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The Nature of Autocatalysis in the Butlerov Reaction

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Abstract—The effect of the nature of an initiator on the kinetics of formaldehyde consumption and on product composition in the Butlerov reaction was studied in a stirred flow reactor and a batch reactor. It was found that, under flow conditions, the kinetics and the product composition of this reaction are independent of the nature of the initiator. The reaction schemes proposed previously for an autocatalytic process mechanism based on the formation of glycolaldehyde from two formaldehyde molecules are incorrect. A correlation between the initiating activities of various monosaccharides and the rates of their conversion into an enediol form was found with the use of a batch reactor. Solid enediol complexes with Ca^{2+} ions were isolated for glucose, fructose, ribose, and sorbose; the initiating activity of these complexes was found to be much higher than the initiating activity of pure monosaccharides. A self-consistent mechanism was proposed for Butlerov reaction initiation. The formation of the enediol forms of monosaccharides followed by degradation to lower carbohydrates plays a key role in this mechanism. In turn, the initiating activity depends on the position of the carbonyl group in the monosaccharide molecule. The condensation reactions of glycolaldehyde, glyceraldehyde, and dihydroxyacetone with each other were studied. Based on data on the condensation products of lower carbohydrates, a scheme was proposed for the Butlerov reaction. According to this reaction scheme, C_2 and C_3 carbohydrates mainly undergo an aldol condensation reaction with formaldehyde, whereas the formation of higher monosaccharides occurs by the aldol condensation of lower C_2–C_3 carbohydrates with each other.

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INTRODUCTION

In 1861, Butlerov performed the oligomerization of formaldehyde in an aqueous solution in the presence of calcium and barium hydroxides and obtained a complex mixture of monosaccharides (so-called formose) [1, 2]. This process is currently known as the Butlerov reaction [3]. Subsequently, it was found that many inorganic and organic compounds exhibit catalytic activity in this reaction. However, calcium hydroxide, which was first used by Butlerov, is the most active catalyst [4]. It is currently well established that the oligomerization of formaldehyde under discussion is an autocatalytic reaction because it is initiated by various monosaccharides.

The Butlerov reaction is a complex set of several types of processes, which occur in the system with alkaline catalysis: the direct formation of carbohydrates from formaldehyde, the competing Cannizzaro reaction, the cross-Cannizzaro reaction [5], the Lobry de Bruyn–van Ekenstein reaction [6–8], the retroaldol cleavage of monosaccharides, and the rearrangement of carbohydrates into saccharinic acids. The oxidation of sugars to aldonic acids can also occur in the presence of atmospheric oxygen [9, 10]. As a consequence of the autocatalytic character of the Butlerov reaction and the simultaneous occurrence of the above side reactions in a formose system, the synthesis of carbohydrates from formaldehyde under batch conditions is an uncontrollable process because it results in the formation of a mixture of more than ten various carbohydrates [4].

Although the Butlerov reaction has been known for almost 150 years, the mechanism of formaldehyde condensation, the reason for the autocatalytic behavior of this process, and the role of alkaline earth metal ions in this process remain unclear to this day. Previously, many versions of the test reaction mechanism have been discussed. It is likely that the mechanisms proposed in the publications by Weiss et al. [11], Mitsuno [12], and Harsch et al. [13, 14], which complement each other, are most realistic. These publications imply a decisive role of the aldol condensation of formaldehyde with carbohydrates (in an excess of a substrate) and the aldol condensation of lower monosaccharides with each other (in a deficiency of formaldehyde).

The main disadvantage of the above mechanisms is the hypothesis that sugars can also be formed from formaldehyde in the absence of an initiating carbohydrate. The possibility of glycolaldehyde formation from two formaldehyde molecules as the first step of the Butlerov reaction was assumed. However, more recently, Weiss et al. [11] found that the formation of glycolaldehyde is impossible in a pure aqueous alkaline solution of formaldehyde, which is free of monosaccharide impurities. Consequently, the formation of glycolaldehyde in a formose system occurs in another manner, probably by the retroaldol cleavage of higher monosaccharides, as proposed by Breslow [15] as early as the mid-1900s.

Kuzin [16] was the first to hypothesize that the initiating activity of various monosaccharides is related to their ability to form enediols. More recently, Ruckert et al. [17] hypothesized that the reaction of formaldehyde condensation is catalyzed by the complex compounds of an alkaline earth metal hydroxide and a monosaccharide in the enediol form. Two research groups prepared (apart from the reaction mixture) and isolated (as solids) the complexes of monosaccharides (glucose, xylose, and fructose) with calcium ions [18–21]. In all cases, a considerable decrease in the induction period of formaldehyde condensation was observed upon the replacement of a parent monosaccharide by its complex. Unfortunately, Ziemecki et al. [19] failed to determine the structure of the complex formed by calcium hydroxide with a monosaccharide (glucose). Data obtained by Ziemecki et al. [19] do not invalidate but do not support the assumption that the complex under discussion is formed by the enediol form of the monosaccharide. Based on ESCA and IR-spectroscopic data, a conclusion was drawn that one carbohydrate molecule constitutes a complex with $Ca(OH)_2$ and the coordinated adduct is weakly polarized. Based on the results of a study of the rates of deuterium exchange at the C_1 and C_2 atoms of a carbohydrate, Fujino et al. [21] assumed that calcium is coordinated to the enediol form of a monosaccharide.

