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Homogeneously Catalyzed Formaldehyde Condensation to Carbohydrates

III. Concentration Instabilities, Nature of the Catalyst, and Mechanisms

ALVIN H. WEISS AND TOM JOHN

Chemical Engineering Department, Worcester Polytechnic Institute,
Worcester, Massachusetts 01609

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The formose reaction, the homogeneously catalyzed condensation of formaldehyde to sugars, proceeds simultaneously with Cannizzaro and cross-Cannizzaro reactions. Reaction studies in a continuous stirred tank reactor have shown that rate instabilities are exhibited. There are temperature instabilities as well as concentration instabilities in calcium hydroxide catalyst, formaldehyde reactant, and hydroxyl ion. It is postulated that $Ca(OH)^+$ is the actual catalytic species for the formose system. A unifying mechanism is developed that uses observed rate phenomena to explain why almost any base, regardless of valence, is a catalyst for the formose and Cannizzaro reactions of formaldehyde. The mechanism postulates that reactions proceed from a common intermediate complexed species, and the selectivity for each reaction depends on the nature of the catalyst forming the carbohydrate complex. The catalytic mechanism explains the Lobry de Bruyn-van Eckenstein aldose-ketose rearrangements and mutarotations of sugars that also proceed in the system.

INTRODUCTION

The calcium hydroxide catalyzed condensation of formaldehyde to carbohydrates is known as the formose reaction. The reaction proceeds in aqueous solution, is autocatalytic in nature, and extremely complex. Both branched and straight chain carbohydrates with carbon numbers ranging from two to eight and possibly higher are produced. The formose reaction is basically an aldose condensation. Since it occurs in aqueous medium, Lobry de Bruyn-van Eckenstein rearrangements occur to produce both aldose and ketose forms of carbohydrates. Mutarotations of optical isomers also occur. The formose "syrup" is highly toxic, and feeding studies as well as sugar characterizations and reaction chemistry are reviewed by Mizuno and Weiss (*1*). It is believed that the toxicity of formose is mainly due to the presence of large quantities of branched chain carbohydrates, which do not occur as natural sugars. Definitive identification of such species in formose are reported by Partridge, Weiss, and Todd (*2*).

Simultaneously with the formose aldol type condensation, Cannizzaro reaction to produce methanol and higher polyols proceeds *in situ*. It has been found that branched species are so subject to reduction by cross-Cannizzaro reaction with formaldehyde that species such as hydroxymethylglycerol are also made in large quantities in the formaldehyde condensation. The idea of using the formose reaction to produce this compound in quantity has been promulgated (*3*).

In the first paper of our formose series (*4*), experimental results of reaction studies made in a continuous stirred tank reactor (CSTR) were reported. The results suggested that the decomplexing of products was the rate limiting step of the reaction and a kinetic expression was derived for the formose condensation. The expression, in which a semantic substitution of complexing–decomplexing for adsorption–desorption was made, is basically a Langmuir–Hinshelwood equation form. The model degenerates to autocatalytic behavior at low conversion levels, zero order behavior at intermediate conversion levels, and first order dependency in formaldehyde at high conversion levels, all of which are experimentally observed.

The Cannizzaro reaction was also found in the same work to exhibit peculiar kinetic behavior. Its rate passes through a maximum near 50% formaldehyde conversion, then a minimum and, near complete conversion, again ascribes to a maximum.

In the second paper of the formose series (*5*) it was shown that both the Cannizzaro and formose condensations were subject to remarkable $Ca(OH)_2$ concentration instabilities. At fixed formaldehyde feed rate to the CSTR, the slightest change in calcium hydroxide concentration was capable of effecting dramatic swings in formaldehyde conversion at ostensibly identical conditions. These instabilities were found to occur at both low and high calcium hydroxide concentrations. One purpose of this present work is to characterize the formose reaction concentration instabilities in both formaldehyde and calcium hydroxide and to explain them.

It has also been observed that a lowering of pH below that of saturated calcium hydroxide solution occurs in the formose reaction. Values as low as 10.5 has been measured at 40°C (*5*) and 8.6 at 76°C (*6*). pH Minima correspond to reaction rate maxima. The calcium hydroxide in reacting mixtures with formaldehyde is highly complexed and calcium ion activities are significantly lower than the solubility of calcium hydroxide (*5*). This is the case even in situations where the amount of calcium hydroxide in clear solution was more than 15 times the solubility limit (*5*, *6*). The formaldehyde complex, in accordance with the suggestion of Franzen and Hauck (7), is believed to be of the type

$$HOCH_2OCaOH.$$

Rendleman (*8*) has provided a review paper on the subject of complexes of alkali metals and alkaline earth metal salts with carbohydrate. Formose products as well as formaldehyde can complex, and Angyal and Davies (*9*) define the structural configuration required for alkaline earth metal ion complexing in aqueous solution. Most recently Roy and Mitra (*10*) have shown that glucose and maltose form 1:1 adducts with the hydroxides of barium, calcium, and strontium, all of which are divalent base catalysts for the formose reaction. The amount of adduct formed is related to the pH of the sugar solution. Glotova and Enikolopyan (*11*) suggest that in formaldehyde condensation kinetics the equilibrium between formaldehyde and the anionic catalysts must be taken into account. Their data obtained using both potassium hydroxide and calcium glutamate catalysts suggest that the character of the rate curves they present is independent of the nature of the catalyst. This observation is particularly meaningful when it is recognized that almost any alkaline substance can be an effective catalyst for the formose condensation. However, the relative proportions of Cannizzaro to formose reactions depend on the catalyst itself, i.e., Ackerloff and Mitchell (*12*) report batch experiments with formaldehyde which show that although the main reaction is Cannizzaro in the presence of KOH, at extreme conversions formose condensation does occur. On the other hand, with a highly selective catalyst such as calcium hydroxide, the formose rate greatly exceeds the Cannizzaro rate, except at very low conversions.

