Carbohydrate Research, 199 (1990) 91–109
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Mechanism of formation of 5-(hydroxymethyl)-2-furaldehyde from D-fructose and sucrose*

Michael Jerry Antal†, Jr., William S. L. Mok,
Department of Mechanical Engineering and the Hawaii Natural Energy Institute, University of Hawaii at Manoa, Honolulu, Hawaii 96822 (U.S.A.)

and Geoffrey N. Richards,
Wood Chemistry Laboratory, University of Montana, Missoula, Montana 59812–1201 (U.S.A.)

(Received May 31st, 1989; accepted for publication October 5th, 1989)

ABSTRACT

The literature contains two alternative hypotheses for the mechanism of dehydration of fructose to 5-(hydroxymethyl)-2-furaldehyde (HMF), namely (*1*) a sequence of reactions commencing with and retaining the fructofuranose ring intact, and (*2*) a succession of reactions proceeding mainly *via* open-chain intermediates. The existing evidence for hypotheses (*1*) and (*2*) is reviewed and found to favor (*1*). The major products from fructose in water at 250°, (with and without acid catalysis) have been investigated on a time-resolved basis and analysis of the results was found to confirm the first hypothesis. A necessary fructofuranosyl-cation intermediate in this hypothesis is produced directly by the hydrolysis of sucrose, and reacts to produce HMF in high yields.

INTRODUCTION

Kinetic studies have played a key role in the mechanistic elucidation of many chemical reactions. A classic example is Bodenstein and Lind's experimental investigation[1] of the gas-phase homogeneous reaction of molecular bromine and hydrogen. Thirteen years after they deduced the rate expression which correlated the experimental data, three other investigators[2–4] all proposed the same free-radical mechanism to explain the observed kinetics. Unfortunately, the high temperature, aqueous phase reaction chemistry of ketoses and aldoses has not been a focus of similar kinetic scrutiny. Often models have been proposed with many adjustable parameters that seem to fit experimental data, but these models have not offered critical insights into the underlying reaction mechanisms. The purpose of this series of papers is to report the results of a sustained experimental and theoretical investigation of the acid-catalyzed kinetics of ketose and aldose reactions in liquid water at high temperatures (200–250°) and pressure (34.5 MPa) with pH values at NTP (25°, 0.1 MPa) ranging from 2 to 7. These conditions were selected because they result in commercially attractive yields of 5-(hydroxymethyl)-2-furaldehyde (HMF) and 2-furaldehyde (furfural) from the sugar

*Part 1 of the series Kinetic Studies of the Reactions of Ketoses and Aldoses in Water at High Temperature. For Part 2 see following paper.

†Corresponding author.

0008-6215/90/$03.50

substrates. HMF and furfural are versatile, polyfunctional compounds which can serve as intermediates in the synthesis of many types of polymers[5-7].

Because the acid-catalyzed reactions of carbohydrates are part of a very complex reaction network involving a variety of isomerization, condensation, fragmentation, and dehydration reactions, a methodology is needed to gain insight into the underlying reaction-mechanisms. We have found the following steps helpful in elucidating complex reaction-networks:

1. Identify all stable products, preferably by two or more different analytical techniques. The carbon balance of each experiment should be calculated. Experiments with poor carbon balances offer only limited insights into the reaction chemistry, because some significant products must not have been identified.

2. Identify species which are co-products of the same reaction pathway. To do this, the various reaction pathways and stoichiometries must be posited. In the absence of secondary reactions, the rates of formation of the putative co-products should be related by the reaction stoichiometry.

3. Identify the early time-behavior of the reaction products to distinguish (*a*) primary reaction-pathways from secondary reaction-pathways, (*b*) the potential role of unobserved, rate-limiting intermediates in product formation, and (*c*) the influence of autocatalytic reactions on product formation.

4. Identify the influence of pH on product formation to (*a*) gain insight into the reaction mechanism and (*b*) establish the role of autocatalysis by acidic reaction-products.

5. Identify the influence of reactant concentration on the rates of product formation to gain insight into the orders of the reaction pathways.

6. Verify the roles of posited secondary reactions (from *3* foregoing) and autocatalysis (from 3 and 4 foregoing) by experiment.

7. Pose a model mechanism for the reaction network based on elementary reaction-steps. If possible, use the steady-state hypothesis to establish the qualitative behavior of the model. Use a non-linear least-squares algorithm to determine whether the model is quantitatively able to fit the experimental data.

8. Based on the proposed mechanism, identify model compounds which are able to mimic the functional groups active in the mechanism. Test the hypothesized mechanism using these model compounds. Labelled compounds can offer particularly critical insights into the reaction mechanism.

9. Establish the influence of solvent properties on the rates of product formation, and use this data to test the hypothesized mechanism.

10. Establish the influence of various Brønsted and Lewis acid catalysts on the rates of product formation, and use these data to test hypothesized mechanism.

In the following sections we employ this methodology (except 6–10, which will be the subject of future papers in this series) as a framework within which we review the findings of earlier workers, and present our own results. Because of our interest in the formation of 2-furaldehydes, we emphasize studies whose experimental conditions

favor the formation of these dehydration products. Thus we are not concerned with base-catalyzed reactions. Furthermore, because this paper emphasizes the reaction chemistry of D-fructose, the literature concerning the formation of 2-furaldehydes from aldoses will be introduced only when necessary. Later parts of this series will examine the formation of 2-furaldehydes from aldoses in more detail.

Four broad classes of compounds result from the moderate- to high-temperature decomposition of sugars in water: products of isomerization, dehydration, fragmentation, and condensation. Table I summarizes the findings of earlier workers concerning the appearance of these products from fructose. We have not attempted to list all of the workers who have detected each product listed in Table I; instead we have emphasized recent studies in water at moderate to high temperatures.

The co-products and pathways associated with the fragmentation products listed in Table I require some discussion. Formic acid and levulinic acid are co-products of the acid-catalyzed hydrolysis of HMF. Dihydroxyacetone and glyceraldehyde result from a reverse aldol reaction of fructose. 2-Furaldehyde is a product of the facile, acid-catalyzed dehydration of pentoses[12], which may form (together with formaldehyde) by a reverse aldol reaction, although we have failed to obtain conclusive evidence of the significant presence of either a pentose or formaldehyde in the products of our reactions. Pyruvaldehyde is a dehydration product of glyceraldehyde, and lactic acid results from a benzilic acid rearrangement of pyruvaldehyde. A possible co-product with glycolaldehyde, if derived from a reverse aldol reaction, would be a tetrose, but none has been detected. The mechanisms of formation of acetol, 2,3-butandione, and of formic and acetic acids are unclear, but it should be noted that they are all significant products of the pyrolysis of carbohydrates. We postpone further discussion of the fragmentation products until later in this paper.

