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# Unifying Mechanistic Analysis of Factors Controlling Selectivity in Fructose Dehydration to 5-Hydroxymethylfurfural by Homogeneous Acid Catalysts in Aprotic Solvents

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**ABSTRACT:** The need for liquid fuels from inexpensive and abundant biomass sources continues to increase in light of the growing environmental and strategic consequences of relying on depletable petroleum. Fructose, a monomeric sugar derived from biomass, can be dehydrated to 5-hydroxymethylfurfural (HMF), an intermediate to furans that are high-energy-content compounds miscible with petroleum. To be economically competitive, production of HMF from fructose must achieve high selectivities and yields, but the design of catalysts that achieve high-yield HMF production is made difficult by the lack of understanding of the mechanistic aspects of fructose conversion to HMF. Various studies examining fructose conversion to HMF by homogeneous acids have proposed that different factors control selectivity, including the acid type, fructose tautomer distribution, and solvent type. A high-throughput system was utilized to develop detailed insights into mechanisms and factors controlling HMF selectivity from fructose dehydration by homogeneous acid catalysts. The high-throughput system utilized a 96-well Hastelloy plate reactor to facilitate the development of extensive data over a range of aqueous solvent systems, temperature, time, acid types, and acid concentrations. In situ NMR was also employed to analyze the relative distribution of fructose tautomers as a function of solvent type and temperature. HMF selectivity was directly correlated with the distribution of furanose and open-chain tautomers of fructose as a function of reaction temperature, time, and solvent composition. The observed correlation supported the hypothesis that selectivity in fructose conversion to HMF is primarily controlled by the equilibrium between the tautomeric forms of fructose in solution. Further, it was identified that difructose anhydrides act as slow-converting, protective intermediates that increase HMF production during longer reaction times to a selectivity higher than that which would be predicted by the fructose tautomeric distribution alone.

**KEYWORDS:** 5-hydroxymethylfurfural, fructose, acid catalysis, biomass, selectivity
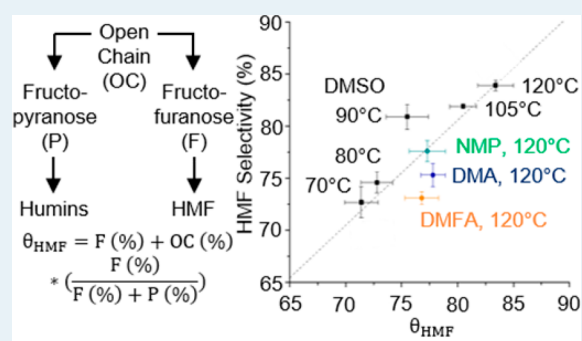
## ■ INTRODUCTION

$CO_2$ accumulation in the atmosphere resulting from the consumption of nonrenewable petroleum resources can potentially be reduced by a transition to the production of chemicals and fuels from renewable biomass feedstocks.[1−4] Biomass-derived furans have received attention as promising renewable intermediate chemicals, because they can be converted into an array of valuable fuels and chemicals.[5−7] Although furans can be produced directly from biomass in appreciable yields,[8] their production typically involves an initial liquid-phase pretreatment coupled with biological conversion to release C5 and C6 sugars, such as xylose and glucose, followed by their selective conversion into value-added intermediates and chemicals.[7,9−12] 5-Hydroxymethylfurfural (HMF) is a highly desirable chemical, as it is an intermediate to attractive fuel components, such as furans[13−15] and alkanes.[16] Addition-

ally, HMF can be oxidized to produce 2,5-furandicarboxylic acid (FDCA) and 2,5-bis(hydroxymethyl)furan (BHMF),[17] which are potential derivatives for biopolymer production. Thus, polyesters and fuels can be derived from renewable biomass sources through HMF as an intermediate, although the commercial viability of these routes requires high yields in each process step.