Berlin, Krylov and Sinyak (*13*) provide not only reviews of catalysts for the formose reaction, but also show that rare earth hydroxides are quite effective catalysts. Inorganic bases that are useful include not only those with mono- and divalent cations but also those that are tri- and tetravalent (*13, 15*). Cairns-Smith, Ingram, and Walker (*16*), in a paper relating formose reaction to the primordial origin of carbohydrates, provide a list of minerals that have been found to be active catalysts for the formose reaction. Mizuno *et al.* (*17*) report formose catalytic activity with organic bases such as pyridine, collidine, the picolines, 2-dimethylaminoethanol, *N*-methylmorpholine and tetraethylammonium hydroxide. Another purpose then of the present paper will be to attempt to shed light on the common nature of the diverse catalysts of the formose reaction.

EXPERIMENTAL PROCEDURE

The CSTR used for this study is a magnetically stirred beaker in which temperature is controlled to ±0.1°C. Two feed streams, a solution of paraformaldehyde in distilled water and a slurry of calcium hydroxide in distilled water were pumped at fixed rates to the reactor separately. In experiments designed to force the system away from autonomic pH levels a third feed solution of either sodium hydroxide or formic acid was pumped to the reactor. Calcium hydroxide consumption in the reaction was measured by acid titration, formaldehyde consumption by the Na_2SO_3 titration technique. Materials, the reactor, its operation and analytical procedures have been described in detail earlier (*4*).

Experiments reported in earlier studies were made at fixed formaldehyde feed rate and space time and varying calcium hydroxide combined feed concentrations. In this present work, the combined feed molarity of both calcium hydroxide and formaldehyde were fixed and space time was varied.

In general the reactor was started at room temperature and filled with a solution of calcium hydroxide and formaldehyde of the appropriate concentrations. Feed and withdrawal pumps were started and temperature was raised to the desired operating level. If a low conversion steady state were reached, and conditions were such that an instability was possible, addition to the reactor of formose syrup prepared separately would result in a reflection to high formaldehyde conversion level when the new steady state at identical operating conditions was reached. If the operation were intrinsically stable, then the perturbation would have no permanent effect and the reaction would return to its initial steady state level. Both the volume of solution in the reactor or the feed rate of the streams to the reactor were used to control space time to the system.

In experiments to determine the effect of pH on the reaction, the reactor was operated so that the high conversion level of any instability would be reached. In these experiments, the reactor was filled initially with product near complete conversion (e.g., 93%) and brought to reaction temperature. Pumps were then started. The system was allowed to reach steady state before sampling for analysis.

The formose rate is defined as the rate of conversion of formaldehyde to higher molecular weight carbohydrates. Cannizzaro rate is defined as the rate of calcium hydroxide conversion in the reaction below:

$$4HCHO + Ca(OH)_2 \rightarrow Ca(OOCH)_2 + 2CH_3OH. \quad (1)$$

The sodium sulfite titration measures the total formaldehyde disappearance rate. This total rate, less the four times the Cannizzaro rate, is then numerically equal to the formose rate as used in this paper. Since Cannizzaro rate is usually low relative to formose rate, total rates (except near zero conversion) are a good approximation of formose rate in this system.

RESULTS

Figure 1 is a plot of formaldehyde conversion as a function of space time at temperatures ranging from 40 to 60°C. Fixed concentrations of both calcium hydroxide and formaldehyde were used in the combined feed to the CSTR. For these values, which were 0.571 and 1.313 *M*, respectively, it was found that 52°C was an unstable operating temperature. At 5 min space time, the minutest shift in space

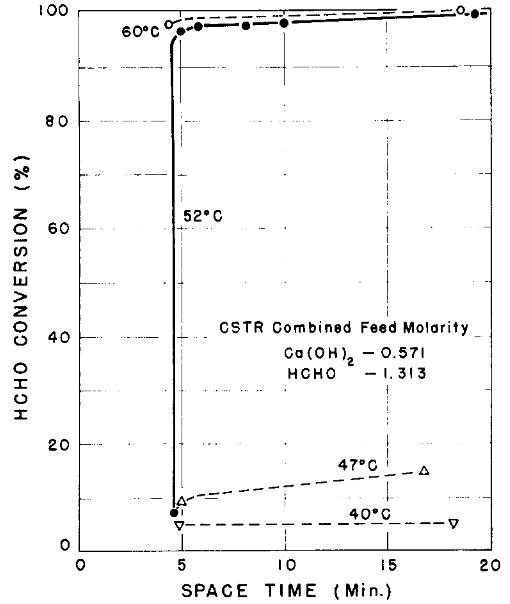


FIG. 1. A minute change in space time at 52°C results in a rate instability at fixed CSTR combined feed concentrations. Lower and higher temperatures result in stable operations.

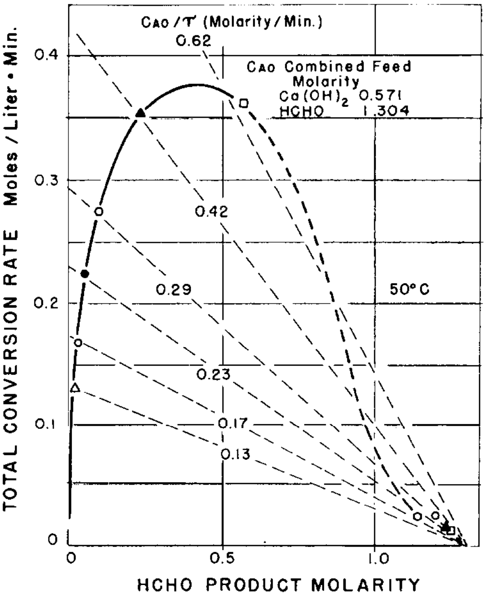


FIG. 2. The formose reaction exhibits autocatalytic concentration instabilities. Identical symbols correspond to identical feed concentrations and CSTR conditions.