TABLE I

Reported Products of Fructose Decomposition in Water at Elevated Temperatures

Isomerization	*Dehydration*	*Fragmentation*	*Condensation*
D-Glucose[8,a]	5-(Hydroxymethyl)-2-furaldehyde[9,a]	formic acid[7,a]	'humin'
	5-Methyl-2-furaldehyde[9,b]	levulinic acid[9,a]	
	α-Angelica lactone[9,b]	dihydroxyacetone[10,a]	
	β-Angelica lactone[9,b]	glyceraldehyde[a,c]	
	2-(2-Hydroxyacetyl)furan[9,b]	2-furaldehyde[a,c]	
	2-(2-Hydroxyacetyl)furan formate[9,b]	pyruvaldehyde[10,a]	
	Isomaltol[9,b]	lactic acid[a,c]	
	4-Hydroxy-2,3,5-hexanetrione[9,b]	acetol[a,c]	
	4-hydroxy-2-(hydroxymethyl)-5-methyl-3(2*H*)-furanone[9,b]	glycolaldehyde[b,c]	
		acetic acid[9,b]	
		2,3-butandione[b,c]	

[a]Major products (generally > 1% absolute yield). [b]Minor products. [c]Identified for the first time in this work.

Only one previous study[11] is available which presents time-resolved product evolution data from the acid-catalyzed dehydration of D-fructose at varying levels of reactant and catalyst concentrations. At 95° with D-fructose concentrations ranging from 0.25 to 1.0M, and HCl concentrations from 0.5 to 2M, Kuster and van der Baan[11] showed the rate of D-fructose disappearance and HMF appearance to be essentially first order in D-fructose concentration. A kinetic analysis of the data suggested the role of an unprotonated (uncharged) intermediate in a two-step reaction sequence which formed HMF from D-fructose. Their data clearly show that the formation of levulinic acid (with formic acid) results from a secondary reaction involving hydrolysis of product HMF.

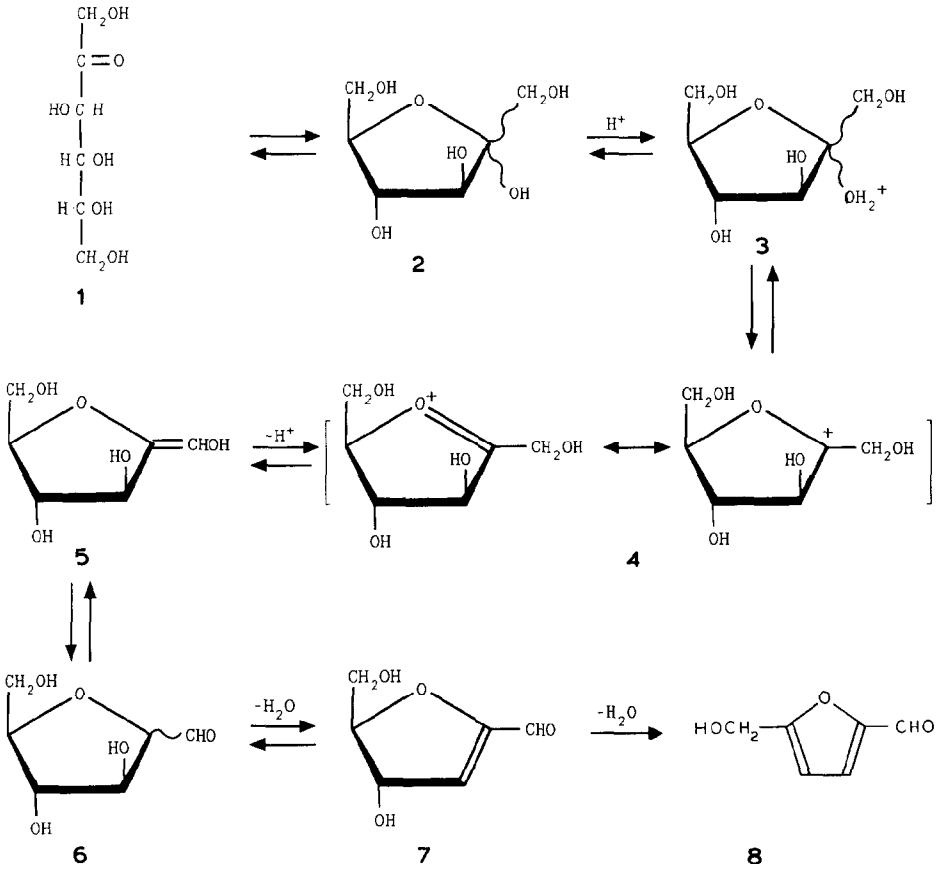
In a subsequent publication, Kuster and Temmink[13] described the formation of HMF, and of levulinic and formic acids at 175° in a stirred tank reactor at pH levels from 1 to 6. Recognizing the potential for autocatalysis by formic acid, Kuster and Temmink[13] made a great effort to control the pH of the reacting mixture, as measured at 60°. Their results do not reveal significant autocatalysis by the formic acid. However, the results establish the role of pH in producing maximum stability of D-fructose at pH 3.1, and in catalyzing the formation of levulinic acid from HMF at lower pH levels.

An examination of the concentration dependence of D-fructose conversion and of HMF yields, reported by Kuster and van der Baan[11], corroborates their conclusion that the rates of disappearance of D-fructose and the formation of HMF are essentially first order in fructose concentration.

Two differing schools of thought have evolved to explain these (and earlier) experimental observations. The first, which posits the role of the fructofuranosyl cationic intermediate in the formation of HMF from fructose (see Scheme 1), was originally advanced in a simpler form by Nef[14] (see Anet, ref. 31), and similar mechanisms were later propounded by Haworth[15,16]. This type of mechanism has been the favorite of practitioners whose experiments employ conditions which actually result in the formation of high yields of HMF from fructose[17–20]. The second school of thought[21–29] is based on the well known, base-catalyzed β-elimination of the hydroxyl group, which can form a 3-deoxyhexosulose from either a ketose or an aldose *via* an enediol intermediate (see Scheme 2). Since several excellent reviews[30–33] of the elementary steps comprising these alternative mechanisms are available, our purpose here is to examine the experimental evidence that has been accumulated to support these two viewpoints.

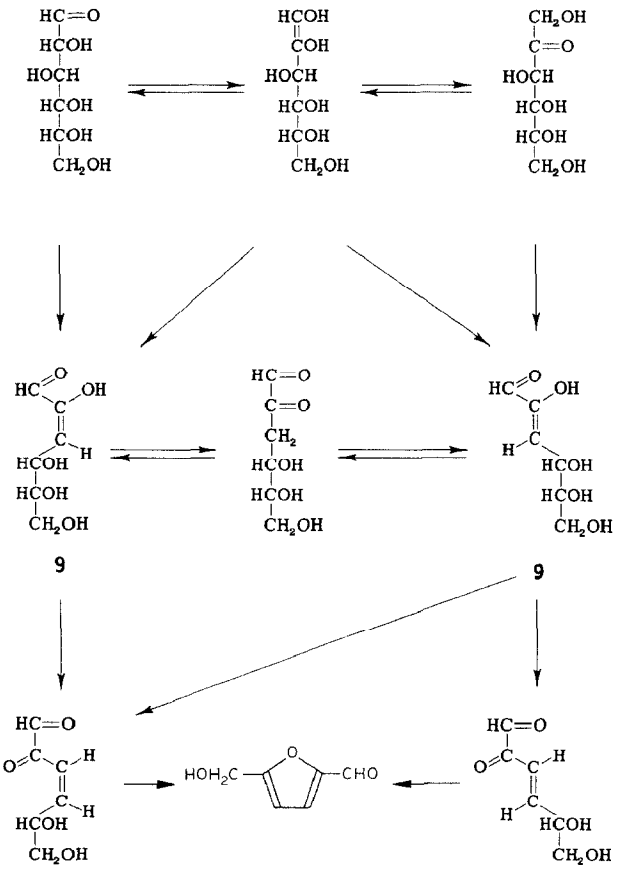
Experimental evidence supporting Scheme 1 consists of: (*i*) the ease of formation of HMF from fructose and from the fructosyl moiety of sucrose relative to glucose and the aldohexoses, and (*ii*) the facile conversion of 2,5-anhydro-D-mannose [which is the parent aldehyde of the enol intermediate (**5**) in Scheme 1] into HMF[30].

