[68] where yeast was cultured on synthetic carbohydrates. Table 3 presents qualitative data from the study of Chermside et al.[139] for the utilisation of various sources of carbon by certain yeast species. They show that certain yeast species are capable of effectively assimilating synthetic carbohydrates.

Table 3. The utilisation of various sources of carbon by certain yeast species*.

Yeast species	Glucose	Mannitol	Glycerol	Dihydroxyacetone	Synthetic carbohydrates		
					1%	3%	5%
Candida krusoides	++	++	++	++	+	—	—
Lipolytica	++	++	++	++	+	—	—
Atilis	++	++	++	++	+	+**	—
Rhodotorula pilimanae	++	++	++	++	++	+**	—
Saccharomyces carlsbergensis	++	—	—	++	+	+**	+**
Cerevisiae	++	—	—	++	—	—	—

* Notation: ++ effective utilisation; + utilisation; — no utilisation.

** The utilisation was greater in a 14 day experiment than in a 7 day experiment.

Data obtained in a study[141] where it was shown that good results can be secured in the growing of yeast (*Candida tropicalis* CK-4) using as a source of carbon complex mixtures of organic acids obtained by oxidising synthetic carbohydrates are of interest in connection with the problem under discussion.

The literature data considered in this Section show that there are a number of promising versions of the formaldehyde condensation process for the recycling of food under the conditions of prolonged space flights. At the same time it is evident that only preliminary studies have so far been

carried out in each of the relevant fields and that extensive and thorough research is necessary before the practical application of these procedures will become possible.

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