Uspenskaya et al. [22] studied the kinetics of formaldehyde consumption in a batch reactor in the presence of monosaccharides, such as glycolaldehyde, sorbose, erythrose, arabinose, mannose, glucose, fructose, tagatose, xylose, and galactose, as initiators. According to these data, the autocatalytic activity of a carbohydrate increased with decreasing numbers of carbon atoms in a chain and ketoses were more active than aldoses at equal numbers of carbon atoms. In the cited work, only the qualitative analysis of reaction products was performed and a noticeable effect of the nature of the initiator on the composition of products was not found. On the other hand, the kinetics of formaldehyde consumption was analyzed quantitatively using rate equations for autocatalytic reactions, which implied the replication of autocatalysts and, consequently, the effect of their nature on the composition of reaction products; this is in contradiction with the above experimental observation.

Thus, although the Butlerov reaction has been intensively studied to advantage in the 1970–1980s, the reaction mechanism remains unclear. Therefore, the ways to improve the selectivity of the reaction under discussion have not been developed.

In this work, we studied the effects of the nature of a monosaccharide initiator on the reaction kinetics and product composition in both a flow reactor and a batch reactor in order to understand better the mechanisms of the Butlerov reaction and its initiation. We also studied the formation of the enediol forms of monosaccharides and the participation of these species in the Butlerov reaction. The condensation reactions of lower carbohydrates occurring in a formose system are also considered.

EXPERIMENTAL

Reagents. The following reagents were used in this study without preliminary purification: $Ca(OH)_2$ (pharmacopeial), NaOH (analytical grade), KOH (analytical grade), $Na_2S_2O_3$ (analytical grade; titrimetric standard), chromotropic acid disodium salt (analytical grade), $CaCl_2 \cdot 6H_2O$ (pharmacopeial), H_2SO_4 (high-purity grade), HCl (analytical grade; titrimetric standard), acetonitrile (high-purity grade; grade A), acetone (high-purity grade), ethanol (96%), paraformaldehyde (reagent grade), and an I_2 solution (analytical grade; titrimetric standard). The following carbohydrates were used: glycolaldehyde (>99%, Aldrich), glyceraldehyde (>95%, Aldrich), dihydroxyacetone (>98%, Acros Organics), D-erythrose (60% solution, Aldrich), D-L-arabinose (>99%, Aldrich), D-ribose (>99%, Aldrich), D-lyxose (>99%, Aldrich), D-L-xylose (>99%, Aldrich), D-glucose (reagent grade), L-sorbose (>99%, Sigma), D-fructose (>99%, Sigma), D-mannose (>99%, Aldrich), and D-galactose (>99%, Aldrich). The following indicators were used: Bromthymol Blue, murexide/NaCl (1 : 100), and a Trilon B solution (analytical grade; titrimetric standard).

The solution of formaldehyde was prepared by dissolving paraformaldehyde in water in a flask equipped with a reflux condenser and placed in a boiling water bath. 2,4-Dinitrophenylhydrazine (pure grade) was recrystallized from ethanol. Water purified using a Milli-Q system (Millipore, USA) was used for the preparation of all solutions.

Butlerov reaction in a stirred flow reactor. The following solutions were supplied to a reactor thermostated at 38.5°C, which was equipped with a thermometer and a magnetic stirrer, at equal flow rates via three independent channels: 0.42 M formaldehyde, 0.082 M calcium chloride, and 0.18 M sodium hydroxide solutions. The contact time of the mixture in the reactor was 15.9 min, as calculated from the ratio of the reactor volume to the total supply flow rate of solutions. The solutions were deaerated with argon before the supply to the reactor. The design of the reactor excluded the contact of a reaction mixture with the atmosphere in the course of the reaction. When the reactor was filled with the reaction mixture, a crystalline initiator in the amount of 1.5 mol % of the initial formaldehyde concentration in the reactor was introduced into the reactor through a thermometer socket in order to initiate the reaction.

Butlerov reaction in a batch reactor. A solution of $Ca(OH)_2$ (65 ml), which was prepared by mixing 0.63 ml of a 3.0 M $CaCl_2$ solution and 3.9 ml of a 0.98 M NaOH solution with water, was placed in a three-neck reactor thermostated at 38°C, which was equipped with a thermometer, an argon supply tube, and a magnetic stirrer. The solution was deaerated with argon for 30 min. Thereafter, 4.5 ml of a 2.17 M formaldehyde solution and an initiator in the amount of 1.5 mol % of the initial formaldehyde concentration in the reactor were added to the solution. The initiator was added either in a crystalline form or as a concentrated aqueous solution. The solid sample was dissolved sufficiently rapidly; this allowed us to ignore this time in the subsequent kinetics of detected transformations. The initial concentrations of formaldehyde and calcium hydroxide were 0.14 and 0.027 mol/l, respectively.

Accumulation of the enediol forms of C_5–C_6 carbohydrates in solution. A 0.005 M $Ca(OH)_2$ solution (50 ml) was placed in a three-neck reactor thermostated at 41°C, which was equipped with a thermometer, a gas supply tube, and a magnetic stirrer, and deaerated with argon for 30 min. Then, a weighed portion of a carbohydrate was added so that the initial carbohydrate concentration was also equal to 0.005 mol/l. In the course of the reaction, the solution was sampled for measuring pH on an I-135 ion meter (Soviet Union) and UV–Vis spectra on a UVIKON 923 spectrophotometer (Kontron, Italy) and for determining carbohydrate concentrations in the mixture. To determine the concentration of monosaccharides, the reaction was stopped by acidifying with a 4 N H_2SO_4 solution to pH 0.7.

Condensation of C_2–C_3 lower carbohydrates. All of the reaction conditions were analogous to the conditions of the preparation of the enediol forms of higher carbohydrates. In the study of the conversion of a lower monosaccharide, a weighed portion of the test substance was added to the reactor so that the concentration was 0.005 mol/l. In the study of the interaction of two different lower monosaccharides, the initial concentration of either of the monosaccharides in the reactor was 0.0025 mol/l.