Although fact (*i*) is normally recognized, the force of its implications is often lost because the actual conditions which offer high yields of HMF from fructose, sucrose, and glucose are usually not emphasized in a mechanistic discussion of the chemistry. In water after several h at 80–95°, a good yield of HMF (e.g. 20%) is obtained from fructose in the presence of >0.25M HCl or other strong mineral acids which offer[11] a pH ~ 0, or in the presence of highly acidic ion-exchange resins[19]. Under similar condi-



Scheme 1

tions, HMF yields from glucose and other aldohexoses are very small[27], although Regal and Gaset did detect a 9% yield from glucose in the presence of a highly acidic resin after 22 h at 78°. At much higher temperatures (175–390°) excellent yields of HMF from fructose and sucrose and good yields from the aldohexoses are obtained after a few seconds in the presence of a much lower concentration (typically 10^{-2} to 10^{-3} M) of mineral or Lewis acids[13,17,20,34–38]. In Scheme 1 it is probable that some of the steps leading up to the initial formation of the aldehyde **6** are relatively slow compared with the subsequent development of conjugation via further dehydrations. These steps given in Scheme 1 are consistent with the facts already detailed. On the other hand, the same facts are not compatible with alternative mechanisms (Scheme 2)[33] requiring initial elimination of the 3-hydroxyl group and formation of the 3-deoxyhexulose (**9**), shown as the enol as an intermediate in HMF formation, since the elimination of the 3-hydroxyl should occur at least as rapidly from glucose as from fructose. Yet the latter yields HMF much more rapidly.



Scheme 2

Experimental evidence supporting the involvement of 3-deoxyhexosuloses and related compounds as intermediates in the formation of HMF has been based on the following observations:

(*i*) U.v. absorption bands were detected at 227 μm and later at 277 μm during the continuous refluxing of an aqueous solution of D-xylose, which Wolfrom *et al.*[25] supposed to indicate the successive formation of increasingly conjugated acyclic enol intermediates resulting from β-hydroxycarbonyl eliminations, the first product being the 3-deoxypentosulose. However, later work reveals that the isolated 3-deoxypentosuloses have no significant absorption maximum in the range [31,39] 400 to 210 μm. Thus a major motivation for positing the role of the 3-deoxyhexosulose is erroneous.

(*ii*) HMF was obtained in high yield[27] from two different 3-deoxyhexosuloses after several h in 2 N and 0.03N aq. acetic acid at 100°. Under identical conditions in 0.03M acetic acid the formation of HMF from D-fructose was barely detectable and no HMF was formed from D-glucose[27]. The reader should note that the conditions employed in these experiments involve hydrogen-ion concentrations three orders of magnitude less

than those ordinarily employed to generate HMF from fructose. One explanation for these results is that the rate-determining step for the dehydration reaction occurs prior to the formation of the 3-deoxyhexosulose, for example, the formation of the 1,2-enediol.

(*iii*) 3-Deoxyhexosulose and 3,4-dideoxyhexosulos-3-enes are formed[28,29], together with a 1.5% yield of HMF, from D-fructose and L-sorbose in 2M acetic acid and 0.02M oxalic acid after several h at 100°. However, in these experiments, >50% of the D-fructose was consumed, while the combined yield of the dicarbonyl compounds was only 0.7%. Thus >90% of the reaction products were not identified.

(*iv*) A "kinetic analysis" purported to account for less than half of the observed rate of formation of HMF from D-fructose via the 3-deoxyhexosuloses[29]. But the reported "kinetic analysis" contains far less detail than is usually offered in such analyses and involves many assumptions, hence it cannot be regarded as offering strong support for the mechanism.

We would summarize the foregoing observations as follows. Under weak acid conditions, the formation of small amounts of HMF from D-fructose is accompanied by the formation of trace, but detectable amounts of 3-deoxyglycosuloses, which may then form HMF in weak acid solutions. The formation of the 3-deoxyglycosuloses has not been observed under conditions which provide good yields of HMF. Presumably the rates of formation of the 3-deoxyglycosuloses, and also their conversion into HMF, are both slow under such conditions. The alternative reaction channel for conversion of fructose into HMF (Scheme 1) appears to operate at higher acidity and/or higher temperature. Unfortunately, previous work has not indicated whether higher temperatures or higher hydrogen-ion concentrations result in higher or lower rates of formation of the 3-deoxyglycosuloses from D-fructose. No evidence exists for the formation of 3-deoxyglycoses from aldohexosuloses in neutral or acid solution.

A key insight into the mechanism of HMF formation from fructose is gained from studies of the reaction chemistry in D_2O. Anet[40] claimed to have refuted the finding of Fodor and Sachetto[41] that deuterium is not incorporated into the 3-deoxyglycosulose when it is formed in D_2O. However, two years later in a critical series of experiments, Feather and Harris[42] showed that no deuterium is incorporated in HMF formed from D-fructose or D-glucose at 250° in D_2O containing 15 mM sulfuric acid. Now if the conversion of fructose into HMF had involved the 3-deoxyglycosulose **9** as an intermediate, the latter would be expected to incorporate carbon-linked deuterium via equilibration with its enolic tautomers. This type of carbonyl intermediate then would inevitably have resulted in incorporation of deuterium into the HMF. In contrast with this interpretation, Feather and Harris[42] supposed that the enol does not equilibrate with the 3-deoxyglycosulose, but this supposition contradicts the facts that (*i*) the 3-deoxyglycosulose (and not the enol) was actually isolated from fructose[31], and (*ii*) equilibrium so strongly favors the formation of the 3-deoxyglycosulose that no spectroscopic evidence for the formation in water of the enol from the 3-deoxyglycosulose exists (ref. 31, p.187). On the other hand, unnoted by earlier researchers and reviewers, the formation of HMF from fructose via Scheme 1 is fully consistent with the absence of deuterium in HMF formed from fructose in D_2O.

The concurrent formation of 2-hydroxyacetylfuran (HAF) with HMF from D-fructose and D-glucose has been used to justify various hypotheses concerning the mechanism of HMF formation[43–45]. However, we wish to postpone further discussion of HAF formation and its implications to a later paper.

