"Study of the Techniques Feasible for Food Synthesis Aboard a Spacecraft"

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by

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ABSTRACT

Synthesis of sugars by $Ca(OH)_2$ catalyzed formaldehyde condensation (the formose reaction) has produced branched carbohydrates that do not occur in nature (as well as straight chain aldoses and ketoses). The kinetics and mechanisms of the homogeneously catalyzed autocatalytic condensation were studied and analogies between homogeneous and heterogeneous rate laws have been found. Aldol condensations proceed simultaneously with Cannizzaro and crossed-Cannizzaro reactions and Lobry de Bruyn-Van Eckenstein rearrangements. The separate steps as well as the interactions of this highly complex reaction system were elucidated. The system exhibits instabilities, competitive catalytic, mass action, and equilibrium phenomena, complexing, and parallel and consecutive reactions.

Specific findings that have been made on the problem will be of interest for synthesizing sugars, both for sustained space flight and for large scale food manufacture. A contribution to methodology for studying complex catalyzed reactions and to understanding control of reaction selectivity was a broad goal of the project.

Introduction

This Final Report covers a wide range of technology divided into four areas: 1. The Formose Reaction, 2. The Cannizzaro Reaction, 3. Branched Carbohydrate Products, 4. Selectivity Control. The areas of the research are interrelated but nevertheless distinct. Technical details of research in each topic are developed. These discussions are then followed by a discussion of the Overall Research Project which gathers the various topics and provides an overview of how the project was approached and what was learned.

The Formose Reaction

The homogeneously catalyzed formose reaction is the autocatalytic condensation in the presence of alkaline catalysts of formaldehyde to a complex carbohydrate mixture, first reported by Butlerow (1) in 1861. The formaldehyde condensation reaction is catalyzed both by divalent metal bases such as $Ca(OH)_2$, $Ba(OH)_2$, $Sr(OH)_2$, $Mg(OH)_2$ and $Pb(OH)_2$ as well as by monovalent bases such as KOH, NaOH and TlOH (2). Krylov and others (3,4) have recently shown that tri- and tetravalent bases such as $Dy(OH)_3$, $Er(OH)_3$, $Eu(OH)_3$, $Sm(OH)_3$, Ce(OH) and $Th(OH)_4$ catalyze the formose condensation reaction. Organic bases such as pyridine, collidine, and α-, β-, γ-picoline also are catalysts (2).

Glycolaldehyde (CH_2OHCHO) has been reported (5,6) to be the primary reaction product. Studies by Katschmann (7) suggest a dual process for autocatalytic reaction in which the slow primary formation of glycolaldehyde is followed by rapid condensation and formaldehyde addition reactions. Franzen and Hauck (8) proposed that complexing of formaldehyde with $Ca(OH)_2$ might occur to produce a complex salt $HOCH_2OCaOH$. Weiss, et al. (9,10) observed complexing in a study at 60°C of the $Ca(OH)_2$ catalyzed reaction and proposed a mechanism involving decomplexing of products as the rate limiting step. The mechanism proposed is analogous to a Langmuir-Hinshelwood mechanism for a heterogeneously catalyzed reaction, in which a semantic substitution of "complexing-decomplexing" for adsorption-desorption" was made.

The rate law developed explained in its degeneracies the observed 60°C experimental behavior of the $Ca(OH)_2$ catalyzed formose reaction:

Autocatalytic at low conversions

Zero order in organics at intermediate conversions

First order in formaldehyde at high conversions and a suggestion was made that this type of analysis may be applicable to other autocatalytic homogeneously catalyzed reactions. It is not a requisite that the rate limiting step of a homogeneously catalyzed reaction be the reaction step itself.

In our earlier study (9) when formaldehyde conversion rate approached the feed rate of formaldehyde to the reactor, experimentation was terminated (since reaction rate in a CSTR cannot exceed the feed rate to the CSTR). Since then, we have made experiments at higher reaction severities, i.e., past the $Ca(OH)_2$ catalyst concentration levels that were required for complete HCHO conversion. Isothermal experiments were made at constant formaldehyde feed rate while $Ca(OH)_2$ molarity in the combined feed was progressively increased.

Figure 1, which is a plot of formose rate versus $Ca(OH)_2$ concentration in the reactor (and, hence, in the product stream) shows that at 0.4 molar $Ca(OH)_2$ and at temperatures of 30°C and 40°C, an unexpected decrease in rate with increasing catalyst concentration was obtained. At 60°C, the decrease in reactivity was observed to a marked extent, but at very high $Ca(OH)_2$ concentration - 1.3 molar. Data tabulated below comparing formaldehyde and $Ca(OH)_2$ molarities suggest that, at these high catalyst concentrations, formaldehyde could be isolated in complexes with $Ca(OH)_2$ so separated that there may be a low probability of one complex interacting with another.

Reaction temp. (°C)	HCHO feed rate (moles/liter/ min.)	$Ca(OH)_2$ conc. in combined feed (moles/liter)	HCHO conc. in combined feed (moles/liter)
30	0.0325	0.4916	0.248
40	0.0325	0.54	0.166

At very low formaldehyde conversion, mainly Cannizzaro reaction occurs. The table below compares the formaldehyde disappearance rate by Cannizzaro reaction and by formose reaction at typical low HCHO conversion operation.

Reaction temp. (°C)	HCHO feed rate (moles/l/min)	$Ca(OH)_2$ conc. (moles/liter)	HCHO disappearance rate (mol/liter/minute)	
			By Cannizzaro	By Formose
40	0.135	0.0968	0.002	0.0013
30	0.325	0.355	0.0012	0.0004

The reaction system exhibits two concentration instabilities: for a small difference in $Ca(OH)_2$ catalyst concentration there is a large difference in formose reaction rate. Figure 1 shows that the instabilities occur both at low and at high catalyst concentration at 40°C. These instabilities are also seen on the low side at 60°C, on the high side at 30°C. Catalyst concentration instabilities of this nature are not known by us to have been reported before for any system, let alone for the formose system. Matsura and Kato (11) point out that reactant concentration instabilities are possible for autocatalytic CSTR reactions.

Figure 1 also shows the line approximating the zero order behavior of formose rate (in formaldehyde and product concentrations) at intermediate conversion levels. The line is taken from the earlier correlation (9) at 60°C. At that time data points at very low conversion levels were recognized as points scattered from the zero order correlation but not as indicators of an instability.

The nature of the catalyst concentration instabilities needs to be explained. We still have work in progress in which we are deliberately attempting to operate our isothermal CSTR in metastable $Ca(OH)_2$ concentration regions to cause reflections to high or low stable conversion levels. Our goal is to document and verify the instabilities shown on

Formose Instabilities And Maxima

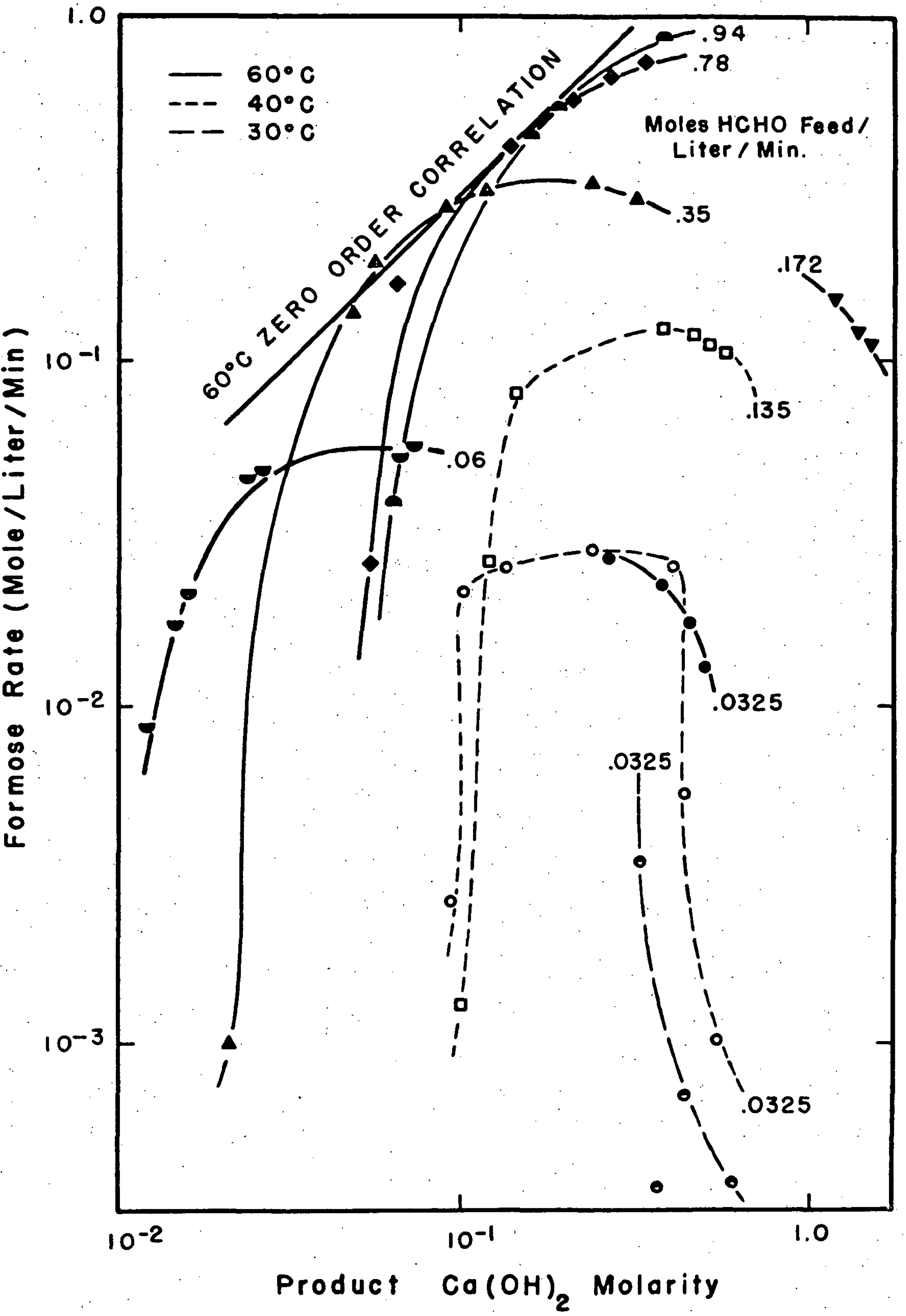


Figure 1

Figure 1 to demonstrate if there are multisteady states and to develop both mathematical and mechanistic models.

We have not yet found results that refute the Langmuir Hinshelwood kinetics we reported in the Journal of Catalysis (9); and we are still intrigued by the fact that we were able to explain homogeneous kinetics by heterogeneous rate laws. The least understood step of the formose reaction is the very first step - the condensation of two molecules of formaldehyde to glycolaldehyde. A satisfactory understanding of both this step and the very nature of the $Ca(OH)_2$ complex still needs to be achieved.