time in the reactor reflected the formaldehyde conversion from 8 to 93%. This is really a concentration instability behavior, and the formaldehyde concentration instabilities of the system at 50°C are shown on Fig. 2. Experimental data are listed in Table 1. Figure 2 is a plot of the total conversion rate of formaldehyde versus formaldehyde product molarity at fixed combined feed molarities of calcium hydroxide and formaldehyde at 50°C. The broken operating lines in Fig. 2 are the experimental conditions of formaldehyde feed concentrations divided by space time. Experimental data fall on the appropriate operating lines at both low and high con-

TABLE 1

FORMOSE CONCENTRATION INSTABILITY DATA AT 50°C

CSTR molarities									
Combined feed		Product		Space time (min)	pH	HCHO conv. (%)	Rates (moles/liter min)		
HCHO	$Ca(OH)_2$	HCHO	$Ca(OH)_2$				Total	Cannizzaro	Formose
1.315	0.560	0.0615	0.544	5.65	11.5	95.4	0.222	0.00395	0.210
1.32	0.564	0.105	0.550	4.40	11.5	92.0	0.276	0.003175	0.263
1.332	0.581	0.251	0.564	3.05	11.4	81.2	0.354	0.00557	0.331
1.35	0.580	0.582	0.570	2.12	11.4	57.0	0.362	0.00480	0.343
1.34	0.565	1.20	0.550	5.67	11.25	10.45	0.0247	0.00265	0.0140
1.25	0.568	1.14	0.554	4.45	11.2	8.90	0.0244	0.00315	0.0118
1.28	0.570	1.24	0.566	3.03	11.3	3.12	0.0133	0.00100	0.0093
1.275	0.573	1.25	0.571	2.15	11.3	1.96	0.00116	0.00093	0.00868
1.295	0.570	0.0371	0.552	7.47	11.5	97.1	0.1682	0.00963	0.1586
1.28	0.581	0.017	0.564	9.63	11.5	98.7	0.131	0.00706	0.1239

version, and corresponding points are indicated by identical symbols.

The data reported earlier (*5*) showed that there was a concentration instability in calcium hydroxide in this system. These present data show a concentration instability in formaldehyde. With this in mind, results for experiments in which the autonomic pH of reaction was forcibly varied by pumping either sodium hydroxide or formic acid into the system simultaneously with the feed calcium hydroxide and formaldehyde, are now presented. Figure 3 is a plot of total formaldehyde conversion rate as a function of combined feed molarity of either formic acid or sodium hydroxide. Formaldehyde molarity in the combined feed was fixed at 1.30 *M* and temperature and residence time were fixed at 40°C and 10 min, respectively. Figure 3 shows that excessive amounts of either formic acid or sodium hydroxide in the reactor suppressed the reaction dramatically when calcium hydroxide was used as a catalyst. The rather low total conversion rates at extremely high sodium hydroxide molarity are due mainly to the fact that Cannizzaro rather than formose reaction is favored at such extremely high pH levels.

The data on Fig. 3 are cross plotted on Fig. 4 as parameters of combined feed concentration of sodium hydroxide rather than calcium hydroxide. The $Ca(OH)_2$ concentration instability is clearly shown. In Fig. 5, pH is plotted as a function of

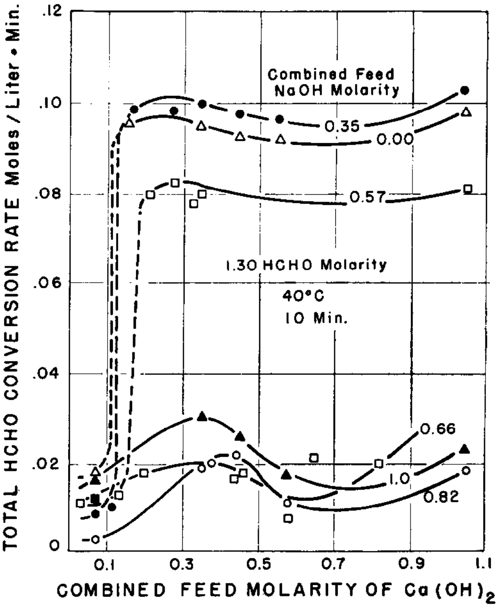


FIG. 4. The $Ca(OH)_2$ concentration instability is shown superimposed on the NaOH quenching effect.

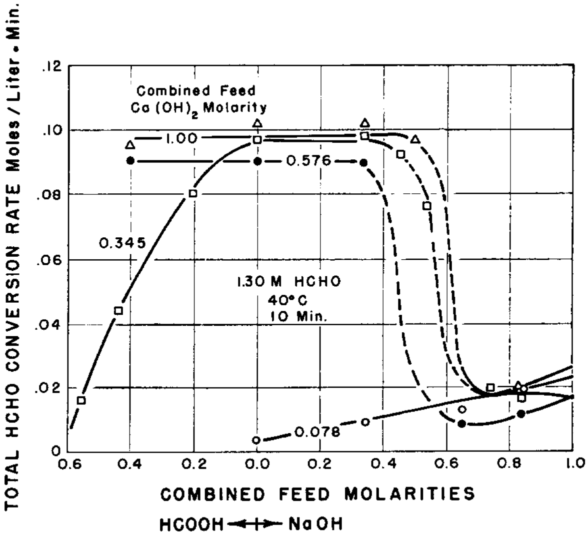


FIG. 3. Either excessive quantities of acid or base can quench the formose reaction at fixed CSTR conditions.

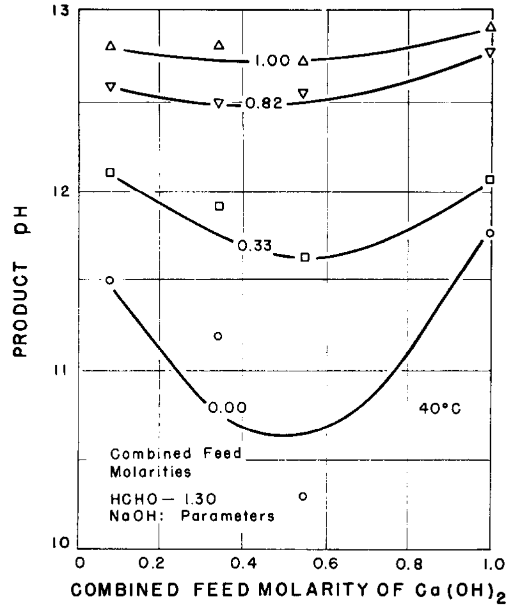


FIG. 5. pH passes through a minimum as $Ca(OH)_2$ molarity is increased.