Isolation of enediol complexes in a solid form. The procedure for the isolation of the enediol complexes of carbohydrates with calcium hydroxide as solids was described elsewhere [19]; we used this procedure with minor changes. The complexes were kept in a refrigerator in an atmosphere of argon. To determine the concentrations of calcium and carbohydrates in the synthesized complexes, they were dissolved in an acid and the resulting solution was analyzed (see Analytical procedures).

Analytical procedures. The concentrations of formaldehyde in solutions prepared from paraformaldehyde and in the reaction mixtures were determined by iodometric titration and spectrophotometry using a reaction with chromotropic acid, respectively [23]. To determine the extent of the Cannizzaro reaction, acid–base titration was performed [24]. The higher and lower carbohydrates were analyzed by high-performance liquid chromatography (HPLC) with precolumn derivatization using 2,4-dinitrophenylhydrazine [25, 26] on a Milikhrom A-02 liquid chromatograph (Ekonova, Russia). The concentrations of Ca^{2+} ions in the solutions of enediol complexes were determined in accordance with a published procedure [27].

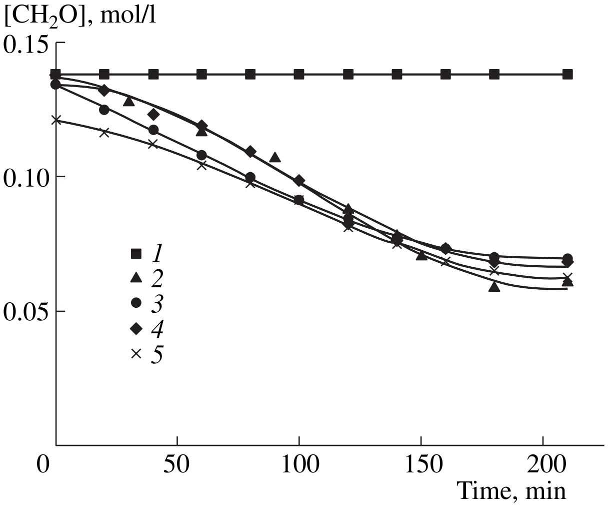

Fig. 1. Kinetic curves of formaldehyde concentration changes in a stirred flow reactor after the introduction of various initiators: (*1*) glucose, galactose, ribose, lyxose, and fructose; (*2*) sorbose; (*3*) dihydroxyacetone; (*4*) glyceraldehyde; and (*5*) glycolaldehyde. $[CH_2O]_0$ = 0.14 mol/l; $[Ca(OH)_2]_0$ = 0.027 mol/l, T = 38°C. Contact time, 15.9 min.

Simulation of the spatial structures of monosaccharides. The spatial structures of monosaccharides were simulated using the HyperCube Hyperchem Professional Release 7.5 software [www.hypercube.com]. The monosaccharide structures from the database of the HyperChem SugarBuilder 7.5 program were used for the simulation. The modified neglect of the diatomic overlap (MNDO) semiempirical method was used for the structure geometry optimization [28].

RESULTS AND DISCUSSION

Initiating Activity of Carbohydrates

Effect of the nature of an initiator on the Butlerov reaction in a stirred flow reactor. The following carbohydrates were used as initiators for the Butlerov reaction: glycolaldehyde, glyceraldehyde, dihydroxyacetone, ribose, lyxose, glucose, galactose, mannose, fructose, and sorbose. Under flow conditions, all of the lower carbohydrates (C_2 and C_3) initiated the condensation of formaldehyde, whereas only sorbose was found active among the higher carbohydrates. The fact that sorbose is the most active initiator among the higher carbohydrates is consistent with published data [22].

Figure 1 shows kinetic curves for the formaldehyde concentration in a flow reactor with the use of various initiators. A steady state in the reactor was established within ~3 h. For all of the initiators, the products of the

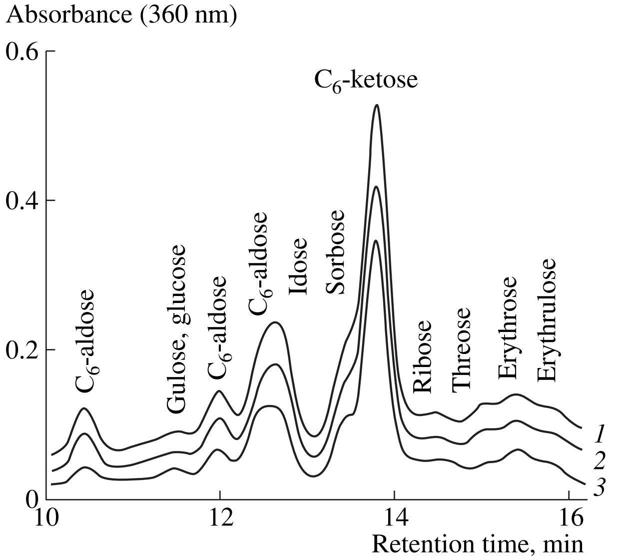

Fig. 2. HPLC data on the composition of higher (C_4–C_6) carbohydrates in Butlerov reaction products in a steady state with the use of a stirred flow reactor depending on the nature of the initiator: (*1*) sorbose, (*2*) dihydroxyacetone, and (*3*) glycolaldehyde. $[CH_2O]_0 = 0.14$ mol/l; $[Ca(OH)_2]_0 = 0.027$ mol/l, $T = 38°C$. Contact time, 15.9 min.