The Cannizzaro Reaction

In the process of the formose reaction, the Cannizzaro reaction occurs simultaneously with the condensation of HCHO to aldoses and ketoses. The Cannizzaro reaction takes place with aldehyde molecules having no hydrogen on the ∝-carbon atom (that adjacent to the -CHO group) and with HCHO (12)

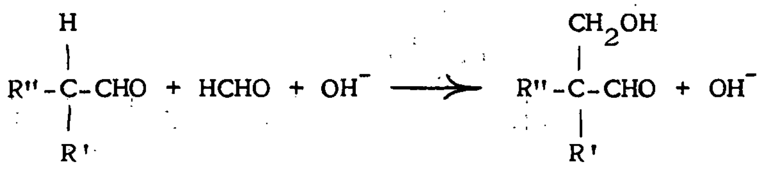
$$2RCHO + OH^- \longrightarrow ROH + RCOO^- \qquad (1)$$

$$2HCHO + OH^- \longrightarrow CH_3OH + HCOO^- \qquad (2)$$

Aldehydes with no ∝-hydrogen atoms can also undergo cross-Cannizzaro reactions in the presence of both HCHO and alkali.

$$RCHO + HCHO + OH^- \longrightarrow RCH_2OH + HCOO^- \qquad (3)$$

Aldehydes having ∝-hydrogen atoms undergo aldol condensation (HCHO addition) reactions in the presence of formaldehyde, until ∝-hydrogens are removed.

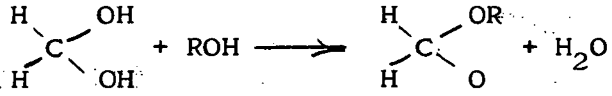


$$R''\text{-}\underset{R'}{\overset{H}{C}}\text{-}CHO + HCHO + OH^- \longrightarrow R''\text{-}\underset{R'}{\overset{CH_2OH}{C}}\text{-}CHO + OH^- \qquad (4)$$

According to Pfeil and Schroth (13), the extent of the Cannizzaro reaction occurring in the formose system varies with different basic catalysts in the following order

$$TlOH < Ca(OH)_2 < Ba(OH)_2 < LiOH, NaOH$$

Cupit (14) has shown that alcohols influence the rate of the Cannizzaro reaction both by providing a medium of lower dielectric constant and by chemical inhibition resulting from hemiacetal formation with methylene glycol

 (5)

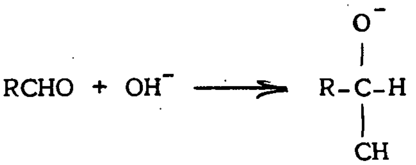
According to Cupit, the degree of chemical inhibition per mole of added alcohol is in the order

glycerol > methanol > ethanol > n-propanol

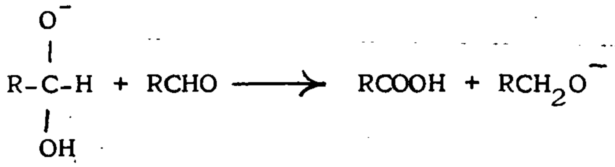
Ingold (15) discusses the mechanism of the Cannizzaro reaction that was suggested by Hammett (16). Aldehyde, by interaction with OH^-, can produce two reducing anions, the first more easily than the second.

$$\begin{array}{c} O^- \\ | \\ R-C-H \\ | \\ OH \end{array} \qquad \begin{array}{c} O^- \\ | \\ R-C-H \\ | \\ O^- \end{array}$$

Either of these can transfer a hydride ion in bimolecular fashion to a suitable acceptor, in particular to a carbonyl carbon atom of another aldehyde molecule. Geissman (12) published a review of Cannizzaro literature that includes the mechanisms proposed by Lock (17) and March (18) which are in accord with a hydride ion transfer process.

 (6)

$$RCHO + OH^- \longrightarrow \begin{array}{c} O^- \\ | \\ R-C-H \\ | \\ CH \end{array}$$



$$R\text{-}\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}\text{-}H + RCHO \longrightarrow RCOOH + RCH_2O^- \qquad (7)$$

It was predicted on the basis of these mechanisms (9) and shown that, at 60°C and low formaldehyde conversion levels in a continuous stirred tank reactor, the kinetics of the Cannizzaro reaction of formaldehyde with $Ca(OH)_2$ is first order with respect to both HCHO and $Ca(OH)_2$. This was also shown by Ackerlof and Mitchell (19) in batch studies. We also studied in our earlier paper the variation of Cannizzaro reaction with formaldehyde conversion at 60°C (9), and found that the Cannizzaro rate passed through a maximum at intermediate conversion levels, then decreased with increase in conversion. Near 85% conversion, it passed through minimum and then increased sharply beyond 90% formaldehyde conversion levels. The behavior was explained and it was predicted that maximum Cannizzaro rate should occur near 50% HCHO conversion.

Cannizzaro effects in the $Ca(OH)_2$ catalyzed formose reaction are dependent on both the formaldehyde concentration and on the conversion level. Plots of Cannizzaro rate* versus total formaldehyde conversion rate, with parameters of HCHO feed rate and temperature (over a wider range than reported in (9)) are given in Figure 2. Note that total formaldehyde conversion rate equals formose rate plus 4 x Cannizzaro rate; and this line is shown on Figure 2. Figure 2 shows that Cannizzaro rate passes through a maximum near our predicted 50% conversion level over remarkably wide ranges.

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*Cannizzaro rate is defined as the rate of $Ca(OH)_2$ consumption in the reaction: $Ca(OH)_2 + 4HCHO \rightarrow 2CH_3OH + Ca(OOCH)_2$.

Cannizzaro reaction rate is plotted as a function of $Ca(OH)_2$ concentration in the product on Figure 3. Parameters of constant formaldehyde feed rate and temperatures of 30°, 40°, and 60°C are shown. The data relationships on Figure 3 are quite complex, but, the plots do indicate a rough similarity in form to those for the formose reaction shown on Figure 1. For example: a rate maximum at 40°C and high and low $Ca(OH)_2$ concentration instabilities. Cannizzaro reaction rate appeared first order in both $Ca(OH)_2$ and formaldehyde at $<$10% HCHO conversion and 60°C (9), but Figure 3 shows the limited regimes of utility of such a relationship.

Figure 4 is a plot of pH of the reaction versus $Ca(OH)_2$ concentration in the reactor at 40°C. pH decreases with increased $Ca(OH)_2$ concentration, reaches a minimum, and increases with further increase in $Ca(OH)_2$ concentration. The behavior mirrors the Cannizzaro rate and reflects the formation of acid products by Cannizzaro reaction.

Measured calcium ion activity at 40°C versus $Ca(OH)_2$ concentration in the reactor is plotted on Figure 5. There is a correlative behavior with Cannizzaro rate. The solubility of $Ca(OH)_2$ at 40°C is indicated on the Figure 5. Calcium activity of the reaction lies well below the solubility line, reflecting the fact that the calcium is complexed. This has been reported by Rendleman (20).

Further information on the peculiar and complex Cannizzaro kinetics of formaldehyde will result as a matter of course from the formose studies currently in progress. The cross-Cannizzaro reaction influences whether condensation products are aldoses or polyols.

Experiments are currently in progress in which the pH of the reaction is forced, rather than being allowed to seek its own level. At fixed HCHO

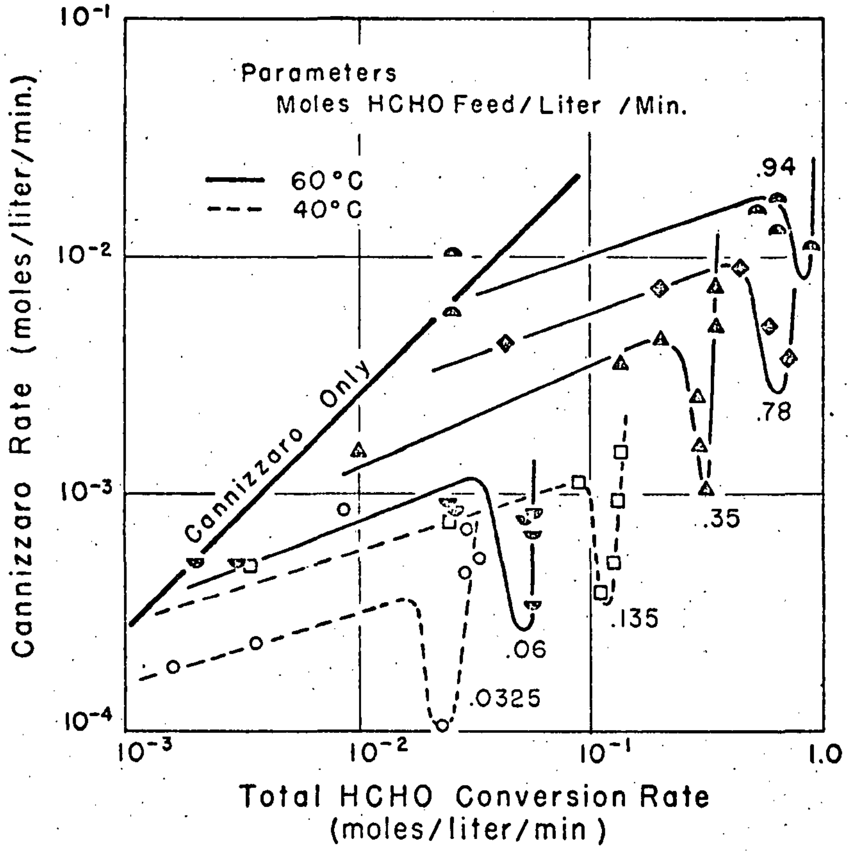


Figure 2.