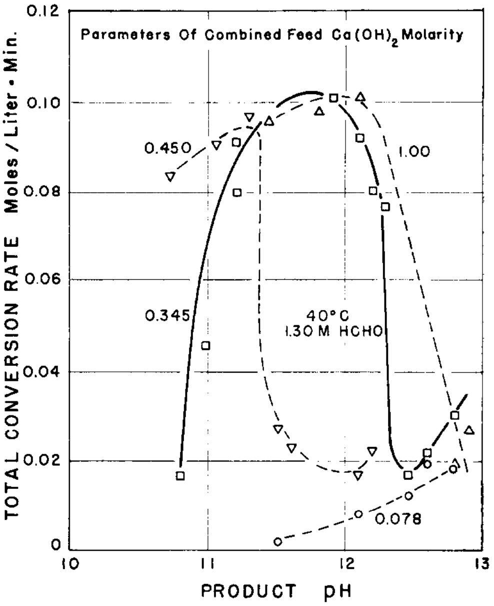


FIG. 6. The formose reaction exhibits both pH (i.e., hydroxyl ion) and $Ca(OH)_2$ instabilities.

combined feed molarity of calcium hydroxide at fixed formaldehyde combined feed concentration. The behavior of pH passing through a minimum as a function of increasing calcium hydroxide concentration is again exhibited as in the earlier work (*5*). Actually this minimum is related to the rate maximum, and this is shown in Fig. 6, which is a plot of total conversion rate versus product pH with parameters of combined feed calcium hydroxide molarity. The instability of the formose reaction as a function of pH (and hence hydroxyl ion concentration) that is shown in Fig. 6 leads to the conclusion that calcium hydroxide is not the sole species influencing the formose reaction. On the other hand, neither is hydroxyl ion, because Fig. 6 shows that the rate is clearly dependent on combined feed calcium hydroxide molarity as well as pH.

Figure 7 is a plot of all of the 1.3 *M* formaldehyde data taken at the constant condition of 40°C and 10 min space time. The points in Fig. 7 indicate the combined feed calcium hydroxide molarity which ranged from 0.08 to 1.00 in the experiments in which sodium hydroxide was added to force the product pH. All of the data fit the same form of correlation as found earlier for Cannizzaro rate (*4*, *5*). In essence, Cannizzaro rate is correlated as a function of total formaldehyde conversion rate and conclusions that are drawn for the effect of process variables on the formose reaction appear to be equally valid for the Cannizzaro reaction.

DISCUSSION OF RESULTS

While temperature instabilities in back mixed combustion reactors (e.g., Bunsen burner) have long been known, there is a paucity of data in the literature for liquid phase reactors. Root and Schmitz (*18*) claim to have reported in 1969 the first experimental results for a liquid phase reaction instability. They studied the reaction of sodium thiosulfate and hydrogen peroxide in an adiabatic loop reactor (*18*, *19*). Vejtasa and Schmitz (*20*) subsequently examined temperature instabilities of the same reaction in an adiabatic stirred reactor.

It is also only recently that it has been recognized that concentration instabilities can occur in isothermal CSTR when re-

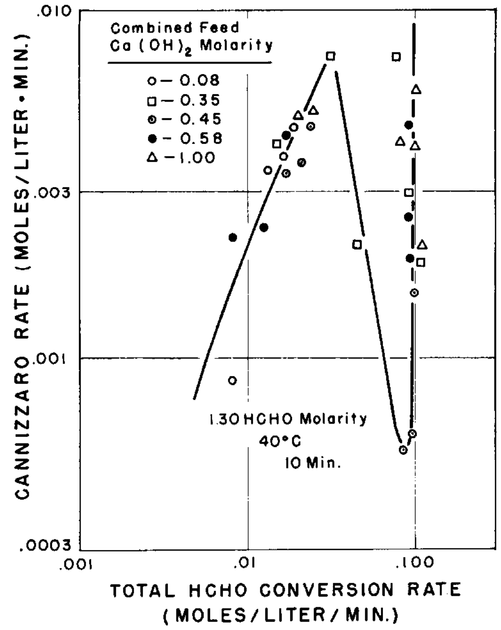


FIG. 7. Cannizzaro rate is invariably correlated to total conversion rate, even at forced pH conditions.

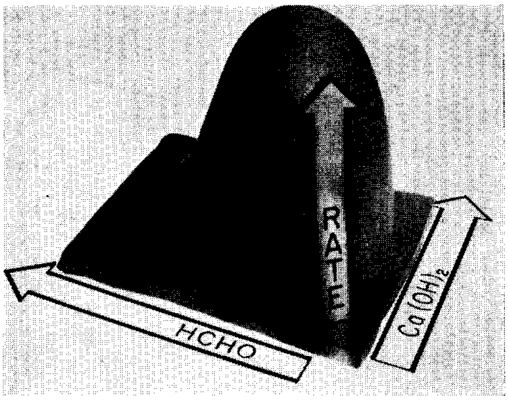


FIG. 8. Since formose rate is autocatalytic both in $Ca(OH)_2$ and in HCHO, the true phenomenological rate law must be a three-dimensional rate response surface.

actions are autocatalytic. Matsuura and Kato (*21*) developed in 1966 a mathematical analysis for this prediction [see also Perlmutter's text, "Stability of Chemical Reactors," pp. 19–24, for a derivation (*22*)]. The shape of Fig. 2 of this paper is of the form predicted by Matsuura and Kato; and except for the fact that formose is a highly complex rather than a simple autocatalytic system there is nothing in the behavior of the formose instabilities at fixed $Ca(OH)_2$ concentration that cannot be explained by Matsuura and Kato's analysis. However, since there is also an instability in calcium hydroxide concentration, a true rate law for the formose system really involves the equivalent of autocatalytic functions for both calcium hydroxide and formaldehyde. What really must exist is a three-dimensional rate response surface of the form shown on Fig. 8. Depending on whether one proceeds at constant calcium hydroxide or at constant formaldehyde concentration, one will obtain a reaction path of the form proposed by Matsuura and Kato. This three-dimensional conceptualization then suggests that there is only a finite regime in concentration space where measurable rates of formose reaction will occur.