Butlerov reaction were analyzed after a steady state was established. Regardless of the nature of the initiator, both the degree of formaldehyde conversion and the composition and concentration ratio of products detected in a steady state were always equal to within the error of analytical procedures (Fig. 2). Thus, we can claim that the steady state of the system in the course of the Butlerov reaction was stable and independent of the nature of the initiating carbohydrate.

Effect of the nature of an initiator on the Butlerov reaction in a batch reactor. Because the experiments in the flow reactor did not allow us to compare the initiating activities of monosaccharides, we performed experiments in a batch reactor with the same initiators. Moreover, we performed an experiment without the addition of initiating reagents into the system.

In the absence of an initiator, the consumption of formaldehyde was due to the occurrence of the Cannizzaro reaction alone, as monitored by changes in the pH of the reaction mixture. This observation suggests the incorrectness of all of the previous hypotheses [11–14] that the Butlerov reaction can be initiated by the condensation of two formaldehyde molecules with the formation of glycolaldehyde.

The kinetic curves of formaldehyde consumption in the presence of monosaccharides have a shape typical of autocatalytic reactions, and they are characterized by various induction periods, whereas the rates at the periods of rapid formaldehyde consumption are approximately equal for all of the initiators (Fig. 3). With the use of glycolaldehyde or dihydroxyacetone as an initiator, a noticeable induction period was absent from the kinetics of formaldehyde consumption. The duration of the induction period increased in the order sorbose, fructose, ribose, and glucose. The initiating activity of carbohydrates increased with decreasing numbers of carbon atoms in the initiator molecule. Among the C_5–C_6 higher monosaccharides, ketoses were most active, as supported by published data [22].

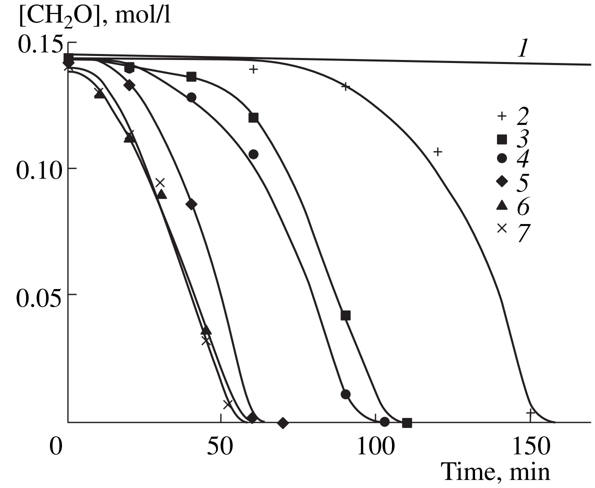

Fig. 3. Kinetic curves of formaldehyde concentration changes in a batch reactor in the presence of various initiators in equal amounts: (*1*) no initiator, (*2*) glucose, (*3*) ribose, (*4*) fructose, (*5*) sorbose, (*6*) dihydroxyacetone, and (*7*) glycolaldehyde. $[CH_2O]_0 = 0.14$ mol/l; $[Ca(OH)_2]_0 = 0.027$ mol/l. $T = 38°C$.

Formation of the Enediol Forms of Higher Carbohydrates in the Presence of Calcium Hydroxide

We hypothesized that the rate of conversion into an enediol form can be a crucial factor for the initiating activity of a monosaccharide. Therefore, we studied spectrophotometrically the kinetics of formation of enediol complexes for all of the carbohydrates used as initiators.

It was found [29, 30] that the spectrum of an alkaline glucose solution in an inert atmosphere exhibited an absorption band at 300 nm, which corresponds to the enediol anion. Figure 4 shows kinetic curves for absorbance buildup at 300 nm in the alkaline solutions of higher monosaccharides in the presence of calcium ions. The composition of the reaction mixture in the course of formation of the enediol forms of monosaccharides was studied by HPLC. It was found that, by the time a constant absorbance was established, glycolaldehyde, glyceraldehyde, dihydroxyacetone, and up to six higher carbohydrates were also present in the mixture in addition to the parent monosaccharide. Thus, the conversion of C_5–C_6 monosaccharides into an enediol form was accompanied by retroaldol cleavage with the formation of C_2–C_3 lower carbohydrates. In turn, the latter condensed with each other to form other higher monosaccharides. Figure 5 shows a correlation

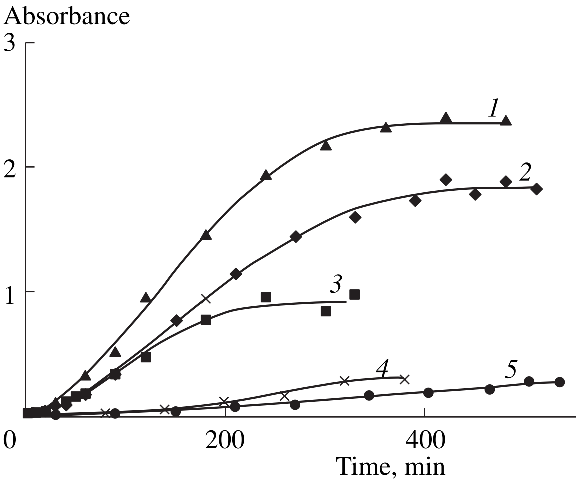

Fig. 4. Absorbance buildup at λ = 300 nm in various carbohydrate solutions in the presence of calcium hydroxide: (*1*) sorbose, (*2*) ribose, (*3*) fructose, (*4*) glucose, and (*5*) mannose. Initial carbohydrate concentrations, 0.005 mol/l; $[Ca(OH)_2]_0$ = 0.027 mol/l. T = 41°C; Ar; optical path l = 1 cm.