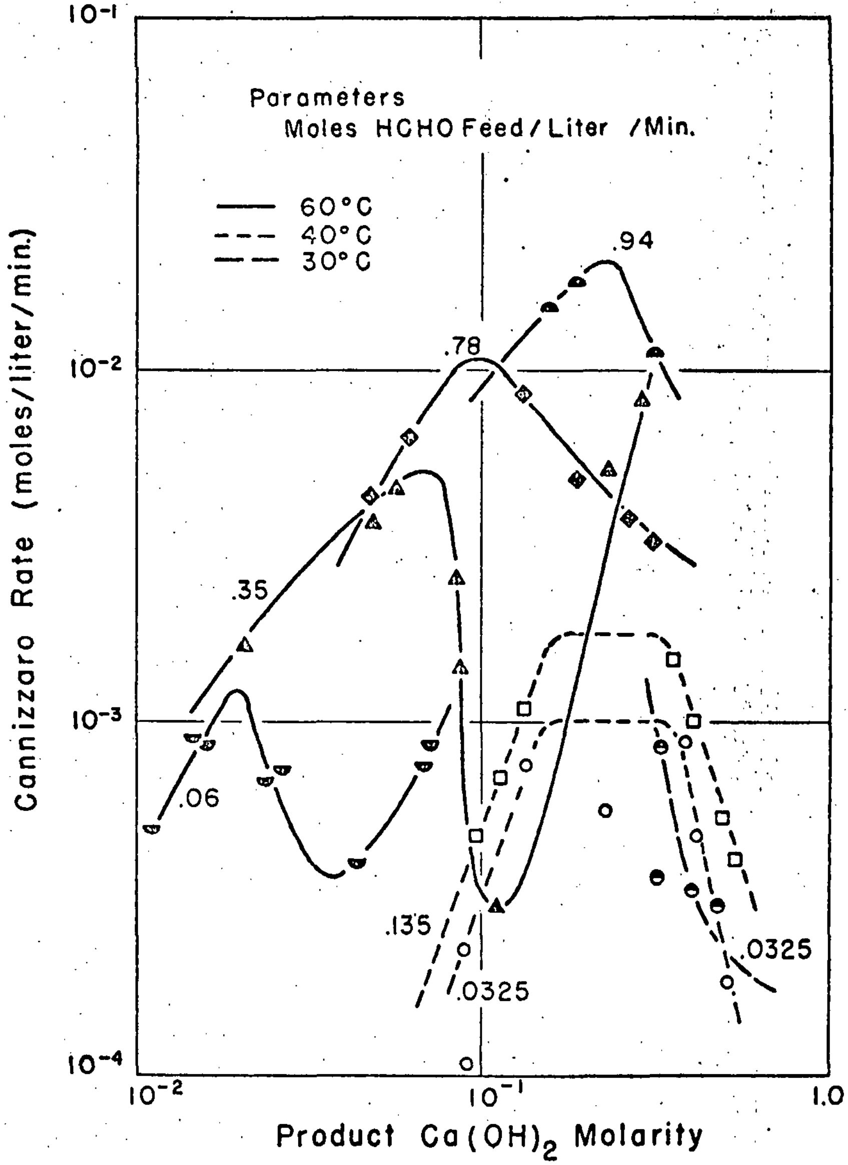


Figure 3

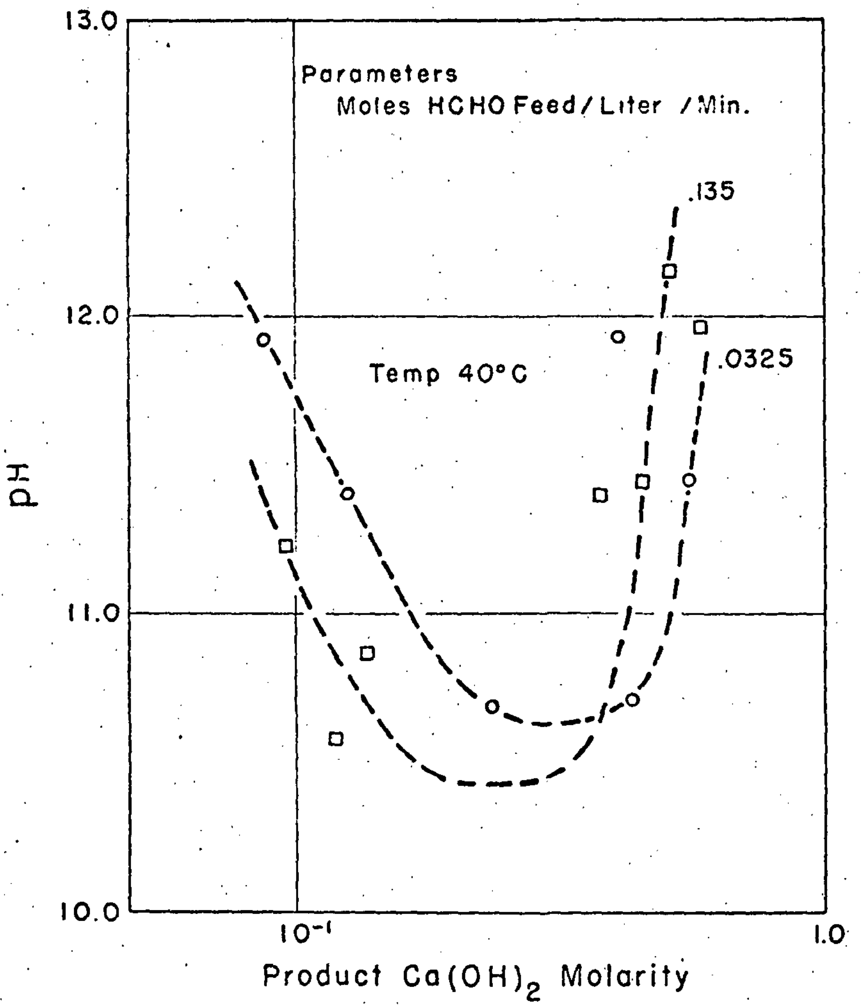


Figure 4

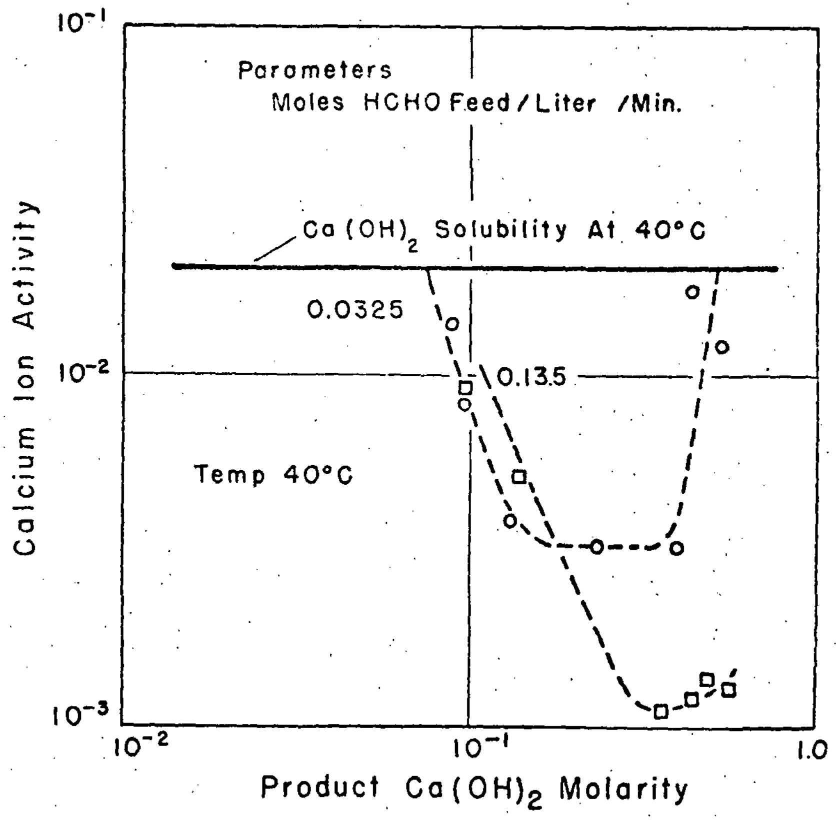


Figure 5

and $Ca(OH)_2$ feed rates, controlled feed rates of formic acid or NaOH are being pumped into the system. pH's higher or lower than the autonomic are being found to profoundly influence reaction rates and instabilities. We have not yet gathered sufficient data to interpret results and product distribution analyses are being made.

<u>Branched Carbohydrate Products</u>

Formose product is a complex mixture of aldose and ketose sugars ranging from the two carbon glycolaldehyde through three, four, five, six and seven carbon and even heavier, species. Both straight and branched chain carbohydrates are produced, and the mixture contains such a variety of structures that one might regard formose sugar as a carbohydrate analogue of petroleum.

The general reaction, to give straight chain aldoses, is

$$(n+2)HCHO \xrightarrow{Ca(OH)_2} HOCH_2(CHOH)_nCHO$$

The condensation to sugars occurs simultaneously with the competing simple Cannizzaro reaction of formaldehyde; the latter is the sole observable <u>initial</u> reaction when NaOH or LiOH are used:

$$NaOH + 2HCHO \longrightarrow NaOOCH + CH_3OH$$

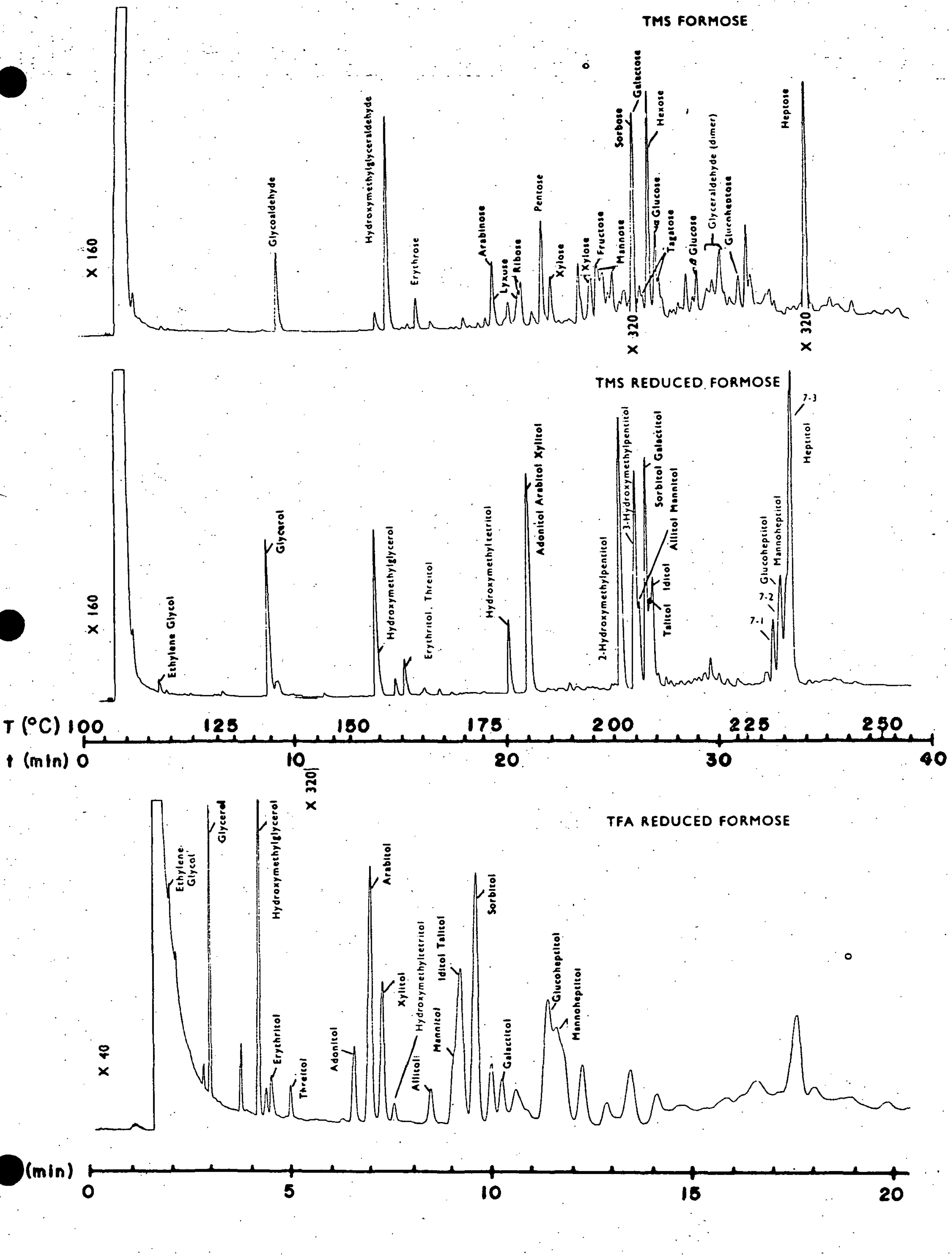
Reviews of the chemistry of the formose reaction have been published recently by Akerlof and Mitchell (19) and by Frankenfield (21). Their work was carried out mainly for the purpose of ascertaining the possibility of using the formose reaction to produce edible carbohydrates in sustained space flights. Metabolic body wastes as CO_2 would be hydrogenated to methane, this partially oxidized to formaldehyde and the latter converted to formose sugar. Akerlof (22) and Shapira (23) provide studies that show the complex formose sugar is toxic, and interest from a space travel feeding point of view has been directed to using the formose reaction, coupled to a reductive step, to produce glycerol rather than sugars. Johnson, et al. (24) have shown that humans can get at least 20-25% of their daily energy requirement from dietary glycerol, and more recent work (23) has shown this value is at least 50%. This goal was the basis for the support of our research by NASA.