It is now well known that non-aqueous solvents facilitate the formation of HMF from fructose[18,34,37,46,47]. No doubt some of this improvement in the yield of HMF results from a decrease in the acid-catalyzed hydrolysis of HMF to levulinic and formic acids. But the remarkable 100% yield of HMF from fructose in dimethyl sulfoxide (Me_2SO) reported (on the basis of relatively unspecific analysis by u.v. absorption) by Szmant and Chundury[18] points to the key role that solvent properties play in the formation of HMF from fructose. This effect may be associated with the fact that mutarotation is generally very slow in Me_2SO solution (compared with water). For example, α-D-glucopyranose was virtually unchanged after 4 days at room temperature in Me_2SO, although equilibration with the β anomer occurred[48] in 2 h at 90°. There is no doubt that the rate of mutarotation of fructose in Me_2SO is several orders of magnitude less than in water at the same temperature. This implies that any other sequence of reactions which, like mutarotation, proceeds via an open-chain form would be expected to take place more slowly in Me_2SO. This effect appears to militate against the mechanisms in both Schemes 1 and 2. In the first case, because the "normal" crystalline form of D-fructose is the β-pyranose (presumably this was the form used by Szmant and Chundury), isomerization must occur to the furanose forms via the open-chain form before entering the productive reaction channel to HMF. In Scheme 2 the reaction sequence also passes through the open-chain form and hence would be slowed in Me_2SO. We conclude therefore that the improved yield in Me_2SO compared with water may be associated with (*i*) operation of the mass-law effect (Le Chatelier's principle) in reaction (*3*) to (*4*), (Scheme 1), which is most probably the rate-determining step, and (*ii*) the tendency of the fructosyl cation[4] to add to hydroxyl ion in water to regenerate fructose and hence decrease the rate of formation and yield of HMF. For these reasons, non-aqueous solvents facilitate the formation of HMF.

In summary, the mechanism of HMF formation given in Scheme 1 is fully consistent with all previous experimental observations concerning its formation from fructose. In this paper we present new kinetic evidence which further supports the mechanism displayed in Scheme 1.

EXPERIMENTAL

Equipment. — The experimental work reported in this series of papers was performed with a system of supercritical flow-reactors (see Fig. 1) built in-house. To provide reliable and versatile kinetic data, these reactors were designed with the following factors in mind.

A. To operate within a wide range of reaction conditions. These include temperatures up to 500°, pressures not exceeding 34.5 MPa, and residence times ranging from 0.5 to 500 s. Commercially available Hastelloy C-276 tubing was chosen as the reactor

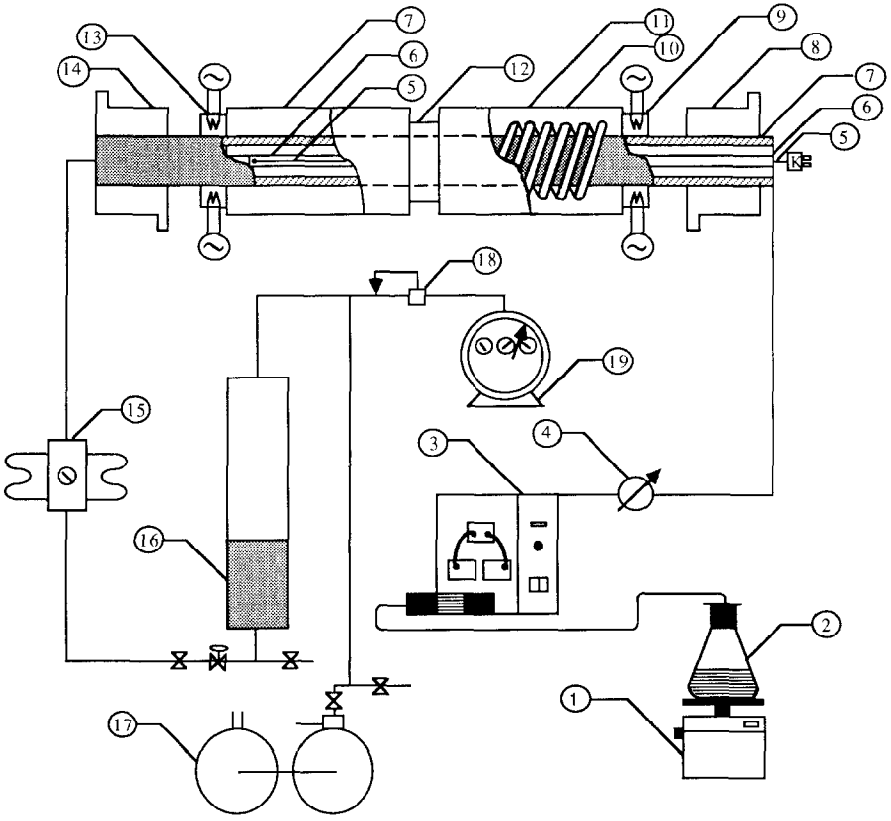


Fig. 1. Supercritical flow-reactor schematic: (*1*) Mettler balance, (*2*) flask with filtered and deaerated distilled water, (*3*) hplc pump, (*4*) bypass (3 way) valve, (*5*) probe thermocouple (type K), (*6*) ceramic annulus, (*7*) Hastelloy C-276 tube, (*8*) entrance cooling jacket, (*9*) entrance heater, (*10*) furnace coil, (*11*) quartz gold plated i.r. mirror, (*12*) window (no coils), (*13*) guard heater, (*14*) outlet cooling jacket, (*15*) ten port dual loop sampling valve, (*16*) product accumulator, (*17*) air compressor, (*18*) back pressure regulator, (*19*) outflow measuring assembly (Wet test meter).

material to meet the temperature and pressure requirements. Because of the limited flow range of the pump (discussed later), two reactors of different cross-sectional area (8.6 and 0.46 mm^2, respectively) are required to provide the desired variations in residence times.

B. To provide extremely stable flow and pressure during the experiment. To accomplish the objective of a constant flow, a high-performance liquid chromatograph (hplc) pump (Waters Associates 6000A solvent delivery system) with adjustable flow (0.1–9.9 $mL.min^{-1}$) was used to feed the reactant solution to either of the two reactors. As an additional check, the actual flow rate is monitored by continuously weighing the reactant feed-container. After passing the reactor and the sampling system, the flow is directed into a hydraulic accumulator (initially charged by an air compressor). This flow displaces air out of the accumulator through a back-pressure regulator. The setting of

the back-pressure regulator determines the reactor pressure. The presence of a highly compressible substance (air) in the flow system effectively damps out any pressure fluctuations during the experiment. Optionally, the vent of the back-pressure regulator can be connected to a wet-test meter which measures the cumulative flow of displaced air. This measurement can be used to back calculate the volumetric reactant flow out of the reactor.

C. To approximate closely the behavior of an ideal isothermal reactor, and provide a precisely defined reactant temperature history. Many aspects of the overall design were planned to make this possible. From a heat transfer point of view, the smallest feasible reactor hydraulic diameter should be employed to minimize the thermal entry length. After taking tubing availability and residence-time requirements into consideration, the two reactor geometries chosen are (*i*) an annular reactor with a 4.6 mm O.D., 3.2 mm I.D. and length of 50 cm and (*ii*) a 27 cm-long tubular reactor with a 0.76 mm I.D. A combination of four (smaller tubular reactor) or five (larger annular reactor) independently controlled heaters, (consisting at the entrance of short, high-powered heaters for rapid heat up, and other heaters to maintain constant temperature), in conjunction with entrance and exit water-cooled jackets provide a close to ideal step-up–step-down temperature-profile along the length of the reactor. For both reactors, the thermal entry length, where the temperature is between 100° and the isothermal reaction temperature, is kept to within 5 cm, while the thermal exit length is ~3 cm. In the case of the annular reactor, the inner core is an alumina tube, which accommodates a movable thermocouple for centerline temperature measurements along the entire reactor length. The measured length of the isothermal region, typically 46 cm, is taken to be the reactor's functional length, and is used to calculate the reaction time. In addition, temperatures are also measured at 10 fixed positions along the outer wall of the reactor. Radial temperature gradients are always found to be negligible (typically $< 5°$). For the smaller tubular reactor, one fixed internal thermocouple measures the fluid temperature immediately after the entrance heaters, where the heatup takes place. This temperature is usually within 1 or 2° of the wall temperatures at eight fixed locations along the reactor wall. This reactor has a fixed functional length of 27 cm.