The production of HMF from fructose has been of interest because higher HMF yields can be obtained from fructose in comparison to other sugar precursors.[18] The conversion of fructose to HMF involves three sequential dehydration steps and is typically catalyzed by Brønsted acids.[19,20] In addition to

the pathway for HMF formation from fructose, various unwanted side reactions can be catalyzed by acids, which result in decreased HMF yields. For example, fructose and HMF can be converted to polycondensation products and humins through acid- or base-catalyzed degradation.[21,22] Furthermore, HMF can be rehydrated into formic acid (FA) and levulinic acid (LA). Previous studies have suggested that reaction temperature, catalyst choice, and solvent composition may all influence yields in fructose conversion to HMF. However, no comprehensive analyses have been applied to determine how reaction selectivity relates to process parameters through mechanistic insights.

A wide variety of Lewis and Brønsted acids, as both heterogeneous and homogeneous catalysts, have been applied to the dehydration of fructose.[23-25] Generally, heterogeneous acid catalysts are preferred due to their ease of separation. However, soluble polymers and humins foul heterogeneous catalysts, requiring regular catalyst regeneration. As a result, homogeneous acids offer benefits, as they are sufficiently inexpensive to avoid the need for costly catalyst regeneration. In particular, experiments that utilized mineral acids, such as sulfuric acid ($H_2SO_4$) and hydrochloric acid (HCl), have shown the highest HMF yields in comparison to other homogeneous acids.[6] Previous studies have proposed that HMF selectivity in fructose dehydration may be influenced by Brønsted acidity[26] or that the acid anion may be involved in stabilizing carbocation intermediates which lead to HMF formation.[9] Effects associated with anion stabilization of carbocation intermediates should be more noticeable in aprotic solvents, as anions are less solvated in these systems in comparison to water and therefore more reactive.[27] However, direct comparisons of Brønsted acid anion influences on HMF formation in aprotic solvents have been not reported.

In addition to the potential influence of acid catalyst characteristics, efforts have been made to analyze how HMF production from fructose is influenced by solvents including water,[19,26,28,29] alcohols,[30] aprotic solvents,[9,31-36] ionic liquids (ILs),[37-39] and organic cosolvent mixtures.[30,40-42] Aqueous systems have received the most attention. However, HMF yields have generally been reported to be low (<65%) in aqueous systems due to HMF rehydration to LA and FA and humins production. Polar aprotic solvents have been utilized as cosolvents in aqueous systems to increase HMF production.[5-7] For example, it was reported that the addition of 20 wt % dimethyl sulfoxide (DMSO) to an aqueous biphasic system increased fructose conversion from 91% to 94% and HMF selectivity increased from 60% to 67%.[40] Higher contents of DMSO have been shown to increase selectivity to HMF to above 80%.[42] These outcomes are clear evidence that the solvent significantly influences both the rate and selectivity of fructose dehydration. However, the majority of reports that utilize DMSO as a solvent have been performed in the presence of oxygen, with the result that DMSO will undergo radical decomposition at temperatures >80 °C to form methylsulfonic acid and other acidic species.[43] As a result, it is unclear whether DMSO or acid produced from DMSO is the primary cause of increased HMF production. The use of other aprotic solvents such as dimethylacetamide (DMA),[9] N-methyl-2-pyrrolidone (NMP),[44] and dimethylformamide (DMFA)[45] have also been reported to enable high HMF yields from fructose when the process is catalyzed by homogeneous acids. Developing mechanistic insights into why these aprotic solvents enable

high selectivity for HMF production is critical for the design of optimized fructose conversion processes.

Various mechanistic studies have attempted to understand the primary pathway for HMF formation from fructose and identify elementary steps that dictate selectivity and reaction rates.[6,46,47] Results from in situ $^{13}C$ NMR spectroscopy have led to the conclusion that cyclic intermediates are the primary species that lead to HMF formation.[33,48,34] The exclusive involvement of cyclic intermediates in HMF formation supported a proposed mechanism based on the fructofuranose tautomer (fructose can exist in pyranose, furanose, and open-chain tautomeric forms) being the primary fructose tautomer that leads to HMF formation, due to their similar five-membered-ring structures. This hypothesis is supported by broader trends observed across solvent systems, for which the tautomeric distribution of fructose in solution has been proposed to control HMF selectivity.[30,32,40] In this proposed mechanism, it has been suggested that the fructofuranose form dehydrates to HMF, while the fructopyranose form dehydrates to humins.[35,49] However, to date, no conclusive relationship has been demonstrated between the tautomeric distribution of fructose in solution and HMF selectivity. As a result, there is a lack of mechanistic insight to guide the design of optimal catalysts and solvents for HMF production.