There has also been major Soviet interest in the utilization of the formose reaction (25). The potential of the formose reaction for large scale sugar manufacture has been considered (10), and the mechanism and kinetics of the reaction have been studied (9).

The chromatogram on Figure 6 shows the complex product distribution of TMS derivatives of formose sugars. Figure 6 also shows greatly simplified chromatograms, obtained by reduction of the formose to the corresponding sugar polyols. The branched polyol species are resolved from the straight chain components as the TMS derivatives. Better resolution of the straight chain species is accomplished using the TFA polyols. However, there is incomplete separation of the branched from the straight chain polyol species as the TFA derivatives.

The mass spectra of the TMS polyols show fragmentation patterns resulting primarily from simple cleavage of the molecule with a minimum of rearrangements. The fragmentation of the molecular ion seems to start with the splitting off of a trimethylsilyloxy radical, m/e 89, followed by molecules of trimethylsilanol, m/e 90, in a manner similar to that of the trifluoreoacetates (26). Major fragments at m/e 147 and m/e 191 have been found in all TMS derivatives reported to date and are explained by rearrangement (27). A base peak of m/e 73 can be explained by the

Figure 6


TMS FORMOSE
X 160
Glycoaldehyde
Hydroxymethylglyceraldehyde
Erythrose
Arabinose
Lyxose
Ribose
Pentose
Xylose
Xylose
Fructose
Mannose
Sorbose
Galactose
Hexose
α Glucose
Tagatose
β Glucose
Glyceraldehyde (dimer)
Glucoheptose
Heptose
X 320
X 320
TMS REDUCED FORMOSE
X 160
Ethylene Glycol
Glycerol
Hydroxymethylglycerol
Erythritol, Threitol
Hydroxymethyltetritol
Adonitol Arabitol Xylitol
2-Hydroxymethylpentitol
3-Hydroxymethylpentitol
Sorbitol Galactitol
Allitol Mannitol
Iditol
Talitol
Glucoheptitol
Mannoheptitol
7-1
7-2
7-3
Heptitol
T (°C) 100
125
150
175
200
225
250
t (min) 0
10
20
30
40
X 320
TFA REDUCED FORMOSE
X 40
Ethylene Glycol
Glycerol
Hydroxymethylglycerol
Erythritol
Threitol
Adonitol
Arabitol
Xylitol
Hydroxymethyltetritol
Allitol
Mannitol
Iditol Talitol
Sorbitol
Galactitol
Glucoheptitol
Mannoheptitol
(min)
0
5
10
15
20

loss of formaldehyde from the m/e 103 fragment (27). Molecular ions were observed only with the TMS tetritols.

The mass spectra (of both the TMS and TFA derivatives) of diastereomeric straight chain polyols coincide within the limits of error. The mass spectra of branched polyols differ from those of straight chain species in the relative intensities of tertiary versus secondary fragments.

Figure 7 reproduces the analysis of the four-carbon region of the TMS reduced formose; and shows possible polyol structures and their fragmentation patterns. There are three possible four-carbon sugar polyol structures: one branched and two diastereomeric straight chain forms. The chromatogram of the TMS reduced formose shows the presence of three peaks in this region. The last peak of the formose chromatogram corresponded in retention time to both TMS erythritol and TMS threitol. The mass spectrum of this peak matched that of both TMS erythritol and TMS threitol, where both the erythritol and threitol derivatives gave identical spectra. The first two peaks then remained to be identified.

The branched tetritol, hydroxymethylglycerol*, was synthesized by diazotization of tris-(hydroxymethyl)-aminomethane (Tris). The total crude product that resulted from this synthesis gave the three TMS peaks shown in Figure 7. The peak identified as hydroxymethyl glycerol of the TMS tris products corresponded identically in retention time to the peak for that compound in the formose tetritol region - a comparison of the mass spectra of these two species on Figure 7 shows that they are

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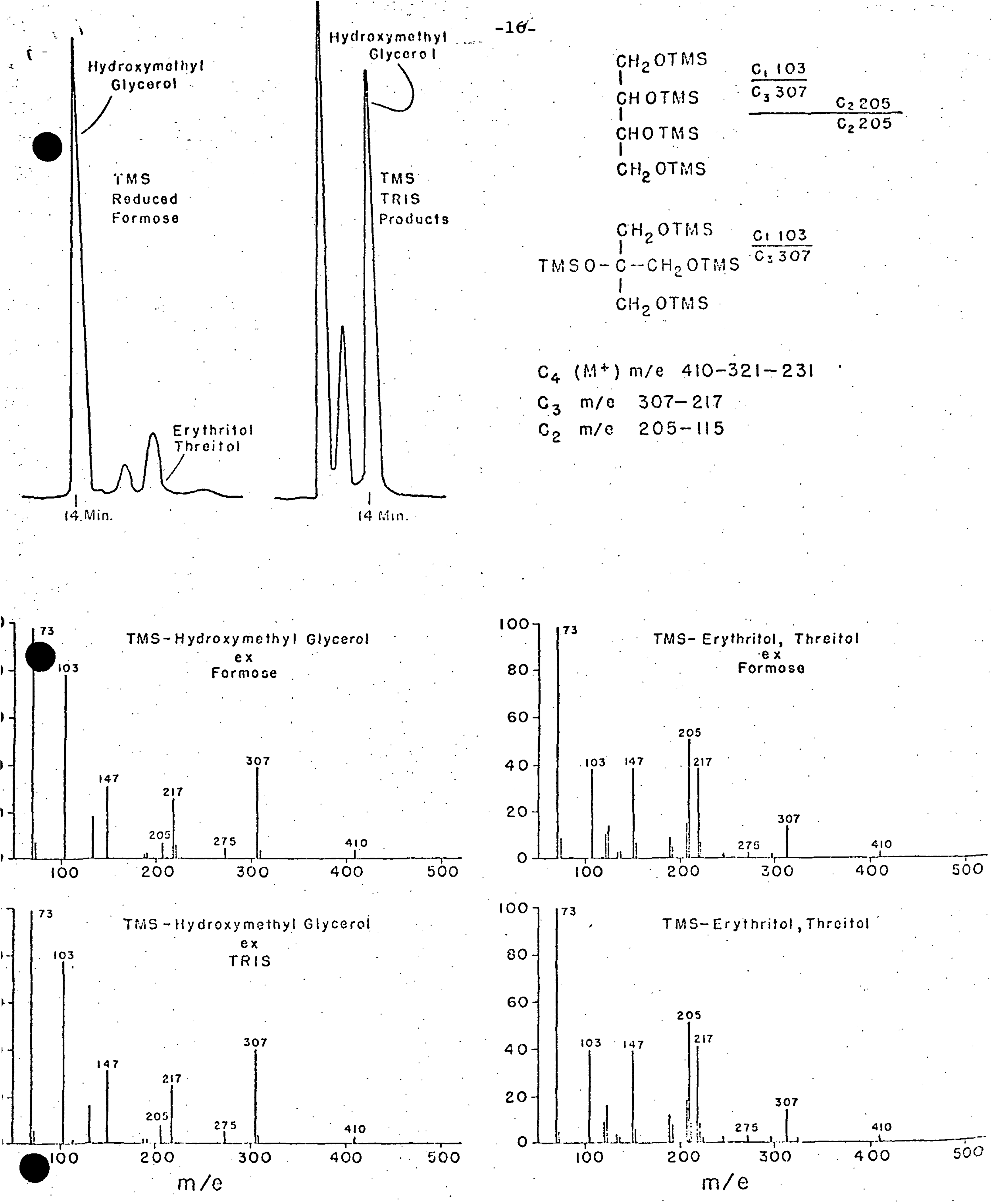
*A preparation of this compound characterized by a carbon-hydrogen analysis has been reported by Hearne and DeJong(28). The triacetate, trisacetoxymethyl-methanol, has been reported in a patent (29).



C_4 (M^+) m/e 410–321–231

C_3 m/e 307–217

C_2 m/e 205–115

Figure 7

identical. The presence of a molecular ion at m/e 410 suggests that the first formose peak - which cannot be a straight chain tetritol - is branched tetritol. The mass spectrum of TMS hydroxymethylglycerol shows a low relative abundance of m/e 205 and a high relative abundance of m/e 307 when compared with the spectra of the straight chain TMS tetritols, indicative of fragmentation from the branched species. The structure of the branched TMS tetritol indicates that there can be no direct formation of m/e 205 by cleavage. Cleavage at C_1 does result in a very stable tertiary fragment at m/e 307. The structures of the straight chain TMS tetritols indicate the formation of m/e 205 proceeds by cleavage at C_2 and of m/e 307 by cleavage at C_1. The lower abundance of m/e 307 in the case of the straight chain structures is due to its lower stability compared to the tertiary fragment from the branched species.

Using similar techniques (31) we have also elucidated the structures of 5,6 and 7 carbon branched carbohydrate compounds produced in the formose reaction. Figure 8 compares hydroxymethylglyceraldehyde formose with authentic erythrose. The mass spectrum fragmentation pattern of TMS hydroxymethylglyceraldehyde provides conclusive evidence of the formation of hydroxymethylglyceraldehyde in the formose reaction and spectra of branched chain polyols derived from formose permit inference of the skeletal branched structure of the parent aldoses and ketoses.

The formose reaction can be considered as a unique method for producing branched chain carbohydrates. The presence of these species may account for the observed toxicity of formose syrups.

Although tests of the product of $Ca(OH)_2$ catalyzed formaldehyde condensation show the presence of small amounts of many known sugars, the present study indicates that the major products of carbon number 4 through 6 are branched chain aldoses and ketoses. Significant proportions of higher molecular weight sugars are also suspected to be branched-chain.

While many known sugars have previously been identified as components of formose, apparently the finding of branched sugars in the course of our work is new.

To what degree the toxicity of formose is due to the L-forms (presumably not easily metabolized because of enzyme specificity) of sugars present, and to what degree it is due to the unnatural branched sugars present, remains to be seen.

Figure 9 shows an attempt that was made to help simplify the interpretations of the mass spectra taken. The top chromatogram of the figure is the normal flame ionization chromatogram of TMS formose. Simultaneously, a "mass" chromatogram was obtained by setting the mass spectrometer to monitor a single ion and by recording the intensity of this ion versus time. Two masses, m/e 204 and m/e 217 were followed in this manner. Greater response of the mass spectrometer for m/e 217 over m/e 204 provides an empirical test to recognize a branched carbohydrate.

Simple compounds such as hydroxymethylglycerol and hydroxymethylglyceraldehyde are not reported in the literature, let alone the higher carbon number species.

We believe that the properties and preparation methods for branched carbohydrates will be of considerable utility for and interest to carbohydrate, food, and organic chemists. Formose is highly toxic. Parsley contains apiose, and a high level of toxicity for parsley has been reported (32)(and ascribed to apiole). Perhaps other common foods with some level of toxicity also contain branched carbohydrates.