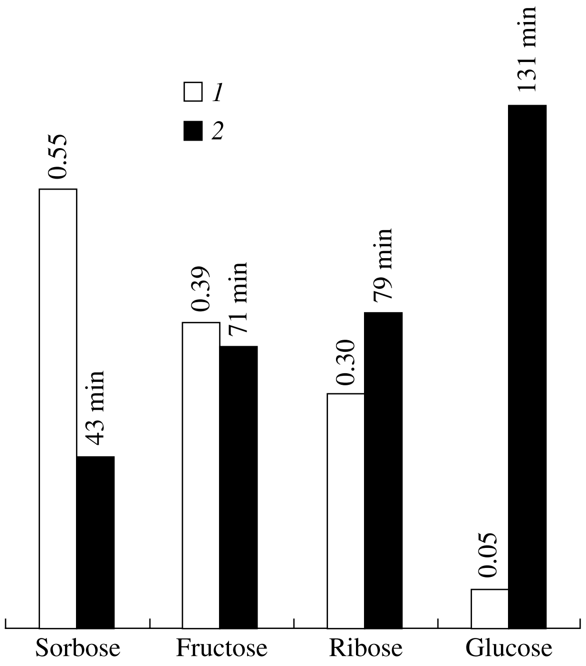

Fig. 5. Correlation between the initiating activities of C_5–C_6 monosaccharides in the Butlerov reaction and the rates of their conversion into an enediol form. (*1*) Absorbance at λ = 300 nm; l = 5 cm; (*2*) half-time of CH_2O conversion in a batch reactor. Butlerov reaction conditions: $[CH_2O]_0$ = 0.14 mol/l; $[Ca(OH)_2]_0$ = 0.027 mol/l; T = 38°C; Ar. Conditions for the preparation of the enediol forms of carbohydrates: initial carbohydrate concentrations, 0.005 mol/l; $[Ca(OH)_2]_0$ = 0.005 mol/l, T = 41°C; Ar; time, 30 min.

between the rates of absorbance buildup in alkaline carbohydrate solutions at the initial stage of the reaction, when only the starting monosaccharide and its isomers are in the mixture (formed by the Lobry de Bruyn–van Ekenstein reaction), and the initiating activities of monosaccharides in a batch reactor.

Solid Carbohydrate Complexes with Calcium Ions and Their Initiating Activity

To test the hypothesis that the initiating activity of carbohydrates depends on the rate of formation of an enediol form, we isolated the solid enediol complexes of glucose, fructose, ribose, sorbose, and dendroketose in accordance with a published procedure [19]. Ziemecki et al. [19] believed that they isolated an enediol complex of dihydroxyacetone with calcium and found that the initiating activity of this complex was much lower than the activity of free dihydroxyacetone. We have repeated this synthesis. However, HPLC analysis demonstrated that, under the conditions used, the enediol complex of dendroketose (a branched ketohexose) rather than dihydroxyacetone was formed. In turn, dendroketose was formed from dihydroxyacetone by aldol condensation in an alkaline medium.

The resulting enediol complexes of calcium with glucose, fructose, ribose, sorbose, and dendroketose were analyzed for carbohydrate and calcium contents: a weighed portion of a complex was dissolved in an acid, and the resulting solution was analyzed. The table summarizes data on the purity of the prepared complexes. It is important that neither lower nor higher carbohydrates other than the parent monosaccharide and corresponding isomeric carbohydrates formed by the Lobry de Bruyn–van Ekenstein reaction [8] were detected as the constituents of calcium complexes with glucose, fructose, ribose, and dendroketose. However, the constituents of the enediol complex of calcium with sorbose were the parent carbohydrate, two isomeric

Weight fractions of carbohydrates and calcium in isolated solid complexes

Carbohydrate		Enediol complex	
		carbohydrate, wt %	Ca, wt %
Glucose		65 (79)	14.8 (80)
Fructose		39 (48)	21.1 (115)
Ribose		40 (51)	21.0 (99)
Sorbose	sorbose	22 (26)	14.8 (80)
	dendroketose	31 (37)	
Dendroketose		59 (72)	22.2 (122)

Note: The fraction (%) of the theoretically expected concentration assuming the $C_nH_{2n-2}O_n$: Ca = 1 : 1 ratio between the carbohydrate residue and calcium in the complex.