D. To permit easy and frequent sampling of the reactor effluent. The key component of the sampling system is a 10-port dual-loop hplc injection valve (Valco Instruments C10W-HC) operating in a reverse mode. Whenever the valve is switched, a sample of the effluent is trapped at reactor pressure and room temperature in one of the two constant-volume loops, and later released into a pair of connected evacuated test tubes. To ensure a representative sample, the sampling-loop volume is always larger than the entire reactor volume. The pressure rise caused by the introduction of a sample into the fixed collection volume (test tubes plus loop) is calibrated to provide a measure of the total quantity of gaseous products produced by the reaction, which is always negligible in the experiments reported in this paper. The effluent is removed from the loop by flushing with either air or water. Flushing by air provides a somewhat more concentrated but only qualitative sample, because these samples suffer unknown dilution by the water trapped in the overhead volumes. Removal by an injection of water four times the

volume of the loop washes the entire contents of the loop into the collection tube, allowing the samples (diluted by a measured total volume) to be analyzed quantitatively.

Operating procedures for a typical experiment. — First, the hydraulic accumulator is isolated from the rest of the flow system and charged with air to the operating pressure. The reactor itself is then purged of air and hydrostatically tested at the operating pressure with water at room temperature. After confirming the system is leak free, the gas system is connected, the heaters are turned on, and a flow of water introduced into the reactor. During this time, the reactant solutions are premixed. After the system has reached the desired temperature at the specified flow rate, a complete temperature profile is taken. When the operator is satisfied that the best possible "step" temperature-profile has been obtained, the pump inlet is switched over to feed the reactant solution into the reactor. After an amount of reactant equivalent to five times the reactor volume is fed, another temperature profile is recorded, and sampling begins. Typically, a total of four samples are taken for every experimental condition.

All substrates and reference compounds were used as received, in the purest commercially available grades.

Analyses of the products. — This was a challenging task because of the complexity of the mixture as well as the diverse chemical affinities of the species involved. The primary tool was an hplc (Waters Associate Model 6000A solvent delivery system, Model 201 R.I. detector, Perkin–Elmer LC600 autosampler, Hewlett–Packard Model 3388A integrator) employing a polymeric cation-exchange column in the H^+ form (Interaction ION-300). A 0.5 mL/min flow of 2mM H_2SO_4 was used as the mobile phase at 80°. This column was chosen because of its ability to resolve a complex mixture of sugars, organic acids, aldehydes and alcohols. Unfortunately, the separation of the product species remains incomplete. The retention times of various relevant compounds are shown in Table II, bracketed into groups that are not adequately resolved. After numerous tests and calibrations, it was found that the peak-height response was linear to concentration within the range of our interest, and more precise than peak area (due to merged peaks, and integrator base-line recognition problems). Chemical species were also identified by g.l.c.–m.s. (Hewlett–Packard Model 5790 GC/5970 MSD equipped with a J&W FSOT capillary column: DB1701 30M × 0.25 mm × 0.25μm). Samples were injected both directly, and after conversion to *O*-trimethylsilyl (Me_3Si) derivatives. Compounds whose identities were confirmed by either of the g.l.c.–m.s. methods are so identified in Table II. In addition to corroborating the hplc results, g.l.c.–m.s. reveals the presence of other species. Compounds indicated by g.l.c.–m.s. but not hplc fall into three categories: unknowns, those tentatively identified by comparison with library spectra, and those positively identified by comparison with injection of authentic standards. 2,3-Butandione is the only compound falling into the third category, whereas category two includes such species as 3,5-dihydroxy-2-methyl-5-6-dihydropyran-4-one.

Compounds that were well resolved by hplc and which had identities confirmed by either of the two g.l.c.–m.s. methods were quantified by referencing against injection of authentic standards. These include glucose, pyruvaldehyde, glyceraldehyde, acetol,

TABLE II

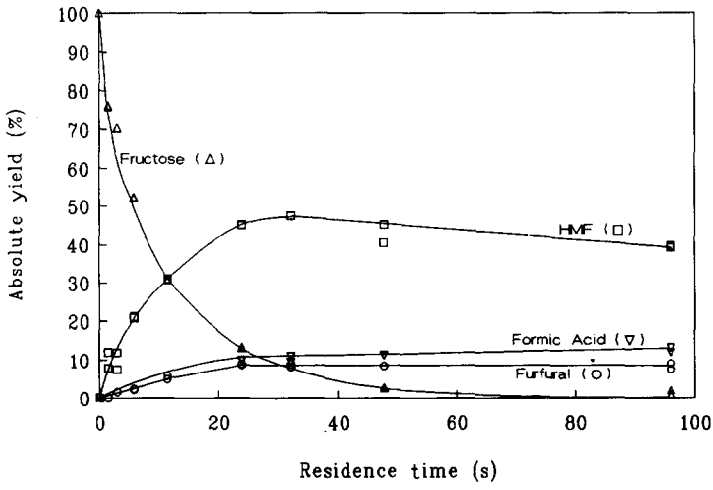
Some major products from fructose in water at 250°

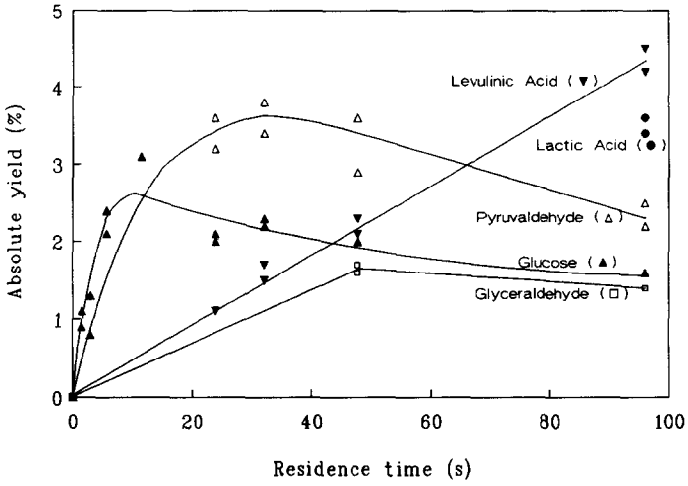
Compound	*Hplc retention time (min)*	*Detected by hplc*	*Detected by g.l.c.–m.s. without derivatization*	*Detected by Me_3Si g.l.c.–m.s.*
Glucose	12.5	yes		yes
Fructose	13.6	yes		yes
Mannose	13.6			no
Arabinose	14.7	trace		no
Glyceraldehyde	15.7	yes		yes
Pyruvaldehyde	16.5	yes		
Levoglucosan	17.0			no
Glycolaldehyde	17.1	yes	yes	yes
Lactic acid	17.4		yes	
Formic acid	18.2	yes	yes	
Dihydroxyacetone	19.4		yes	yes
Acetic acid	20.3	yes	yes	
Levulinic acid	22.0	yes	yes	
Acetol	23.1	yes	yes	
5-HMF	41.9	yes	yes	yes
Furfural	59.1	yes	yes	