A simple physical definition of life-like (including living) systems has been proposed by Decker (*23–26*). He has defined the term "bioid" as an open system that can mutate between several steady states. He proposes that the formose reaction is the bioid that existed under primordial conditions (CH_2O arose from the CH_4 atmosphere) that accounts for the presence of high molecular weight carbon compounds in nature. Decker studied the reaction in a CSTR at temperatures as low as 20°C, at high dilutions, and at feed rates corresponding to living systems—e.g., 1 g HCHO/day liter. He reports CSTR concentration instabilities: "The 'mutation' from the extinct state to the reacting one occurred spontaneously or after inoculation with a reacted mixture" (*26*). He also found that 0.005 *M* nitrophenol quenched the formose reaction and that the presence of sodium cyanide or sodium sulfide resulted in formose products containing nitrogen or sulfur, respectively.

O'Neill, Lilly, and Rowe (*27*) used the example of CSTR enzyme reactors operated at isothermal conditions to predict that multiple steady states can occur when Michaelis-Mentin kinetics (capable of degenerating to autocatalytic behavior at low conversion levels) apply. Horak, Jiracek, and Krausova (*28*) have published the only experimental example other than formose that we have been able to locate of a study of a concentration instability of an autocatalytic reaction in an isothermal CSTR. This is the reaction of bistrichlormethyltrisulfide with aniline in methanol at 20°C. Their data indicate similar sensitivity to adjustment of operating parameters as do the data of this present article.

The next point to consider is the dissociation of calcium hydroxide in an aqueous medium. The dissociation does not proceed in one step as below

$$Ca(OH)_2 \rightleftharpoons Ca^{2+} + 2OH^-, \qquad (2)$$

but rather in two distinct steps, first to produce a monovalent $CaOH^+$ species and then to divalent Ca^{2+} ion.

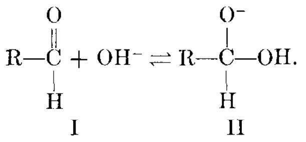
$$\begin{aligned} Ca(OH)_2 &\rightleftharpoons CaOH^+ + OH^-, \\ CaOH^+ &\rightleftharpoons Ca^{2+} + OH^-. \end{aligned} \qquad (3)$$

The experimental data presented clearly showed that reaction rate fell when pH was either too high or too low and that high Ca^{2+} concentration was not a requisite for high reaction rate. Consequenly, one can rule out both OH^- and Ca^{2+} as the active catalytic species in this reaction. However, since there is indeed a pH effect, it follows that the molecular species $Ca(OH)_2$ is not the catalytic agent. The species whose concentration is either drastically lowered or increased by either an excess or a deficiency of hydroxyl ion is $CaOH^+$. *$CaOH^+$ is the formose catalyst.* The cation $CaOH^+$ satisfies the criterion that calcium hydroxide is catalytic, and not just hydroxide. It also satisfies the known background that almost any basic material is a catalyst for formose. Being a catalyst for formose is quite apart from the requirements of being divalent, of having chelating properties, and of forming bidentate complexes with carbohydrates.

The concept that $CaOH^+$ is the catalyst provides a conceptual position to develop a simple general mechanism for Cannizzaro and formose catalysis. Consider the equation for the first dissociation of any base:

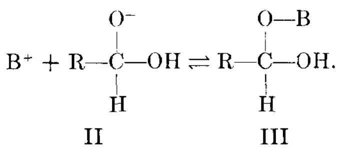
$$BOH \rightleftharpoons B^+ + OH^-. \qquad (4)$$

The anionic form II of any aldose I can form by reaction of the aldose with hydroxyl



$$\underset{\text{I}}{R-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle H}{|}}{C}}} + OH^- \rightleftharpoons \underset{\text{II}}{R-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-OH}. \qquad (5)$$

II is the intermediate form that is generally accepted in mechanisms that are written to explain Cannizzaro processes. Combining the two reaction products results in a complex (III) whose concentration is quite sensitive to the concentration of hydroxyl ion.

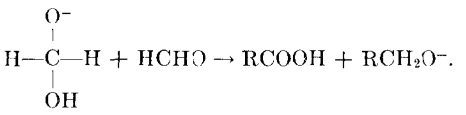


$$B^+ + \underset{\text{II}}{R-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-OH} \rightleftharpoons \underset{\text{III}}{R-\overset{\overset{\displaystyle O-B}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-OH}. \qquad (6)$$

The concentration of the complex (III) will pass through a maximum as hydroxyl ion concentration is increased. This is because the base cation B^+ is suppressed while the aldose anion is favored by increased hydroxyl ion concentration.

The quantitative experimental results that we obtain in our studies indicate invariably that Cannizzaro rate is directly correlated to total formaldehyde conversion rate. This, plus the speed of dissolution of $Ca(OH)_2$ in HCHO solutions leads us to believe that reaction (6) must be extremely fast and at equilibrium (and hence that the ratio of concentrations of II to III must be constant).