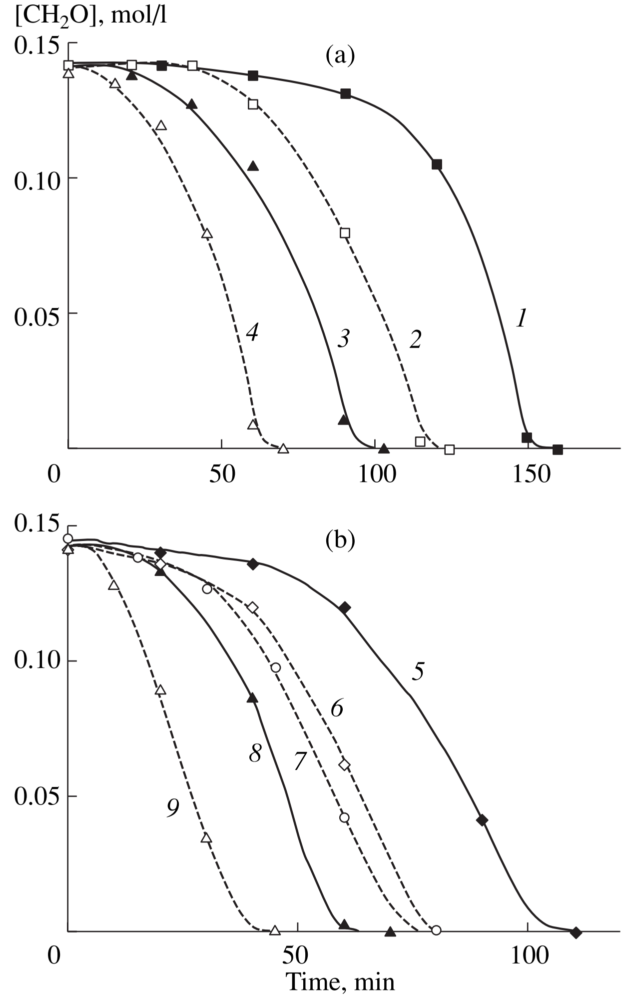

Fig. 6. Kinetic curves of formaldehyde concentration changes in a batch reactor under the initiation of the Butlerov reaction with the enediol complexes of carbohydrates and pure carbohydrates: (*1*) glucose, (*2*) the enediol complex of glucose, (*3*) fructose, (*4*) the enediol complex of fructose, (*5*) ribose, (*6*) the enediol complex of ribose, (*7*) the enediol complex of dendroketose, (*8*) sorbose, and (*9*) the enediol complex of sorbose. $[CH_2O]_0 = 0.14$ mol/l; $[Ca(OH)_2]_0 = 0.027$ mol/l, $T = 38°C$; Ar.

aldoses (idose and gulose), and a considerable amount of dendroketose. The presence of dendroketose can be explained by the cleavage of sorbose into dihydroxyacetone and glyceraldehyde, which, in turn, condensed into dendroketose. Lower carbohydrates were not detected as the constituents of this complex.

Assuming that one monosaccharide molecule and one calcium ion are the constituents of the complexes [31], the theoretical weight concentrations of calcium in the complexes are 18.3% for hexoses and 21.3% for pentoses. In the case of glucose, ribose, and sorbose complexes, this concentration was no higher than the theoretical value, whereas the enediol complexes of fructose and dendroketose contained an excess of metal ions (see table). This can be explained by the fact that we failed to remove adequately an excess of calcium hydroxide from the prepared complexes at the stage of preparation.

The initiating activity of the resulting enediol complexes was studied in a batch reactor. Figure 6 shows the kinetic curves of a decrease in the concentration of formaldehyde in the cases of the use of pure carbohydrates and the corresponding solid enediol complexes as initiators. The complexes exhibited a higher initiating activity. The initiating activity of the enediol complex prepared from sorbose, which contained both sorbose and dendroketose (see above), was higher than the activity of the complex of pure dendroketose. Thus, we believe that, with the use of the enediol complex of sorbose with a dendroketose impurity as an initiator, the complex of sorbose primarily exerted an initiating effect.

The fact that the initiating activity of solid enediol complexes is higher than that of parent carbohydrates partially supports the hypothesis that this form of carbohydrates is active in the initiation of the Butlerov reaction.

Condensation of Lower Carbohydrates

In an alkaline medium, in particular in the presence of calcium hydroxide, lower carbohydrates also form enediol species but at much higher rates than those for higher carbohydrates. The conversion into an enediol form allows lower carbohydrates to undergo aldol condensation with one another. We performed the condensation of C_2–C_3 lower carbohydrates in various pair combinations in the presence of calcium hydroxide and identified the products of these reactions.

Threose, erythrose, erythrulose, gulose, fructose, and sorbose, as well as unidentified C_6 aldose and C_6 ketose, which were observed in Butlerov reaction products in the batch and flow reactors, were identified in an alkaline solution of glycolaldehyde. Along with the above carbohydrates, two C_5 aldoses (ribose and arabinose) were formed by the interaction of glycolaldehyde with C_3 carbohydrates. It is of interest that dendroketose, which is the main condensation product of C_3 carbohydrates, was not detected among the products of the above interaction, as well as among the Butlerov reaction products observed in the batch and flow reactors. This is likely because the rate of reaction between glycolaldehyde and C_3 carbohydrates is higher than the rate of condensation of C_3 carbohydrates. Thus, in this case, trioses participated in the formation of only pentoses.

In the interaction of C_3 carbohydrates with each other, in addition to the expected condensation products (glucose, fructose, sorbose, and dendroketose), small amounts of ribose and xylose (both are C_5 aldoses); erythrose (C_4 aldose); and, most importantly, glycolaldehyde were identified in the reaction mixture. It is believed that the appearance of glycolaldehyde in the mixture resulted in the formation of pentoses and tetrose. The occurrence of glycolaldehyde in the mixture can be explained by retroaldol cleavage of higher monosaccharides in the presence of calcium hydroxide. As mentioned above, all of the lower carbohydrates, including glycolaldehyde, were formed in an alkaline solution of, for example, sorbose, which is present in the condensation products of C_3 carbohydrates. It is important that the composition of products obtained by the interaction of C_2 and C_3 carbohydrates with each other is similar to the composition of Butlerov reaction products.

Mechanisms of the Butlerov Reaction and Its Initiation

The set of the above data on the initiating activities of various carbohydrates and their ability to form enediol complexes, as well as on processes that occur in carbohydrate solutions in the presence of calcium hydroxide, allows us to propose self-consistent mechanisms for the initiation of the Butlerov reaction and, in general, the condensation of formaldehyde into carbohydrates.