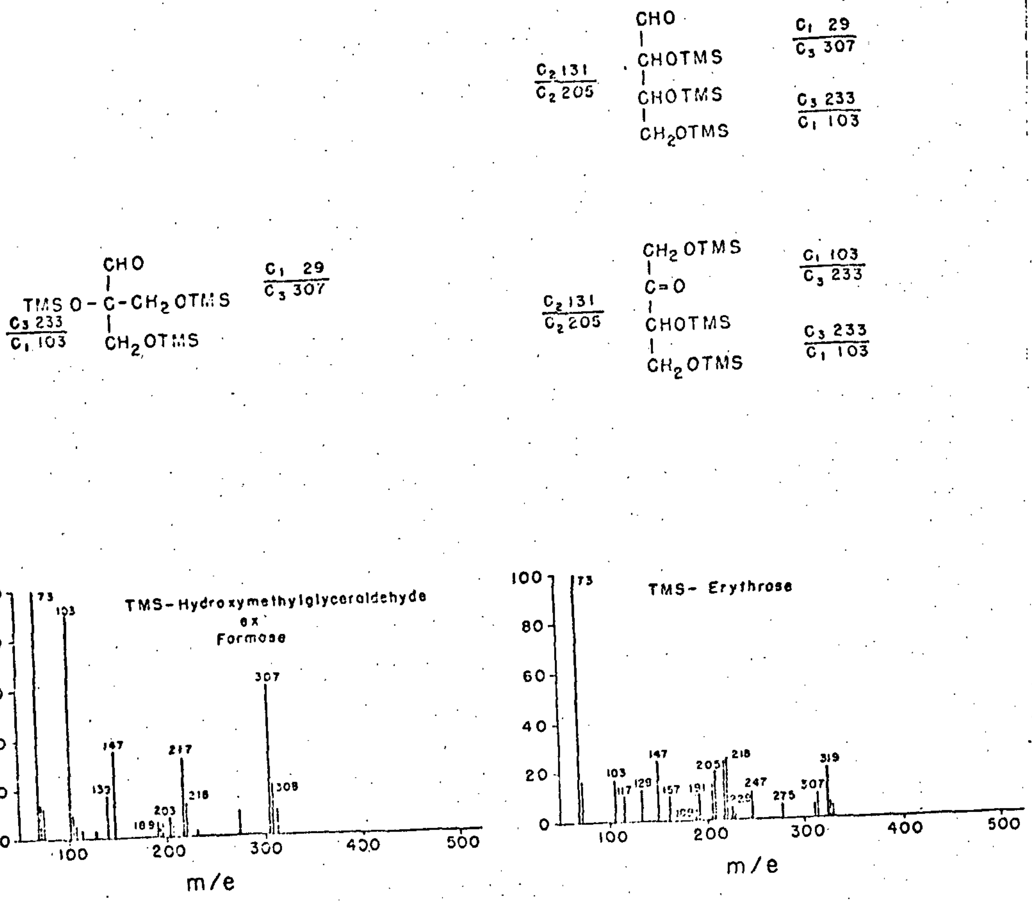


Fig 8

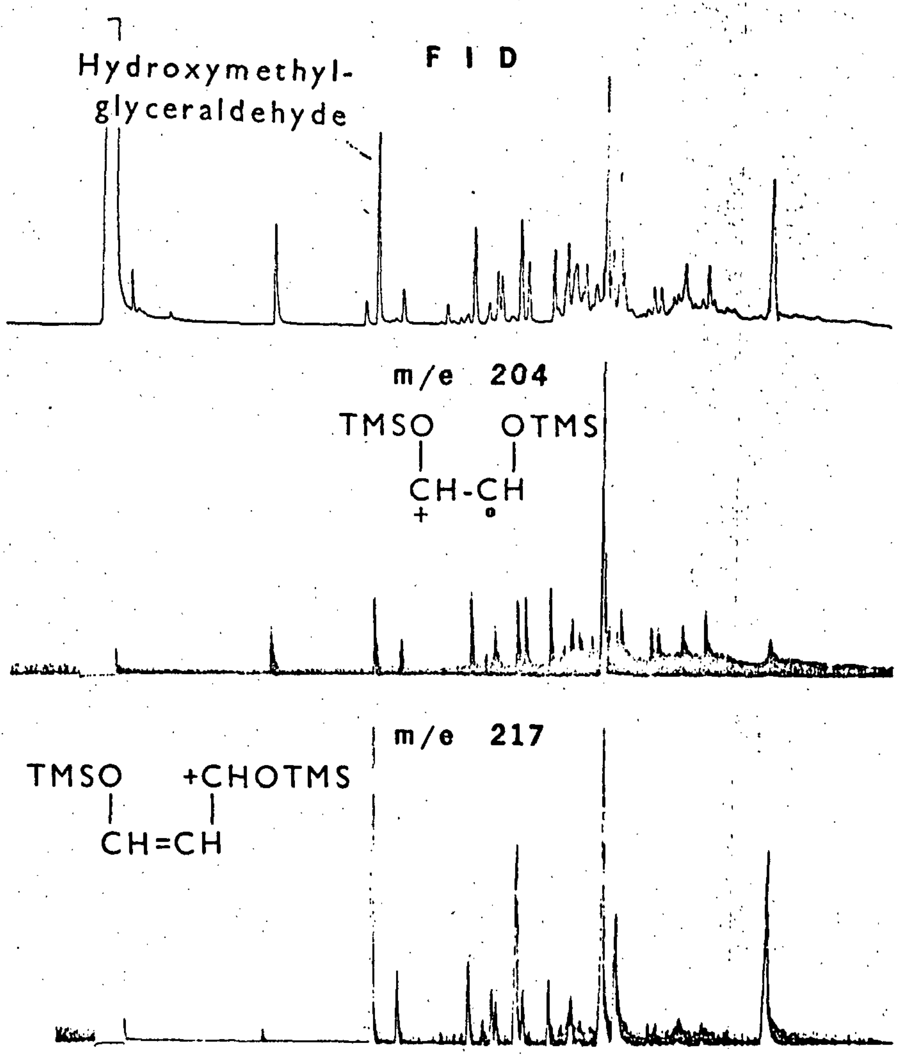


Figure 9

Selectivity Control

Products from the CSTR experiments at 40°C and 0.0325 moles/liter/min. were reduced with $NaBH_4$ and analyzed as the trimethylsilylether derivatives according to the procedure described in (9). Since ethylene glycol analyses are not quantitative and the amounts present were small, selectivities were calculated on the basis of 3-carbon and higher TMS polyol products. Figure 7 is a plot of the distribution by carbon number groupings of these polyol products from reduced formose as a function of $Ca(OH)_2$ concentration in the reactor. A HCHO conversion plot is also included on Figure 10. High selectivity for glycerol is had at low conversion levels, illustrating the consecutive nature of the formose reaction. There is no significant change in the product distribution around the rate maximum. Figure 10 shows that 5 and 6-carbon species predominate near complete conversion.

A most significant aspect of the product distribution is the presence of branched chain compounds at high selectivity levels. Figure 11 is a plot of the fraction of branched chain species present in the 4- and 5-carbon polyols produced vs. HCHO conversion. Parameters of 0.78-0.94 and 0.15-0.35 moles HCHO feed/liter/min. at 60°C and 0.0325 moles HCHO feed/liter/min. at 40°C are shown. Figure 11 exhibits a remarkable selectivity flip. At 50% and lower conversion levels, the C-4 and C-5 aldose and ketose products are practically pure straight chain at 40°C, practically pure branched chain at 60°C. At higher conversion level as much as 40% branched chain is present at 40°C (see also reference (30)).

The distribution of branched versus straight chain species may be a consequence of the base-catalyzed Lobry de Bruyn-van Eckenstein (L-V) equilibrium. Consider the addition of formaldehyde to a mixture of