Eitel and Lock (*29*) proposed in 1939 that the Cannizzaro reaction proceeds by a hydride ion transfer process between an anionic aldose and a free aldose



$$H-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-H + HCHO \rightarrow RCOOH + RCH_2O^-. \qquad (7)$$

Cannizzaro rate is quite sensitive to the basic catalyst used. Pfeil and Schroth (*30*) reported the following series for formaldehyde as an example.

$$\mathrm{TlOH} < \mathrm{Ca(OH)_2} < \mathrm{Ba(OH)_2} < \mathrm{LiOH},\ \mathrm{NaOH}.$$

The selectivity to formose condensation decreases as that for Cannizzaro increases for each catalyst.

Since, in the formaldehyde system, both formose and Cannizzaro reaction are so intertwined, it is reasonable to consider a common mechanism for the two reactions. Let us presume that complexed and free formaldehyde can undergo hydride transfer to form an anion and a cation. As shown in Fig. 9, these can react in two directions: (a) formose condensation by a simple metathesis to form complexed glycolaldehyde and (b) Cannizzaro reaction by a proton transfer from the carbonium ion to form methanol and the formate salt of the base catalyst B. Figure 9 explains the direct relationships observed between formose and Cannizzaro rates. Both reactions proceed from a common intermediate. The selectivity of formose to Cannizzaro is a function of the cation B of the basic catalyst used. The first step of the formose condensation has previously been regarded as difficult to rationalize, but the mechanism of a simple metathesis is straightforward. A great excess of $\mathrm{Ca(OH)_2}$ would suppress free HCHO, and this would account in great part for the experimentally observed $\mathrm{Ca(OH)_2}$ concentration instability at high concentration levels. A dearth of complex would explain the catalyst instability at low $\mathrm{Ca(OH)_2}$ concentrations. [In addition to this reasoning, it should be noted that $\mathrm{Ca(OH)_2}$ is also consumed in small quantities as a reactant in the Cannizzaro process, and so should also exhibit instability on this basis, just as HCHO.]

Although the formose reaction is autocatalytic, it does initiate in the complete absence of condensation products. Fig. 9 allows for this. Our earlier data (*4*) established that only small quantities of glycolaldehyde are present in the formose products even at low conversions. This suggests that the metathesis step leading to glycolaldehyde is highly reversible, in contrast to the proton transfer to Cannizzaro prod-

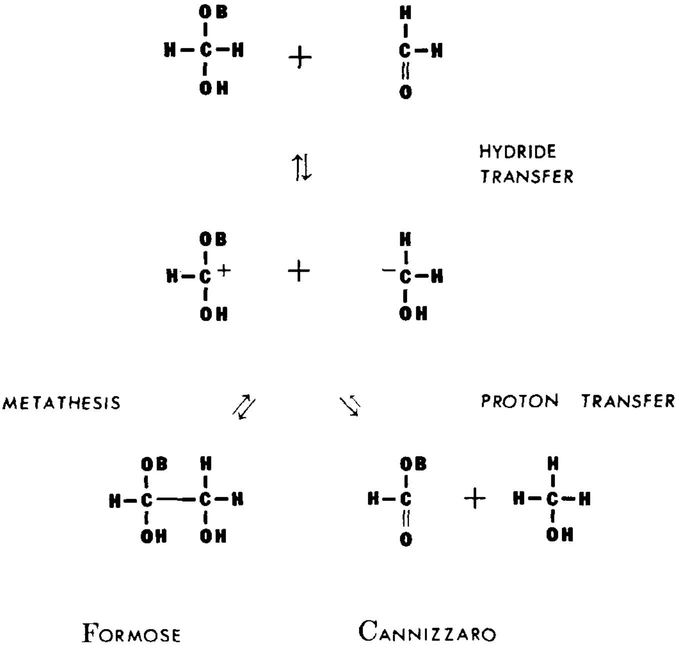


FIG. 9. Cannizzaro reaction of formaldehyde and the first step of the formose reaction proceed from a common intermediate and at relative rates that depend on the nature of the base.

ucts (which are produced practically irreversibly). This postulate is borne out by data of Pfeil and Schroth (*30*) who found that glycolaldehyde produced glyceraldehyde as well as even-numbered condensation products when it reacted in aqueous basic solution with itself.

Once complexed glycolaldehyde forms in the formose system, α-hydrogen is present, and aldol condensation to higher aldoses and ketoses can proceed. Pathways to possible products are diagrammed in (*5*). Figure 10, which is entirely analogous to Fig. 9, shows the highly favored, practically unidirectional reaction between complexed glycolaldehyde and free formaldehyde produces complexed glyceraldehyde by a hydride transfer followed by metathesis of the cations. The α-hydrogens are indicated, and Cannizzaro reaction is disfavored by their presence.

The complexed glyceraldehyde shown in Fig. 10 still has an α-hydrogen and can react once more with free formaldehyde to form complexed hydroxymethylglyceraldehyde. This exhausts the α-hydrogens, and hydroxymethylglyceraldehyde is a terminal formose product (*4*, *5*).

Figure 10 shows how aldol condensation proceeds between a complexed aldose and free formaldehyde. Figure 11 shows that if, instead, the formaldehyde is complexed and the aldose (R–CHO) free, cross-Cannizzaro reaction will occur. This occurs to only a very small extent when α-hydrogens are present, but, in their absence, cross-Cannizzaro is highly favored. For example, formose products contain both hydroxymethylglycerol and hydroxymethylglyceraldehyde (*5*).

The hydride transfer–proton transfer sequence shown in Fig. 11 accounts for the experimentally observed formation of metal formates and higher polyols in the formose system by a mechanism analogous to Fig. 9.