HMF, and furfural. Because repetitive analyses by Me_3Si g.l.c.–m.s. show no presence of mannose, its concentration (if any) is taken to be negligible when compared with fructose. Thus the fructose–mannose peak is quantified as fructose. Although levoglucosan was mentioned in an earlier paper describing our preliminary work[20], its presence was not confirmed by g.l.c.–m.s. Furthermore, semiquantitative Me_3Si g.l.c. of the product solutions indicated that the amount of glycolaldehyde was very small compared with lactic acid. Consequently, the lactic acid–glycolaldehyde–levoglucosan hplc peak is quantified as lactic acid. Finally, semi-quantitative Me_3Si g.l.c. revealed no significant presence of DHA; hence the formic acid–DHA peak is quantified as formic acid.

RESULTS AND DISCUSSION

Figures 2 and 3 display the effect of residence time on absolute product yields at 250°, 34.5 MPa for 0.05M D-fructose reactant in water with and without acid catalyst. The absolute yield is the percentage molar yield of product based on the initial reactant. In the presence of 2mM H_2SO_4 (see Fig. 2) > 60% of the fructose reacts during the first 10 s, forming HMF, glucose, furfural, formic acid, glyceraldehyde, pyruvaldehyde, lactic acid, and levulinic acid. The immediate appearance of HMF and glucose after about 1 s indicates that the first steps in their formation are rate determining and that any intermediates involved in their formation must be present in very low concentrations. The concurrent, almost equimolar formation of formic acid with furfural suggests

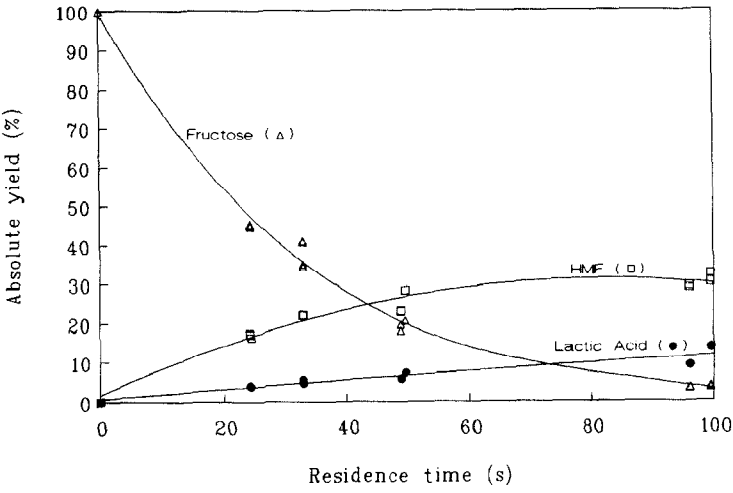


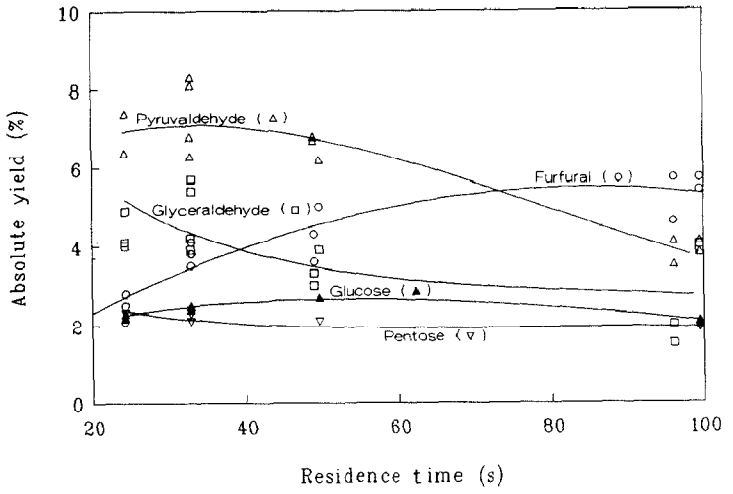


Figs. 2a and b. Absolute yields of reactant and products from 0.05M D-fructose in water with 2mM H_2SO_4 catalyst as a function of residence time. In 2b, lactic acid was detected in smaller amount but not quantified at residence times <90 s.

that these two species are byproducts of the same reaction-pathway. Without acid catalyst (see Fig. 3) the degradation reactions are somewhat less fast and less selective. Over 20 s are required to achieve a 60% conversion of fructose, and the maximum yields of both HMF and furfural decrease significantly. Contrarily, the uncatalyzed yield of glucose is almost identical to the catalyzed yield; whereas the yields of pyruvaldehyde and lactic acid improve dramatically in the absence of acid.

The low yield of glucose (which is relatively stable under these conditions) and the failure to detect significant mannose, suggest that the Lobry de Bruyn, Alberda van Ekenstein transformation is very slow under these conditions. In related experiments





Figs. 3a and b. Absolute yields of reactant and products from 0.05M D-fructose in water at 250° without catalyst as a function of residence time.

starting with glucose, to be reported in detail later, we have found that, under the same conditions, very little fructose is detected. Any explanation of these facts cannot be dependent upon thermodynamic control operating through the glucose–fructose equilibrium. We conclude that this equilibration is very slow under our conditions, and therefore enolization must be very slow. Hence, enols of fructose are not intermediates in HMF formation or fructose consumption. Thus these observations refute the hypotheses in Scheme 2.

The continued formation of lactic acid in the presence of 2mM sulfuric acid is very significant. The most likely source of lactic acid is the reverse-aldol scission of fructose

to glyceraldehyde and dihydroxyacetone (we shall show in the paper following this one that the latter is rapidly converted into the former under these conditions). The glyceraldehyde then dehydrates to pyruvaldehyde, which undergoes a benzilic acid rearrangement to lactic acid. We conclude therefore that the benzilic acid rearrangement occurs at a significant rate under these conditions. Accordingly, we have rigorously sought evidence for presence of 6-carbon saccharinic acids by Me_3Si g.l.c. of the acidic products from fructose, but have failed to detect either glucometasaccharinic or glucosaccharinic acids or lactones. As the former would comprise the major products of benzilic acid rearrangement of the 3-deoxyglycosulose, which is an intermediate in Scheme 2, and as the benzilic acid rearrangement can evidently occur under these conditions, we again conclude that the hypotheses detailed in Scheme 2 are refuted by our experiments.