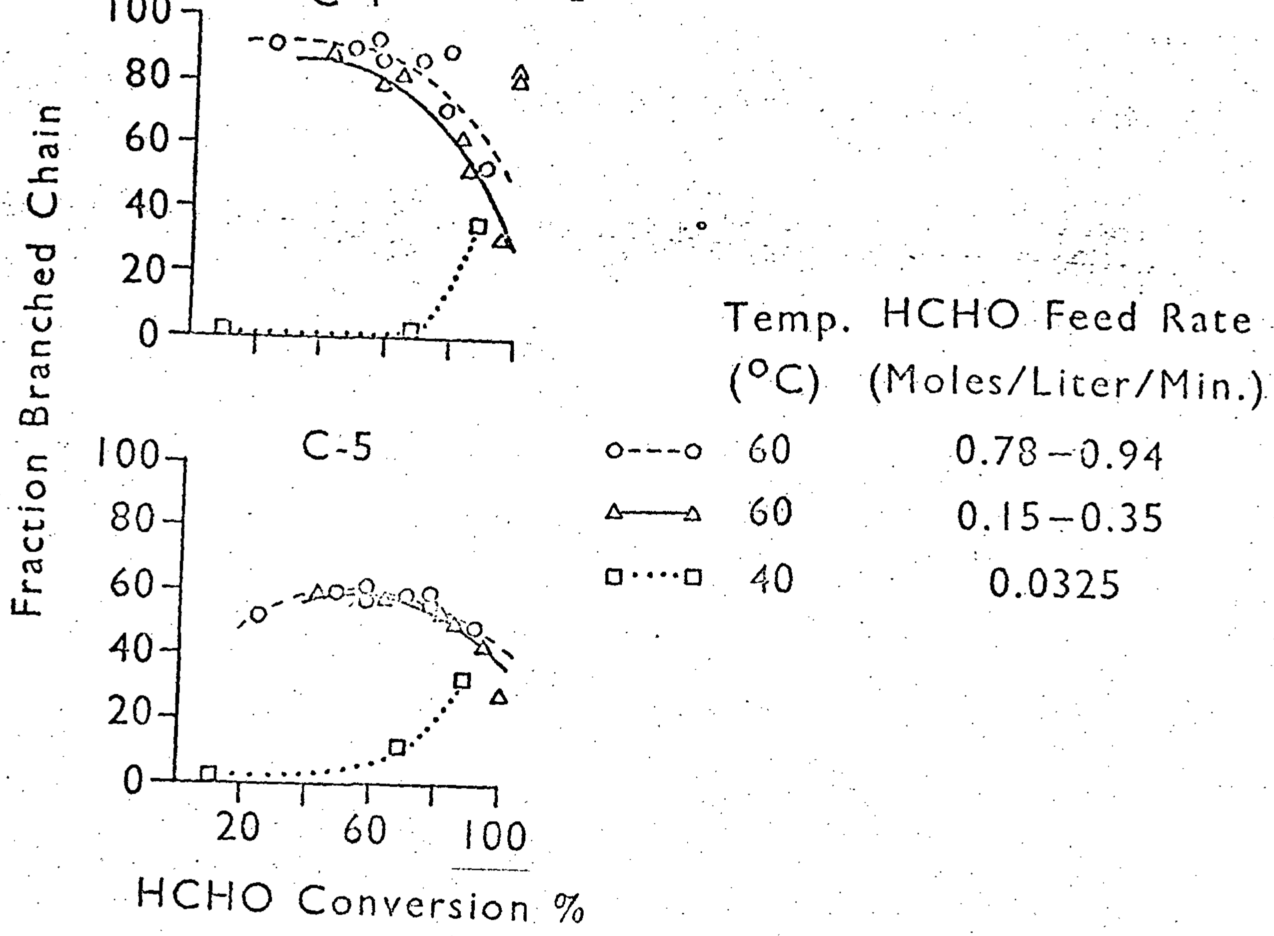


Figure 11

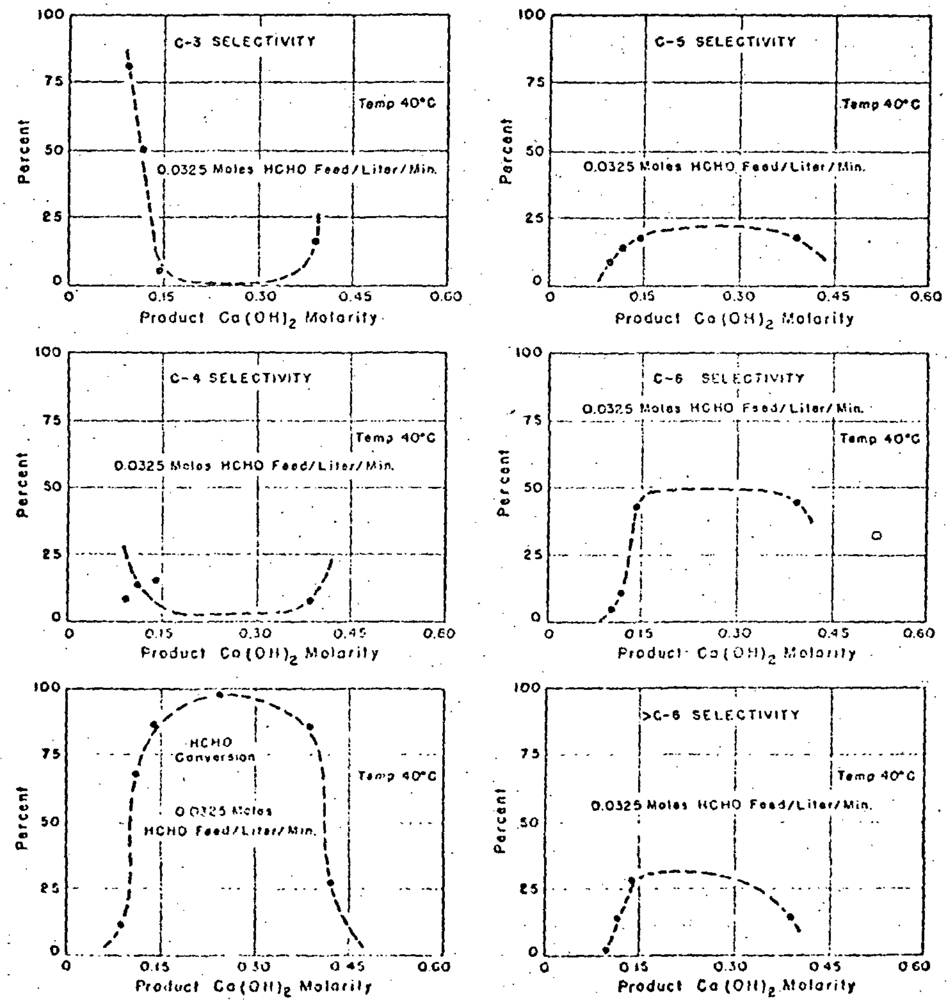
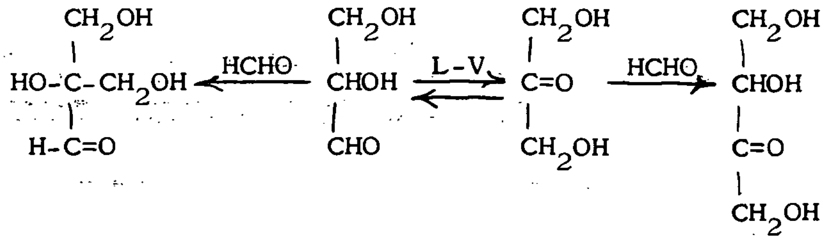


Figure 10

glyceraldehyde and dihydroxyacetone



The relative proportion of dihydroxyacetone to glyceraldehyde will be a function of the rate glyceraldehyde isomerizes to dihydroxyacetone. In turn, the relative concentrations of these species as well as the relative rates of formaldehyde addition to each will define the 4-carbon branched versus straight chain distribution of aldoses and ketoses.

Cross-Cannizzaro Reactions of Formose Products

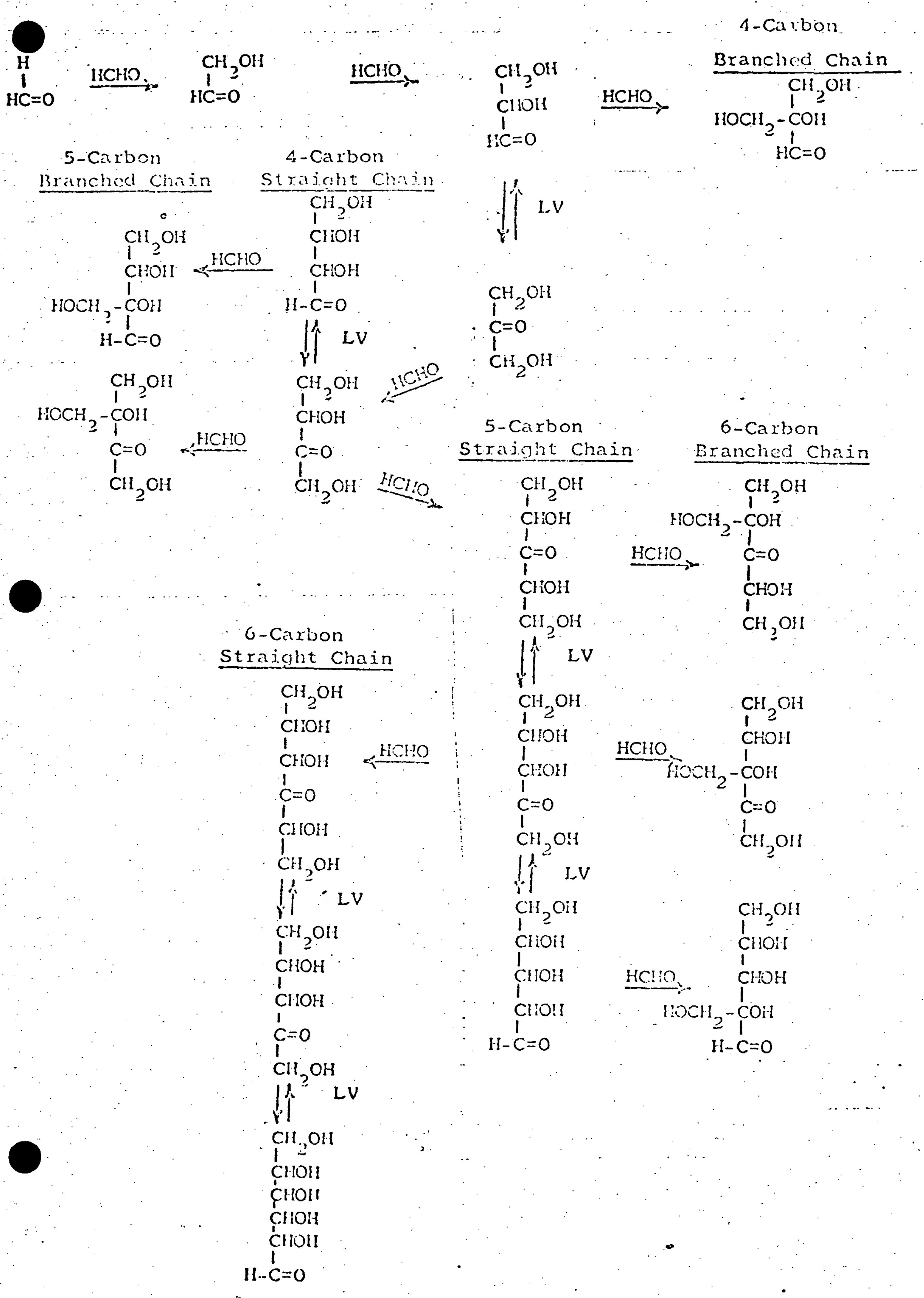
Table 1 shows the condensation scheme of formose products. The first condensation step of formaldehyde is to glycolaldehyde, which has two α-hydrogen atoms. Aldol condensation must then follow to form glyceraldehyde. Glyceraldehyde can react to two pathways - either further aldol condensation to hydroxymethylglyceraldehyde or Lobry de Bruyn-van Eckenstein (L-V) rearrangement to dihydroxyacetone. Note that hydroxymethylglyceraldehyde has no α-hydrogen; and so it is a terminal product.

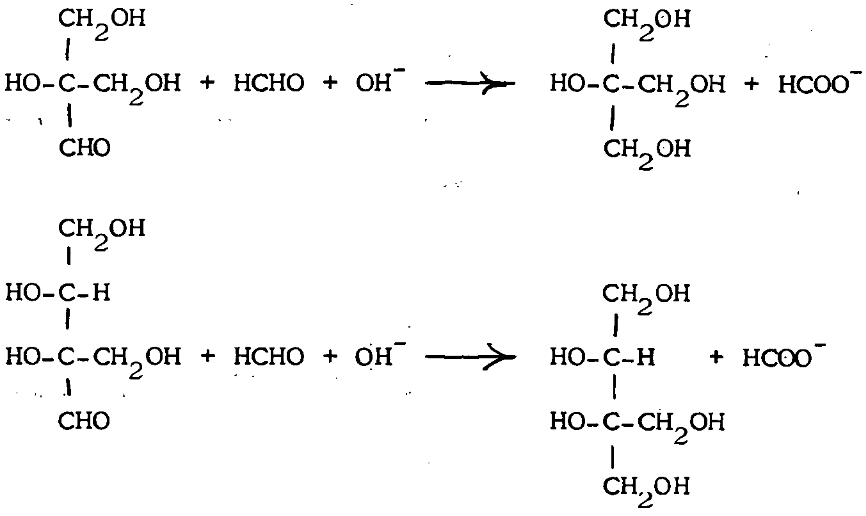
Dihydroxyacetone adds formaldehyde to form a four-carbon straight chain aldose. This species can either add formaldehyde to its α-hydrogen to form hydroxymethyltetroses or isomerize by the L-V equilibrium to form the four carbon ketose, erythulose. Table 1 shows how 5-carbon straight chain aldoses and six carbon branched and straight chain aldoses and ketoses are formed.

Cross-Cannizzaro reactions occur mainly with aldose species with no α-hydrogen atoms - specifically, hydroxymethylglyceraldehyde, hydroxymethyltetroses, etc.