Figure 7 shows the mechanism of reaction initiation using sorbose (C_6 ketose) and isomeric (in terms of the Lobry de Bruyn–van Ekenstein reaction) gulose (C_6 aldose) initiators as an example. At the initial stage of the reaction, the interaction of a monosaccharide initiator with calcium hydroxide results in the formation of an enediol complex with the metal ion. In this case, the monosaccharide participates in this reaction only in a linear form, although it is well known that linear molecules in aqueous solutions of higher monosaccharides occur in equilibrium with cyclic hemiacetal molecules, whose equilibrium concentration is much higher. As demonstrated using a kinetic analysis [32], the ability of C_5–C_6 unbranched monosaccharides to form cyclic species is very important in the reaction under consideration because it leads to the stabilization of these monosaccharides. The equilibrium concentrations of linear molecules in aqueous ketose solutions are higher than those in aldose solutions. It is believed that this fact is responsible for an increased initiating activity of ketoses, as compared with that of aldoses.

Ketoses can form two isomeric complexes with calcium: with the enediol group between the first and second (C1–C2) and between the second and third (C2–C3) carbon atoms. Aldoses can form only one type of C1–C2 complex [11, 18, 21]. In this case, all of the aldoses used as initiators in this work predominantly formed a five-membered enediol complex for steric reasons, as found by the simulation of the spatial structure of monosaccharides. At the same time, the mutual arrangement of the hydroxyl groups of ketoses facilitates the formation of a six-membered enediol complex with calcium ions. As an example, Fig. 8 shows the spatial structures of sorbose and glucose and possible reaction paths for the formation of the enediol complexes of these carbohydrates.

The enediol complex with a six-membered ring can undergo retroaldol cleavage [33, 34]. In this case, the C1–C2 complex of C_6 ketose undergoes cleavage with the formation of glycolaldehyde and tetrose, whereas the C2–C3 complex forms glyceraldehyde and dihydroxyacetone (see Fig. 7). All of the degradation products of the parent ketose (tetrose, dihydroxyacetone, glyceraldehyde, and glycolaldehyde) can undergo aldol condensation with formaldehyde to form C_3–C_5 carbohydrates. Because all of the C_5–C_6 higher carbohydrates and C_4 aldoses can form stable cyclic hemiacetals, it is most likely that lower carbohydrates react with formaldehyde to form C_3 carbohydrates in the case of glycolaldehyde or tetroses in the case of trioses. The condensation of C_2–C_4 monosaccharides with one another results in the formation of higher monosaccharides.

For aldoses, the formation of complexes with a five-membered ring can facilitate only the stabilization of the enediol form and, consequently, isomerization into ketose and epimeric aldose by the Lobry de Bruyn–van Ekenstein reaction. Thus, in the interaction with calcium hydroxide, aldoses are initially isomerized to ketoses, which then undergo cleavage to form lower carbohydrates. These lower carbohydrates undergo condensation with formaldehyde. It is believed that this is the main reason for the increased initiating activity of ketoses, as compared with that of aldoses. The relation between the autocatalytic behavior of the Butlerov reaction and retroaldol cleavage reactions of higher carbohydrates was hypothesized previously [15, 35]. However, this hypothesis was not supported experimentally.

The overall reaction scheme for the Butlerov reaction based on the experimental results is given below.

$$C_iH_{2i}O_i \xrightarrow[-2H_2O]{+Ca(OH)_2} [C_iH_{2i-2}O_i \cdot Ca]$$

$$\xrightarrow[-Ca(OH)_2]{+2H_2O} C_{i-j}H_{2(i-j)}O_{i-j} + C_jH_{2j}O_j,$$

$$C_jH_{2j}O_j + CH_2O \xrightarrow{Ca(OH)_2} C_{j+1}H_{2(j+1)}O_{j+1},$$

$$C_nH_{2n}O_n + C_mH_{2m}O_m \xrightarrow{Ca(OH)_2} C_{n+m}H_{2(n+m)}O_{n+m}.$$

Here, $i = 4, 5$; $j = 2$–4; $n, m = 2$–4.

The above reaction scheme also explains important findings that the steady state of the Butlerov reaction is independent of the nature of the initiator under flow conditions and the composition of the products of the