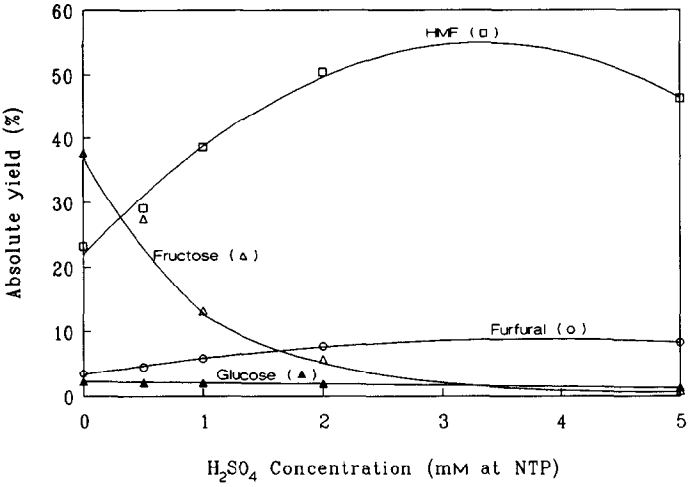


Fig. 4. Absolute yields of reactant and products from 0.05M D-fructose after 32 s in water at 250° as a function of H_2SO_4 concentration at normal temperature and pressure (NTP). Lactic acid, pyruvaldehyde, and some other products were detected but not quantified in these experiments.

Figure 4 displays the influence of H_2SO_4 concentration on product yields at 250°, 34.5 MPa and 32 s residence time. As expected, increasing acid concentration improves the yields of HMF and of furfural. The rapid increase in consumption of fructose, as contrasted with the relative stability of glucose, clearly illustrates the difference in reactivities of these two hexoses. Small amounts of formic, lactic, and levulinic acids and pyruvaldehyde were also detected in the conditions of Fig. 4, but were not quantified.

Figure 5 displays the dependence of product yields on initial fructose concentration without catalyst at 250°, 32 s residence time. The virtual independence of the rate of fructose consumption with change in its initial concentration shows that the overall reaction rate is effectively first-order. The steady yield of glucose with increasing fructose concentration indicates that the fructose–glucose isomerization reaction is also first order. The apparent orders of the reaction pathways which form HMF and furfural

TABLE III

A Comparison of Selected product yields from uncatalyzed and 2.4mM formic acid-catalyzed experiments with 0.05M fructose at 24.5 MPa, 250°, and 32 s residence time

	Yield	
Product	*Uncatalyzed*	*Catalyzed*
Fructose	0.38	0.44
HMF	0.22	0.23
Furfural	0.04	0.03
Glucose	0.02	0.03
Lactic acid	0.05	0.05
Pyruvaldehyde	0.07	0.05

are greater than one. The possibility that this higher-order behavior could be due to autocatalysis (as by acidic initial products[53]) is eliminated by an experiment with added formic acid (see Table III), which clearly demonstrates very little catalytic activity by this acid. This finding is in accord with our experience that only the strongest Brønsted acids (such as H_2SO_4 and HCl) are able to dissociate to a significant degree in liquid water at 250°.

The subtle influence of reactant concentration on product yields exhibited in Fig. 5 can offer definitive insights into the elementary steps comprising each reaction pathway. For a complex reaction network (such as this one) which contains many reaction pathways, numerical methods are required to evaluate the agreement of a kinetic model (representing the elementary steps in each pathway of the network) with

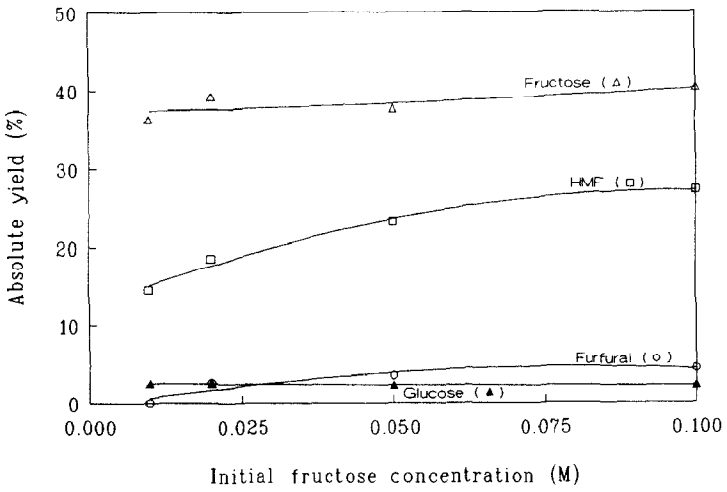


Fig.5. Absolute yield of reactant and products from D-fructose after 32 s in water at 250° without catalyst as a function of reactant concentration at normal temperature and pressure (NTP). Lactic acid, pyruvaldehyde, and some other products were detected but not quantified in these experiments.

the experimental data. The development of such a model, and its implications concerning the mechanisms underlying each reaction pathway, will be the subject of a later paper.

It is well known[52] that the first step in the acid-catalyzed hydrolysis of sucrose is the formation of the fructofuranosyl cation, together with glucose. According to Scheme 1, this cation is the key intermediate in the formation of HMF from fructose. Therefore, if Scheme 1 is correct, the molar yield of HMF per mole of sucrose consumed should be significantly higher than the comparable yield of HMF derived from fructose under identical conditions, after making a correction for HMF derived from the glucose that is simultaneously produced in the initial sucrose hydrolysis. Table IV displays results for 0.05M sucrose treatment in the presence and absence of H_2SO_4 at 250°, 32 s residence time and 34.5 MPa. Using the data given in Table IV, the yield of HMF per mole of hexose *monomer* consumed is 42% without catalyst, and 47% with acid. Under these conditions, the yield of HMF from glucose is 24% without acid and 31% with acid[54]. Employing these values, the estimated yield of HMF per mole of fructose consumed is 47% without catalyst, and 53% with catalyst. These are significantly higher than the values of 36% (without catalyst) and 42% (with catalyst) for the yields of HMF from pure fructose under identical conditions. Clearly then, as shown in Scheme 1, the fructofuranosyl cation, which is specifically produced from sucrose, is a key intermediate in the formation of HMF from fructose.

The question of total carbon balance in our experiments must be addressed. Figure 3 shows that a 50mM solution of fructose in water at 250° for 50 s yields

TABLE IV

Selected[a] Product Concentrations from 0.05M Sucrose after 32 s at 250°, 34.5 MPa

	Concentration (M)			
Catalyst	*Sucrose*	*Glucose*	*Fructose*	*HMF*
none	0.0	0.041	0.023	0.015
1.0mM H_2SO_4	0.0	0.036	0.011	0.025

[a]Other products include glyceraldehyde, dihydroxyacetone, lactic acid, and furfural.

predominantly the following products in the indicated mM amounts: fructose (9.2), lactic acid (2.9), HMF (11.7), furfural (1.9), glyceraldehyde (1.7), and pyruvaldehyde (3.4). The total solute concentration of the product solution derived from these figures is 3.98 $g.L^{-1}$. However, the evaporation to dryness of an aliquot portion of the product solution at 40° in vacuum yielded a residue corresponding to a solute concentration of 6.38 $g.L^{-1}$. It is evident therefore that some significant soluble and non-volatile products are not detected in our analyses. It is unlikely that such undetected material includes anhydro-dimers of fructose, because these would have been detected by the hplc

analysis. In any case, such dimers are only formed in significant amount at high fructose concentrations and high acidity.