Table I

Formation of Branched and Straight Chain Aldoses and Ketoses (Enantiomers and Diastereomers not shown)





$$\begin{array}{c}CH_2OH\\ |\\ HO\text{-}C\text{-}CH_2OH\\ |\\ CHO\end{array} + HCHO + OH^- \longrightarrow \begin{array}{c}CH_2OH\\ |\\ HO\text{-}C\text{-}CH_2OH\\ |\\ CH_2OH\end{array} + HCOO^-$$

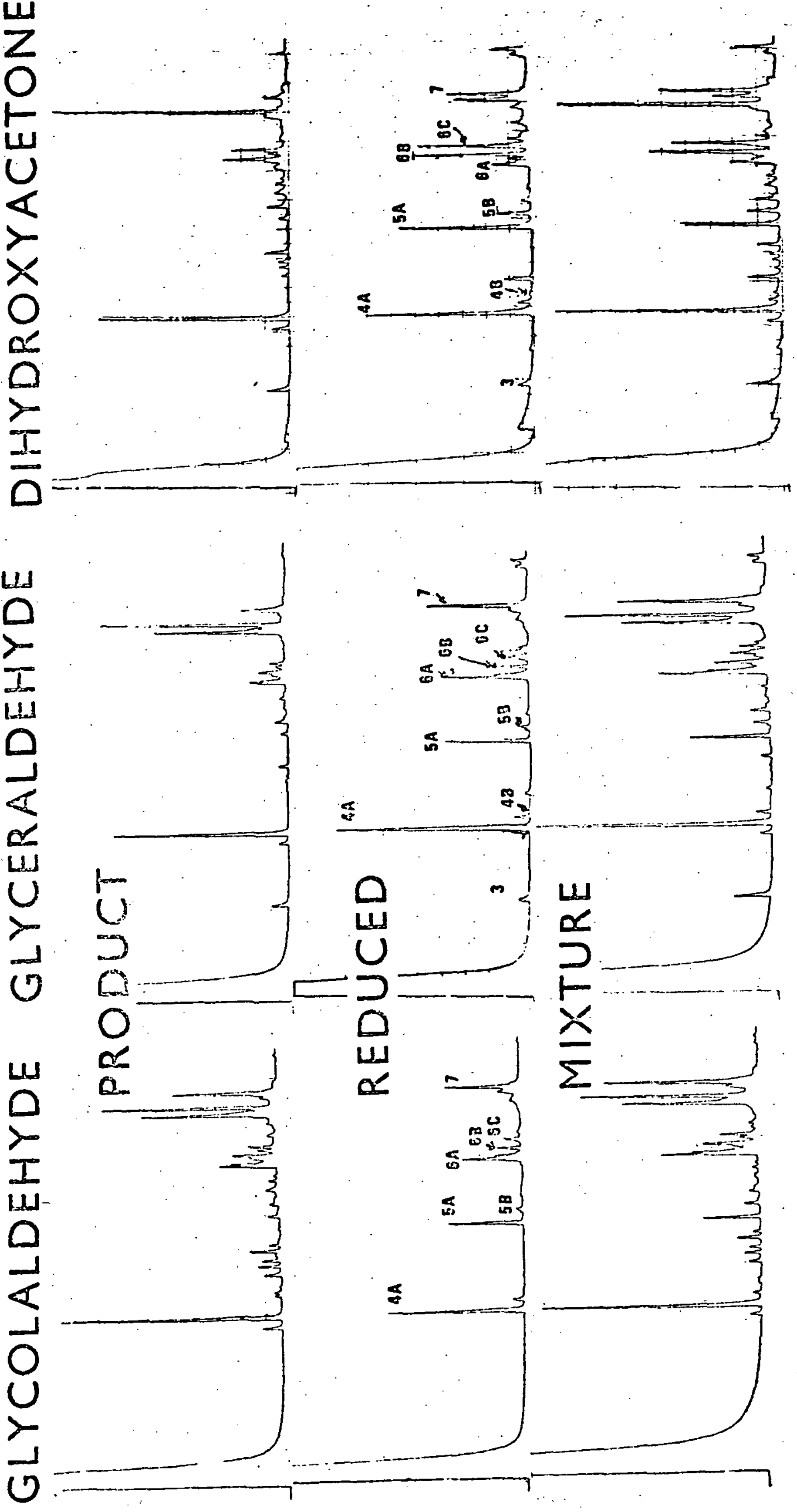
$$\begin{array}{c}CH_2OH\\ |\\ HO\text{-}C\text{-}H\\ |\\ HO\text{-}C\text{-}CH_2OH\\ |\\ CHO\end{array} + HCHO + OH^- \longrightarrow \begin{array}{c}CH_2OH\\ |\\ HO\text{-}C\text{-}H\\ |\\ HO\text{-}C\text{-}CH_2OH\\ |\\ CH_2OH\end{array} + HCOO^-$$

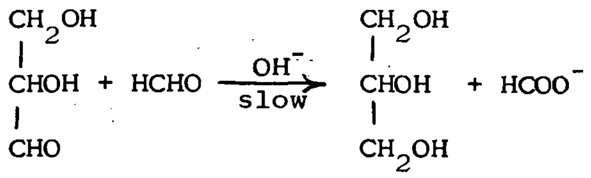
To demonstrate this type of stoichiometry sequence, three batch experiments were made with glycolaldehyde, glyceraldehyde, and dihydroxyacetone. Each of these compounds were separately mixed with HCHO (1.14M) and NaOH (1.204M) and allowed to react for 30 min. at 29°C. Figure 12 shows chromatographic analyses of the trimethylsilylether derivatives of the products formed by these three experiments.

To distinguish between hydroxymethylglycerol and hydroxymethylglyceraldehyde in the products, samples were reduced to the corresponding polyols using $NaBH_4$. The TMS derivatives of unreduced and the reduced products can be compared in Figure 12. A mixture of 2μL each of the TMS derivatives of each unreduced and reduced product was then injected into the gas chromatograph. These analyses are also shown in Figure 12. The hydroxymethylglycerol peak appears at the same retention time in all three analyses and no splitting of hydroxymethylglycerol and hydroxymethylglyceraldehyde peaks is observed in the mixed samples. The product produced in the presence of NaOH is hydroxymethylglycerol rather than hydroxymethylglyceraldehyde.

Glyceraldehyde also undergoes cross-Cannizzaro reaction directly (but to a small extent) with HCHO to yield glycerol.

Figure 12


GLYCOLALDEHYDE
HCHO + GLYCERALDEHYDE
DIHYDROXYACETONE
PRODUCT
REDUCED
MIXTURE
3
4A
4B
5A
5B
5C
6A
6B
6C
7



$$\begin{array}{l}CH_2OH\\|\\CHOH\\|\\CHO\end{array} + HCHO \xrightarrow[\text{slow}]{OH^-} \begin{array}{l}CH_2OH\\|\\CHOH\\|\\CH_2OH\end{array} + HCOO^-$$

Figure 12 shows small amounts of glycerol were so made. A cross-Cannizzaro network can be set up indicating major and minor pathways. This is shown on Table 2, illustrating the process through the five-carbon level. Identification of the species noted on Figure 12 are detailed in Partridge, et al. (31). NaOH is far more effective than $Ca(OH)_2$ for the cross-Cannizzaro reaction. Formose products produced in the presence of $Ca(OH)_2$ contain hydroxymethylglyceraldehyde. Those produced in the presence of NaOH contain instead hydroxymethylglycerol.

Ol-ose selectivity is apparently controlled by the cross-Cannizzaro catalyst -NaOH gives -ols; $Ca(OH)_2$ gives -oses. This again is more probably a pH effect than a catalyst effect; and we expect to answer this in part from results of the continuing kinetics and pH study.

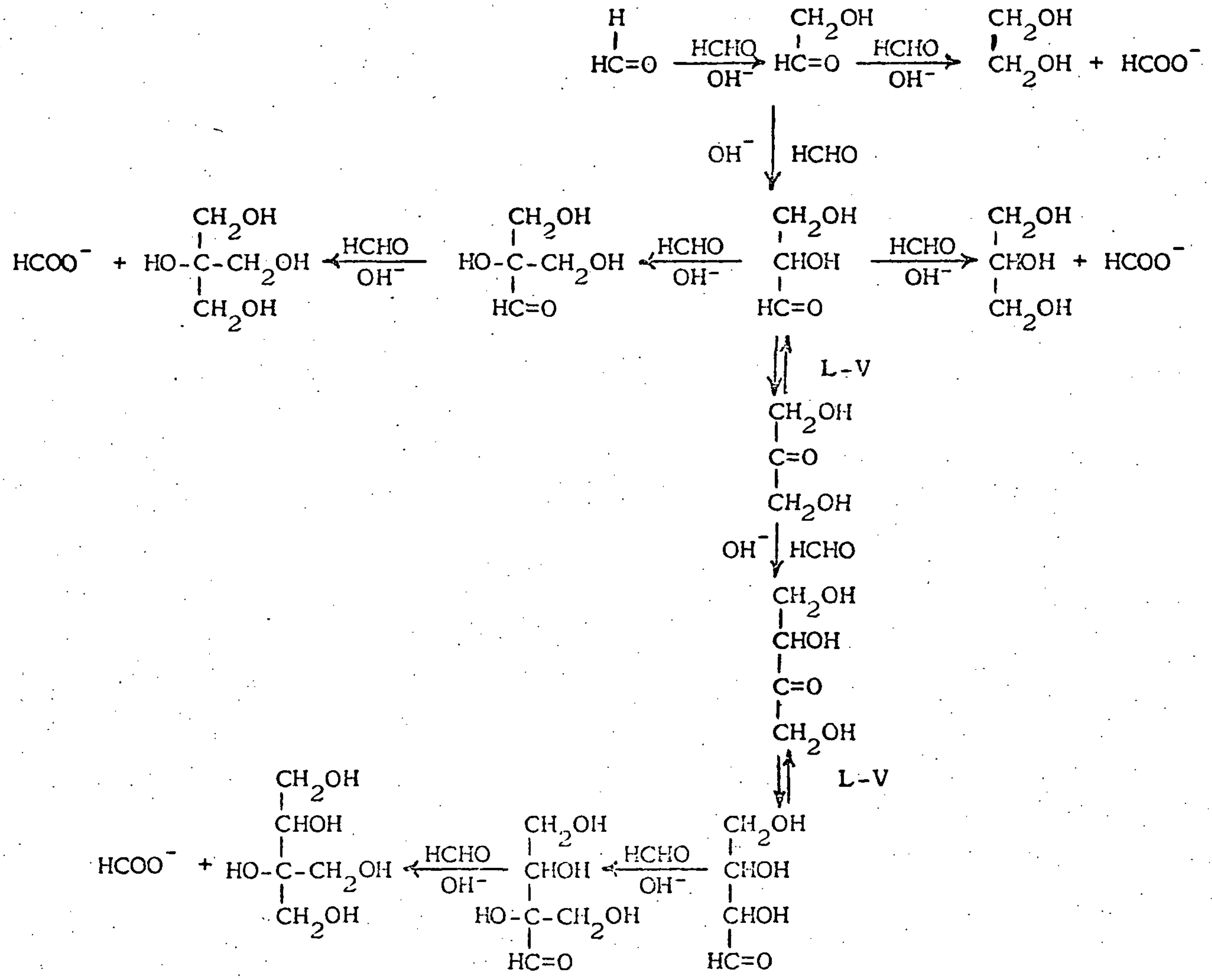
Overall Research Project

So far our work has shown that the Cannizzaro reaction of formaldehyde is far from a simple kinetic process that can be characterized by first or second order kinetics and a single reaction in which methanol and formate are produced. Rather, it proceeds in alkaline medium in conjunction with the formose reaction - the autocatalytic self-condensation of formaldehyde with itself - to produce glycolaldehyde - which is then followed by aldol condensation to higher aldoses and ketoses. Mono-, di-, tri-, and tervalent bases, as well as nitrogen bases, have been reported to homogeneously catalyze both reactions, and the formose to Cannizzaro rate ratio will be not only a function of the catalyst but also of the formaldehyde conversion level.

Table 2

Cross-Cannizzaro Reaction Network

Major Minor



In the present studies with $Ca(OH)_2$ catalyst, it was found that at HCHO conversion levels below 4%, HCHO disappearance by Cannizzaro is triple that by formose condensation. On the other hand, near 50% conversion, which is where the stoichiometry of the Cannizzaro reaction requires that its absolute rate pass through a maximum, HCHO disappearance rate by Cannizzaro is only 5% of that by formose condensation.