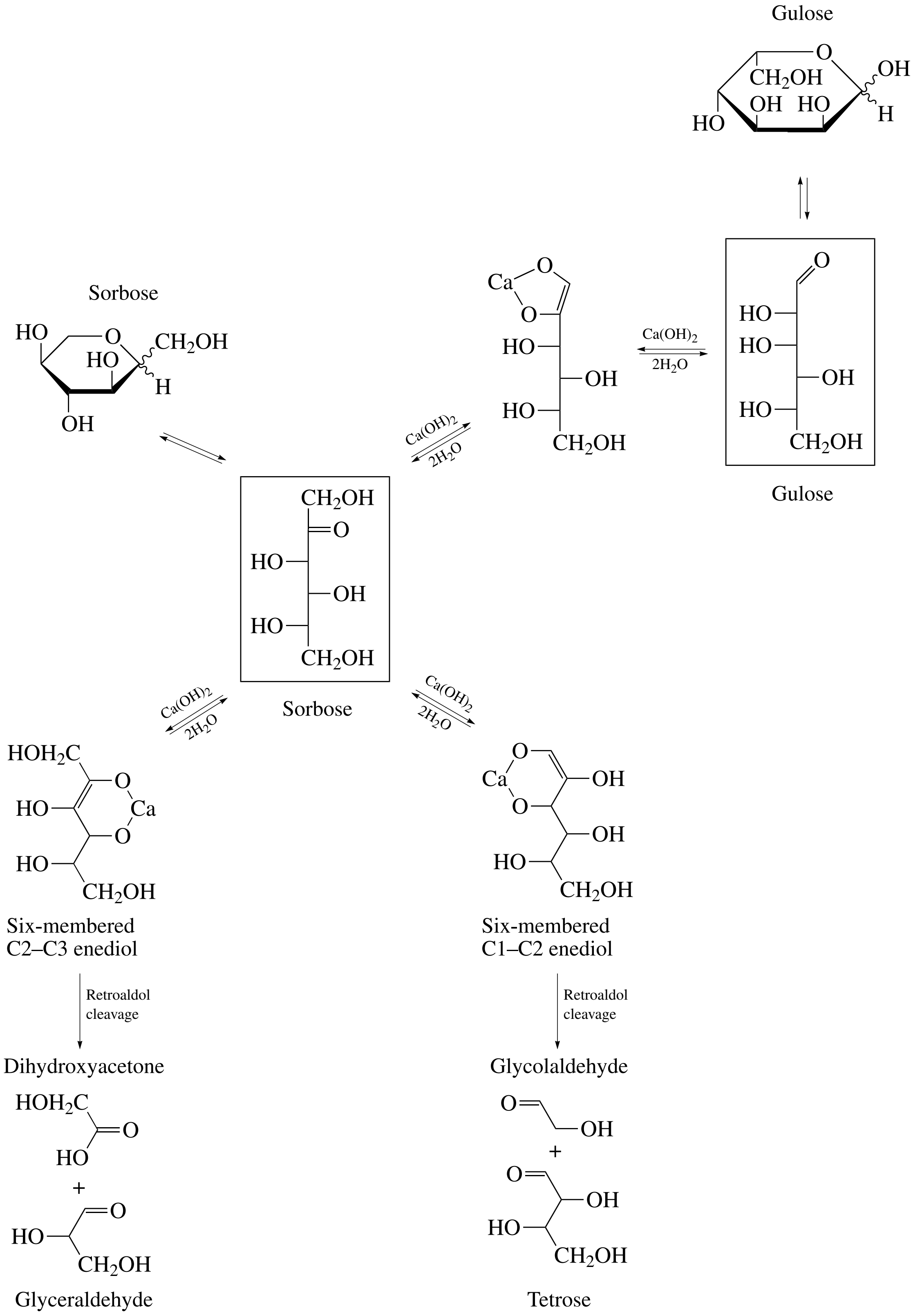

Fig. 7. Formation of the molecules of C_2–C_3 lower carbohydrates in the formose system by the retroaldol cleavage mechanism exemplified in sorbose (C_6 ketose) and isomeric (in terms of the Lobry de Bruyn–van Ekenstein reaction) gulose (C_6 aldose).

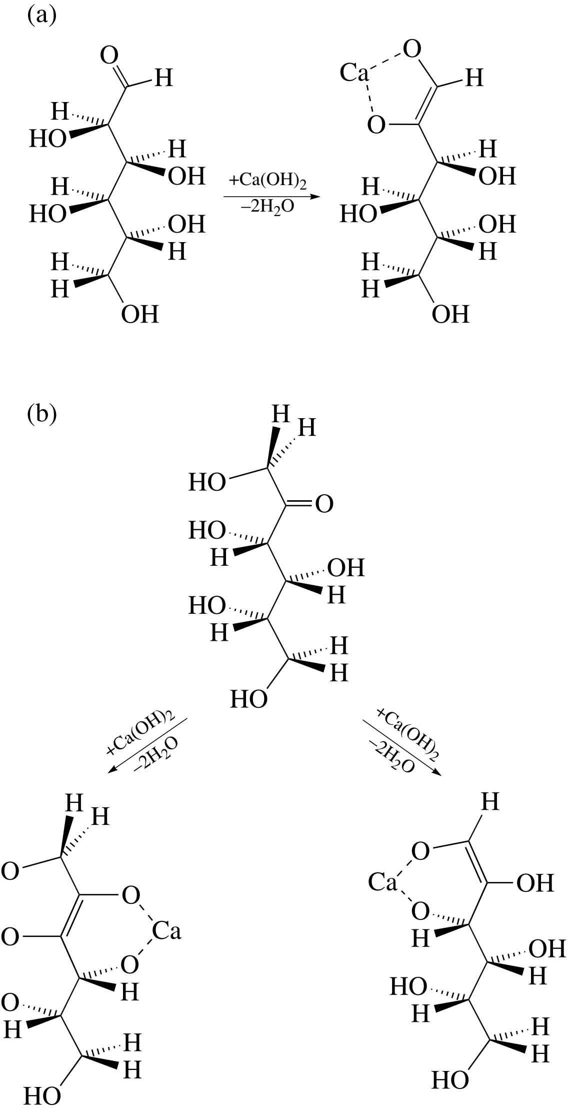

Fig. 8. Possible reaction paths for the formation of enediol complexes with calcium ions for (a) glucose and (b) sorbose.

reaction under consideration and the condensation products of lower monosaccharides are similar.

CONCLUSIONS

The experimental data allowed us to state that the formation of the enediol forms of monosaccharides followed by degradation to C_2–C_3 lower carbohydrates plays a key role in the initiation of the Butlerov reaction. In this case, an important element of the overall Butlerov reaction scheme is that mainly C_2 and C_3 carbohydrates enter aldol condensation reactions with formaldehyde, whereas the formation of higher monosaccharides occurred by the aldol condensation of glycolaldehyde, glyceraldehyde, dihydroxyacetone, and tetroses with each other. Note that the role of calcium ions in the reaction of formaldehyde oligomerization remains unclear.

The experiments allowed us to propose the most probable mechanism for the autocatalytic synthesis of monosaccharides from formaldehyde. In the future, we hope to perform a detailed kinetic analysis of the test system based on the experimental data. In turn, this can clarify the details of the overall reaction mechanism and answer the question of whether control of selectivity in the Butlerov reaction is possible. The structural characterization of the isolated solid enediol complexes of carbohydrates with calcium ions by IR and Raman spectroscopy is in progress; this will allow us to refine the real structures of the isolated process initiators and catalytic intermediates.

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