The overall scheme of reactions is shown in Fig. 12 for the formose aldol condensations as far as the four carbon level and for the important Cannizzaro reactions of the species with no α-hydrogens. Analogous pathways explain reactions for higher molecular weight hydrocarbons. Figure 12 shows the complexed and free state of each aldose, the aldol condensation involving addition of free formaldehyde

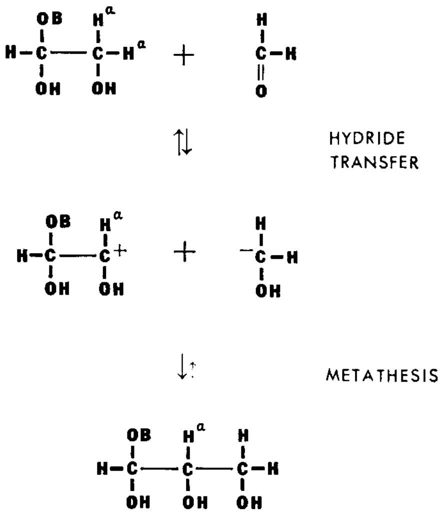


FIG. 10. *Formose* path for higher aldoses. When α-hydrogen is present reaction proceeds with *complexed aldose* and *free formaldehyde* to form a complexed aldose one carbon number higher.

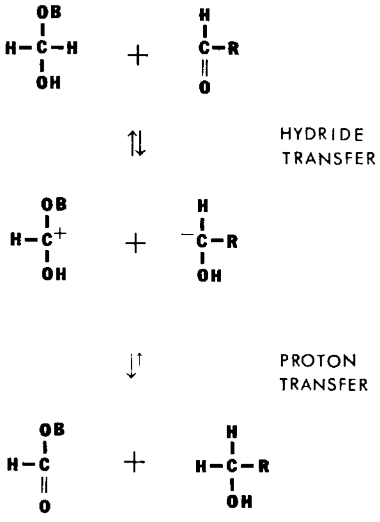


FIG. 11. *Cross-Cannizzaro* reaction proceeds with *complexed formaldehyde* and *free aldose* containing no α-hydrogen. A formate salt and a polyol are produced.

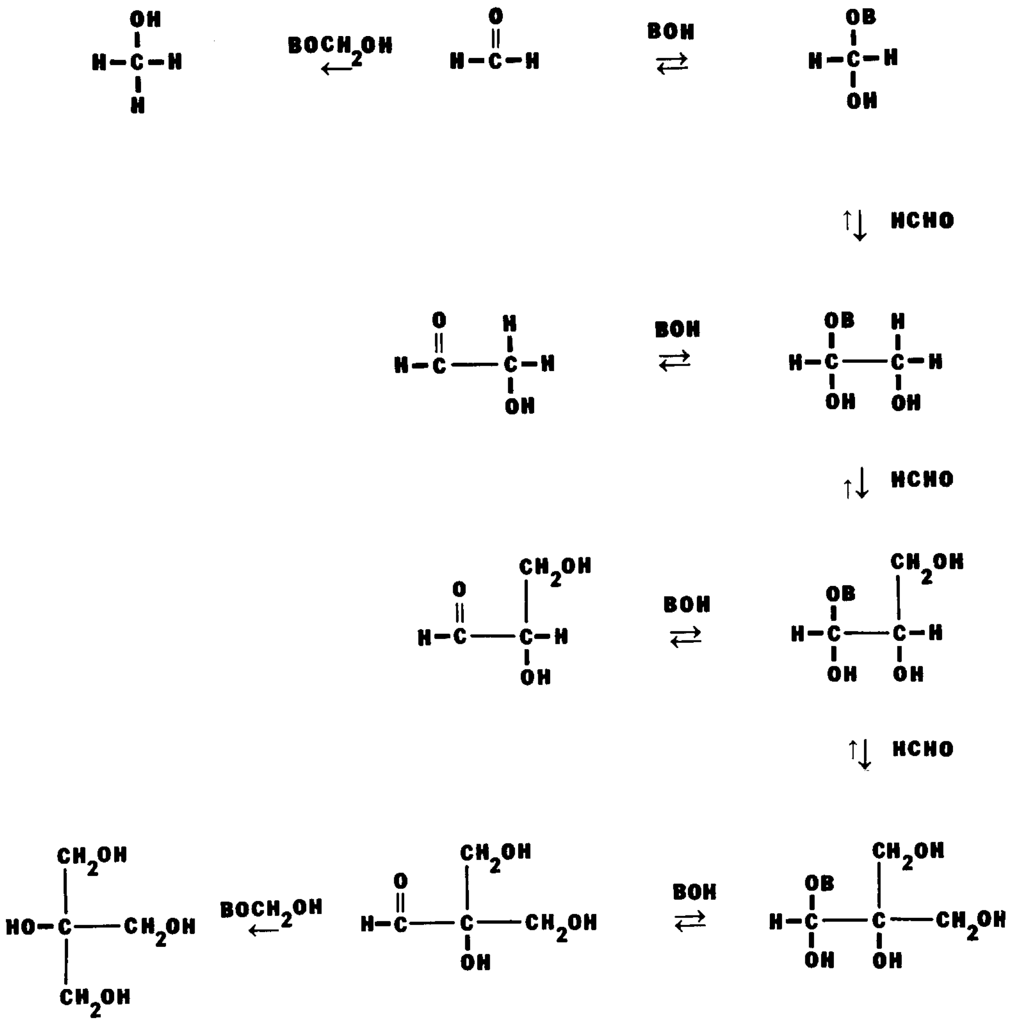


Fig. 12. Overall scheme showing major pathways of formose aldol condensation and Cannizzaro reactions. Analogous reactions proceed to form higher molecular weight species.

to complexed aldose, and the Cannizzaro reactions of complexed formaldehyde with free aldose.

Bases in aqueous solution are also catalysts for both mutarotation and Lobry de Bruyn-Van Eckenstein (L-V) transformations of sugars. We have not as yet investigated the optical isomer distributions and ketose–aldose shifts quantitatively in the formose system. The mechanism we propose, in which the carbohydrate reacting form is complexed with a base does explain these processes. Figure 13 shows the pathways for mutarotation and L-V shifts, using terminally substituted glyceraldehyde and dihydroxyacetone as the model compounds. Starting with glyceraldehyde, one can trace on Fig. 13 its pathway to the complexed form, which dehydrates to the complexed enolic species. This can either rehydrate to the optical isomer (if rotation about the double bond occurs) or can decomplex to the free anionic form of the aldose enediol. The usual mechanistic step to explain the L-V shift is then the shift of this free species to the anionic form of the ketose enediol (*31*). Once this occurs the pathways to the mutarotated complexed forms of the ketose and the free ketose proceed.