As catalyst concentration is increased at fixed formaldehyde initial concentration (i.e., feed rate in a continuous stirred tank reactor), the increase in absolute rate of Cannizzaro reaction neutralizes $Ca(OH)_2$ and pH of the reaction drops from approximately 12 to 10.5 in the range of 0. to 100% conversion. This autonomic behavior may be one reason for the change in reaction rate ratios, cross-Cannizzaro reaction of formaldehyde with condensation products another reason. In any case, increasing catalyst to inordinate levels (e.g., 2 moles $Ca(OH)_2$/mole HCHO) quenches both reactions, an effect that is unexpected in a catalytic system.

In this complex reaction system, where more than one route is possible, interactive effects prevent extrapolation of rates and their ratios beyond regions of actual measurements. Selectivities were of course affected relative to the ratio of -ol to -ose products, but also the carbon number and skeletal structure of the formose condensation product itself depends on the reaction environment attained. The Lobry de Bruyn-van Eckenstein equilibrium controls the ratio of aldoses to ketoses; and, in turn, this ratio determines the ratio of branched to straight chain sugars - e.g., hydroxymethylglyceraldehyde to erythrose. The branched species is so active for cross-Cannizzaro reaction, that considerable hydroxymethylglycerol is produced when NaOH aldol condensation of formaldehyde with glycolaldehyde, glyceraldehyde, or dihydroxyacetone is attempted.

Much remains to be learned of the kinetics and the mechanisms of the multiplicity of interactive processes that proceed when these carbohydrate species react. Formaldehyde in alkaline medium is ostensibly a simple situation, it has been studied for over a century, and yet the system is far from understood and modeled. Continuous stirred tank reactors, in which reaction rates can be measured directly, are a tool of central importance to develop understanding of even the stoichiometry of these complex reactions, let alone the kinetics and mechanism.

To explain the known products of the formose reaction, the following processes suffice:

1) An initiating - and autocatalytic - condensation of two molecules of HCHO to give CH_2OH-CHO, glycolaldehyde.
2) Successive aldol condensations involving HCHO and hydrogens α- to a carbonyl group.
3) Lobry de Bruyn - van Eckenstein (L-V) interconversion.
4) Crossed-Cannizzaro reaction to produce polyols and formate ion.

Branched chain sugars - rarely seen in nature and therefore not looked for by earlier investigators of formose - are major components of formose. Furthermore, if the structural features required for processes (2) and (3) are absent in a product then that product is a terminal one. For example, if glyceraldehyde undergoes aldol condensation with HCHO, the product, hydroxymethylglyceraldehyde, would be expected to either accumulate or undergo crossed-Cannizzaro reduction to the tetritol. Thus, we have at hand a practical process to produce simple branched carbonates.

Significance of the Formose Work

Many scientists prefer an idealized simple reaction system for which a straightforward theoretical model can be predicted and progress in understanding kinetics, mechanism and catalysis has been made on this basis. But nature is not always so accommodating as to provide simple reaction systems. So, there is also a great need for complex reaction methodolgy - for good conceptual and experimental approaches to penetrate a complex reaction.

The theme of the Fourth International Congress on Catalysis, Moscow, 1968, was "Prediction of Reaction Selectivity". In his final address, Professor Roginskii summarized the papers and concluded that progress toward satisfying the theme had not been made. In February, 1971, the Second North American Meeting of the Catalysis Society was held in Houston. Perhaps for the first time, a significant fraction of papers discussed catalytic reactions not in terms of simple single reactions but in terms of all observable products. The scientific community and industry are recognizing that practical reactions - which are generally complex - e.g., reforming, cracking, hydrocracking, etc. - need to be studied in their entirety. This author has published a review paper "Considerations in the Study of Reaction Sets", Catalysis Reviews 5, (2), 293-330 (1971) in which philosophies and ideas that are needed for work in complex reactions are developed.

The story of the formose reaction is, in itself, enough to point out the importance of complex reaction studies. The formose reaction has been studied intensely since 1865, but no definitive kinetic or product stoichiometry was developed. Why? Because of the use of batch reactors in an autocatalytic system. "It reacts or it does not react". "Induction periods rather than rates are reported". Techniques that are common for engineers - e.g., CSTR's - need to be taken advantage of by chemists. Reactions must be studied at controlled conversions using rational rate laws - and modern analytical techniques provide capability for penetrating difficult stoichiometries.

The formose reaction was chosen for its potential practical application for food synthesis for sustained spaceflight. For the present, NASA priorities on manned space flight have been reduced. Hopefully, they will reactivate in the future. At the time of project inception, Dr. Cyril Ponnephoruma of NASA Ames recognized that the formose reaction was useful for explaining primordial carbohydrate synthesis. More speculatively utilitarian was the fact that perhaps one day large scale carbohydrate manufacture will be required, if world population continues to grow. The formose reaction holds promise for this purpose. Major research on the formose reaction is in progress both in Japan (Prof. Takashi Mizuno, Faculty of Agriculture, Shizuoka University) and in the Soviet Union (Prof. Oleg V. Krylov, Zelinski Institute of Organic Chemistry, Moscow). The United States should maintain its role in what is a problem of worldwide interest.

The homogeneous catalysis and reaction kinetics, the complex stoichiometry, the reaction instabilities and the intriguing interaction of homogeneous and heterogeneous rate concepts are of particular interest for catalytic chemists. The new group of simple branched carbohydrates is exciting to explore since glyceraldehyde pathways that could produce them are present throughout nature. Finally, organic and carbohydrate chemists need to learn the engineers' methodology to understand carbohydrate systems even as simple as formaldehyde in alkaline media. The latter reason, in this day of ultrasophisticated chemistry, points out the great contribution that rational study of complex reactions can make.

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Application of Aerospace Technology

The Principal Investigator spent the Summers of 1967 and 1968 at NASA Ames Research Center, Mountainview, California, as a NASA-ASEE Summer Faculty Fellow, working in collaboration with Dr. Jacob Shapira. The research project was "Novel Methods for Synthesis of Food for Sustained Spaceflight"; and we found that the autocatalytic $Ca(OH)_2$ catalyzed formose condensation of formaldehyde to sugars could be controlled in a continuous stirred tank reactor (CSTR). Research support by NASA was provided from February 1, 1968 to January 31, 1972 to develop a process to produce glycerol for sustained space feeding by reduction of these sugars. We have made these contributions toward understanding formose chemistry and toward our goal of controlling the reaction to produce glycerol and to provide astronauts with carbohydrates produced from CO_2 aboard a space ship.

During the course of the carbohydrate work, considerable equipment and instrumentation was purchased with the NASA grant and carbohydrate know-how was developed. Part of this author's background has been in industrial petrochemical process development; and it soon developed that much catalytic and petroleum know-how was brought into play to convert petrochemical formaldehyde to carbohydrates such as glycerol and sugar.

We now have CSTR reactors, pumps, recorders, and controllers, etc. to be applied to continuing formose studies, as well as a high level of expertise in carbohydrate chemistry and analytical techniques. We have developed major understanding of the behavior of sugars in the presence of alkaline catalysts, as well as CSTR technology.

The list of NASA-funded equipment includes a Waters ALS-01 Liquid Chromatograph, a Barber-Colman 6 Port Thermal Conductivity Gas Chromatograph, a Gow-Mac Thermal Conductivity Gas Chromatograph, and a Perkin-Elmer 900 Dual Flame Ionization Gas Chromatograph interfaced to a duPont 21-491 Double Focusing Mass Spectrometer (with camera, oscilloscope, oscillograph, and integrator-recorder). An automatic Fisher titrimeter, Corning Research pH meters, and Orion specific ion meter are some of the items in a diversity of NASA-funded wet analysis equipment that will continue to be utilized.

Table 3 is a list of publications resulting from the NASA-sponsored food synthesis research.

Table 3

Publications and Presentations by A.H. Weiss

Resulting From NASA-Sponsored Food Synthesis Research

1. "The Kinetics of the Formose Reaction", presented at ACS 155th National Meeting, San Francisco, California, April 1968 (with J.A. Shapira).

2. "Manufacture of Sugars", presented at the Amer. Institute of Chem. Eng., Portland, Oregon, National Meeting, August 27, 1969. AIChE Symposium Series, No. 108, 67, 137 (1971)(with J.A. Shapira).

3. "Homogeneously Catalyzed Formaldehyde Condensation to Carbohydrates", Journal of Catalysis 16, 332, (1970), Presented at ACS 159th National Meeting, Petroleum Division, Houston, Texas, February 22, 1970 (with R. LaPierre and J.A. Shapira).

4. "Make Sugars From Formaldehyde", Hydr. Proc., 49, No. 2, 119-126, February 1970 (with J.A. Shapira).

5. "Extraction Procedure for TMS Derivatives", J. Chromat. Sci. 8, 553 (September 1970)(with R.D. Partridge).

6. "Polyols From Formaldehyde", presented at ACHEMA, European Meeting for Chemical Engineering, Frankfurt am Main, June 22, 1970 Neue Verfahren Der Chemischen Technik, Verlag G.M.B.H., Vern Leim/Bergstrasse, 1971, p. 239 (with R.D. Partridge, H. Tambawala, and J.A. Shapira).

7. "The Formose Reaction", presented at the First Spring Symposium of the Catalysis Club of New England, Boston, Mass., April 1, 1970. Presented at Montecatini Edison Bollate Research Laboratory, Milano, June 15, 1970. Presented at Third International Congress of Food Science and Technology, Washington, D.C., August 10, 1970. Proceedings in Press.

8. "Detection of Sugars by Direct Combustion in a Flame Ionization Detector", J. of Chromat. Sci., 9, 266-270 (May 1971)(with E. Foster).

9. "A Study of a Complex Reaction", October 30, 1970, University of Houston, Dept. of Chemical Engineering Seminar Series, Houston, Texas.

10. "Homogeneously Catalyzed Formaldehyde Condensation to Carbohydrates. II. Instabilities and Cannizzaro Effects" Preprints of the Petroleum Division, 163rd American Chemical Society National Meeting, April 9-14, 1972, Boston, Mass. In press. J. Catalysis (with H. Tambawala).

11. "TMS Derivitization in Aqueous Solutions" In press, J. Chromat. Sci. (with H. Tambawala).

12. "Branched Carbohydrate Structures Resulting From Formaldehyde Condensation", Division of Carbohydrate Chemistry, 163rd American Chemical Society National Meeting, April 9-14, 1972, Boston, Mass. In press, J. Carbohydrate Research (with R.D. Partridge and D. Todd).

13. "Solid Waste Conversion and Food Synthesis", Interview with Hugh Downs, September 16, 1971, NBC Today Show.

14. "Considerations in the Study of Reaction Sets", Presented at New York University Chemical Engineering Seminar, March 15, 1971. Catalysis Reviews 5(2), 283-330 (1971).

15. "Study of Techniques Feasible for Food Synthesis Aboard a Spacecraft."

Grant NGR 22-017-008

Semiannual Progress Reports

Number	Period
1	2/1/68 - 7/31/68
2	8/1/68 - 1/31/69
3	2/1/69 = 7/31/69
4	8/1/69 - 1/31/70
5	2/1/70 - 7/31/70
6	8/1/70 - 1/31/71
7	2/1/71 - 7/31/71
8	8/1/71 - 1/31/72