The same type of calculation sheds light on the importance of the formation of water-insoluble products. Thus the original fructose solution contained 9.00 $g.L^{-1}$ of fructose, but after 50 s at 250°, yielded only 6.38 $g.L^{-1}$. Certainly some water was lost in condensation reactions (e.g. to the furfurals), and there are small amounts of other volatile products (such as formic acid). However, a regular examination of the exit filter in the reaction vessel also demonstrated the formation of relatively small amounts of insoluble, dark-colored material, which we describe as humins without further investigation.

ACKNOWLEDGMENTS

This research was supported by the National Science Foundation under grant no. CBT-8514867(UH), the Coral Industries Endowment (UH), and by the University of Montana.

REFERENCES

1 M. Bodenstein and S. C. Lind, *A. Physik. Chem.*, 57 (1907) 168.
2 J. A. Christiansen, *K. Dan. Vidensk. Selsk. Mat.-Fys. Medd.*, 1 (1919) 14.
3 K. F. Herzfeld, *Ann. Physik.*, 59 (1919) 635.
4 M. Z. Polanyi, *Elektrochem.*, 26 (1920) 50.
5 *Chem. Eng. News*, 11 Sept. 1961, 75–76.
6 R. C. Elderfield and T. N. Dodd, Jr., in R. C. Elderfield (Ed.), *Heterocyclic Compounds* Vol. 1, Wiley, New York, 1950, p. 119.
7 A. P. Dunlop and F. N. Peters (Eds.), *The Furans*, Reinhold, New York, 1953.
8 C. J. Moye and Z. S. Krzeminski, *Aust. J. Chem.*, 16 (1963) 258.
9 P. E. Shaw, J. H. Tatum, and R. E. Berry, *Carbohydr. Res.*, 5 (1967) 266–273.
10 G. Bonn and O. Bobleter, *J Radioanal. Chem.*, 79 (1983) 171–177.
11 B. F. M. Kuster and H. S. van der Baan, *Carbohydr. Res.*, 54 (1977) 165–176.
12 R. K. M. R. Kallury, C. Ambridge, T. T. Tidwell, D. G. B. Boocock, F. A. Agblevor, and D. J. Stewart, *Carbohydr. Res.*, 158 (1986) 253–261.
13 B. F. M. Kuster and H. M. G. Temmink, *Carbohydr. Res.*, 54 (1977) 185–191.
14 J. U. Nef, *Ann. Chem.*, 376 (1910) 1–119.
15 W. N. Haworth, E. L. Hirst, and V. S. Nicholson, *J. Chem. Soc.*, (1927) 1513–1526.
16 W. N. Haworth and W. G. M. Jones, *J. Chem. Soc.*, (1944) 667.
17 M. L. Mednick, *J. Org. Chem.*, 27 (1962) 398–403.
18 H. H. Szmant and D. D. Chundury, *J. Chem. Tech. Biotechnolog.*, 31 (1981) 135–145.
19 L. Rigal and A. Gaset, *Biomass*, 3 (1983) 151; see also L. Regal, A. Gaset, and J. P. Gorrichon, *Ind. Eng. Prod. Res. Dev.*, 20 (1981) 719–721.
20 M. J. Antal and W. S. Mok in A.V. Bridgewater and J. L. Kuester (Eds.), *Research in Thermochemical Biomass Conversion*, Elsevier Applied Science, London, 1988, pp. 464–472.
21 C. D. Hurd and L. L. Isenhour, *J. Am. Chem. Soc.*, 54 (1932) 317–330.
22 M. L. Wolfrom, E. G. Wallace, and E. A. Metcalf, *J. Am. Chem. Soc.*, 64 (1942) 265.
23 H. S. Isbell, *J. Res. Nat. Bur. Stand.*, 32 (1944) 45.
24 M. L. Wolfrom, R. D. Schuetz, and L. F. Cavalieri, *J. Am. Chem. Soc.*, 70 (1948) 514–517.
25 M. L. Wolfrom, R. D. Schuetz, and L. F. Cavalieri, *J. Am. Chem. Soc.*, 71 (1949) 3518–3523.
26 E. F. L. J. Anet, *J. Am. Chem. Soc.*, 82 (1960) 1502.
27 E. F. L. J. Anet, *Aust. J. Chem.*, 14 (1961) 295–301.
28 E. F. L. J. Anet, *Chem. Ind. (London)*, (1962) 262.
29 E. F. L. J. Anet, *Aust. J. Chem.*, 18 (1965) 240.

30 F. H. Newth, *Adv. Carbohydr. Chem.*, 6 (1951) 83–106.
31 E. F. L. J. Anet, *Adv. Carbohydr.Chem.*, 19 (1964) 181–218.
32 W. Pigman and E. F. L. J. Anet, in W. Pigman and D. Horton (Eds.), *The Carbohydrates* Vol. 1, Academic Press, New York, 1972, pp. 165–194.
33 M. S. Feather and J. F. Harris, *Adv. Carbohydr. Chem. Biochem.*, 28 (1973) 161–224.
34 Q. P. Peniston, U.S. Patent No. 2,750,394.
35 J. D. Garber and R. E. Jones, U.S. Patent No. 2,929,823, March 22, 1960.
36 R. E. Jones and H. B. Lange, U.S. Patent No. 3,066,150.
37 R. A. Hales, J. W. LeMaistre, and G. O. Orth, U.S. Patent No. 3,071,599.
38 J. D. Garber and R. E. Jones, U.S. Patent No. 3,483,228.
39 G. Machell and G. N. Richards, *J. Chem. Soc.*, (1960) 1938–1944.
40 E. F. L. J. Anet, *Tetrahedron Lett.*, (1968) 3525.
41 G. Fodor and J.-P. Sachetto, *Tetrahedron Lett.*, (1968) 401.
42 M. S. Feather and J. F. Harris, *Carbohydr. Res.*, 15 (1970) 304–309.
43 D. W. Harris and M. S. Feather, *Carbohydr. Res.*, 30 (1973) 359–365.
44 R. E. Miller and S. M. Cantor, *J. Am. Chem. Soc.*, 74 (1952) 5236.
45 C. J. Moye, *Aust. J. Chem.*, 19 (1966) 2317–2320.
46 B. F. M. Kuster, *Carbohydr. Res.*, 54, (1977) 177–183.
47 D. Mercadier, L. Rigal, A. Gaset, and J. P. Gorrichon, *J. Chem. Technol. Biotechnol.*, 31 (1981) 489.
48 L. Poncini and G. N. Richards, *Carbohydr. Res.*, 87 (1980) 209–217.
49 T. G. Bonner, E. J. Bourne, and M. Ruszkiewier, *J. Chem. Soc.*, (1960) 787–791.
50 C. F. Moye and R. F. Goldsck, *J. Appl. Chem.*, 16 (1966) 206–208.
51 Y. Nakamura and S. Morikawa, *Bull. Chem. Soc. Jpn.*, 53 (1980) 3705–3706.
52 W. Moody and G. N. Richards, *Carbohydr. Res.*, 124 (1983) 201–213; *ibid.*, 111 (1982) 23–29. See also T. L. Mega and R. L. Van Etten, *J. Am. Chem. Soc.*, 110 (1988) 6372–6376.
53 G. N. Richards, *Int. Sugar J.*, 88 (1986) 145–148.
54 T. C. Leesonboon, M.S.E. Thesis, U. Hawaii, 1988.