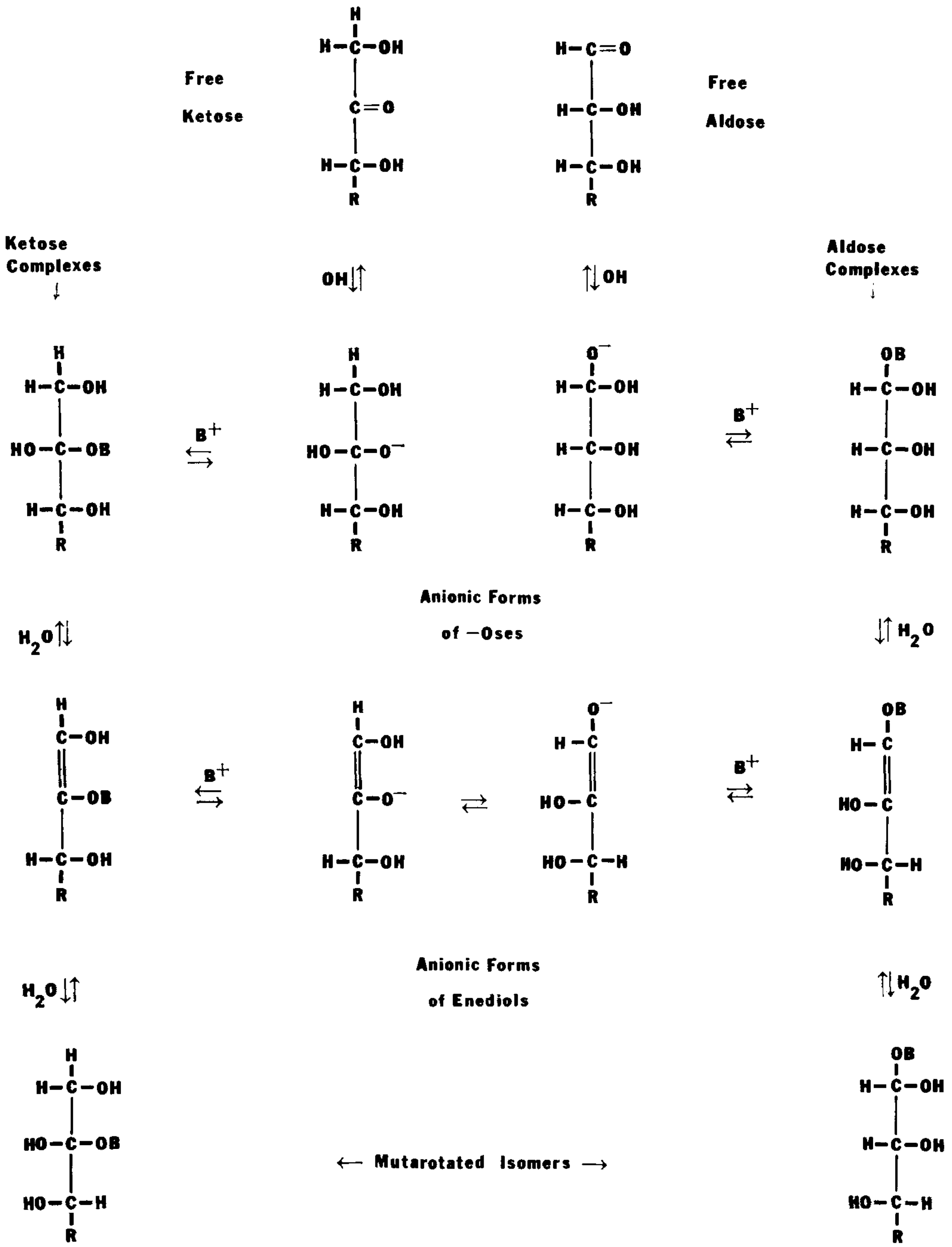


FIG. 13. Possible mechanisms proceeding via complexed species for Lobry de Bruyn-Van Eckenstein aldose-ketose isomerization and for mutarotation. The key step is dehydration of the complexed -ose to produce the complexed enediol.

CONCLUSIONS

The importance of obtaining quantitative rate data in a CSTR in this study cannot be overestimated. Otherwise, the hydroxyl ion, $Ca(OH)_2$, and HCHO instabilities that provide the basis for interpreting the observed stoichiometric and catalytic phenomena would not have been recognized. The concept of a three-dimensional reaction surface has been of great value in visualizing the effect of a change in any of the process variables. The surface's usefulness in the formose system implies that perhaps it would be useful in other autocatalytic reaction schemes.

The unifying mechanism for formose and Cannizzaro reactions has been developed using $Ca(OH)_2$ as the catalyst. We believe, but have not experimentally proven, that rates using other catalysts will show similar instability effects. Also still to be examined are the kinetics of both L-V rearrangement and of mutarotation.

It is apparent that the formose reaction is not a simple case of base catalysis, but, rather, it is a truly homogeneously catalyzed network of reaction types, each catalyzed to a unique extent by a given base. The mechanisms derived for carbohydrate reactions in this paper add to those that have been proffered in the past in that the role of the catalyst is accounted for and that the collection of important reaction pathways are considered, rather than a single reaction type.

In industrial practice, autocatalytic reactions are optimally conducted in CSTR's operating at the maximum rate of the reaction. This is exactly the regime of concentration instability, and a minor concentration or temperature change could either quench or light off a reactor operating at steady state. If such behavior has serious consequences, then it would be well to design a CSTR less optimally, so that operation proceeds outside of the region of instability. We recommend that if an autocatalytic system is to be studied in a CSTR, the experimenter should make it a general practice to test for instabilities.

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