To develop detailed insights into factors that control HMF selectivity in fructose dehydration by homogeneous acids in aprotic solvents, a high-throughput reactor was employed to allow an extensive kinetic analysis from application of a variety of solvent systems, reaction conditions, acid types, and acid concentrations. In particular, we focused on DMSO solutions, due to the high HMF yields reported in previous studies. In addition to kinetic analyses, in situ $^{13}C$ NMR experiments were utilized to quantify the distribution of fructose tautomers in solution as a function of reaction conditions. Through these mechanistic studies, it was concluded that fructose dehydration in DMSO solvent systems must be executed under deaerated conditions to avoid production of acidic species by DMSO oxidation. Furthermore, these systematic kinetic analyses showed that the primary factors controlling selectivity are temperature, solvent composition, and time. The observed HMF selectivity was quantitatively correlated with the distribution of fructose existing in the furanose form under the reaction conditions. This result supports the hypothesis that fructofuranose dehydrates to HMF and the fructopyranose degrades to humins, while the open-chain form rapidly equilibrates to maintain a constant furanose/pyranose ratio that controls selectivity. Further, it was identified that difructose anhydrides (DFAs), oligomers of fructose, act as slow-converting, protective intermediates that increase HMF production during longer reaction times to selectivity higher than that which would be predicted by the tautomeric distribution. The results of this study are expected to serve as a guide for the rational design of HMF-producing processes with maximized yields.

## ■ EXPERIMENTAL DETAILS

**Materials.** The following materials were purchased from Sigma-Aldrich (Carlsbad, CA): D-fructose (≥99%), glucose (≥99), DMSO (99.995%), NMP (≥99.5%), DMA (≥99%), DMF (≥99.8%), HMF (≥99%), levulinic acid (LA; ≥97%), formic acid (FA; ≥95%), hydrochloric acid (HCl; 37%), hydrobromic acid (HBr; 48%), hydriodic acid (HI; 57%)), N-methyl-2-pyrrolidinone-$d_9$ (NMP-$d_6$; 98%), and N,N-dimethyl-
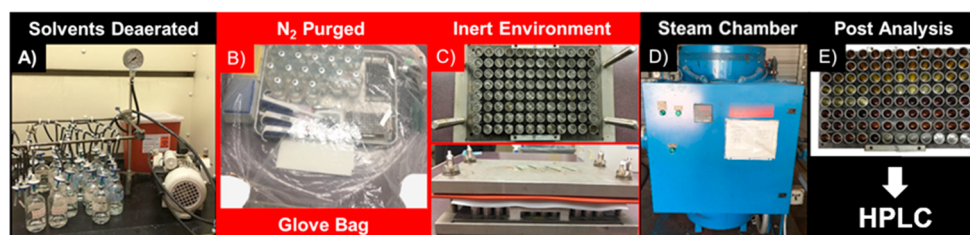
**Figure 1.** Experimental procedure for high-throughput fructose dehydration with control atmosphere: (A) multiple sealed pressure bottles containing the desired solvents, acid, and fructose repeatedly degassed under vacuum and purged with nitrogen. (B) 96-well plate reactor enclosed in a glovebag purged with nitrogen, along with sealed vials containing deaerated reactants and solvents. (C) reactor wells were loaded and sealed with Teflon film, silicone rubber, and steel plate (in that order) while still in purged glovebag. (D) transfer of the 96-well reactor to a steam chamber and heating with pressurized steam at controlled temperatures for controlled times. (E) unsealing of the 96-well reactor and analysis of the solution via HPLC.

formamide-$d_7$ (DMFA-$d_6$; ≥99.5%). Sulfuric acid ($H_2SO_4$; ≥99.999%) and nitric acid ($NO_3$; 70%) were purchased from Fisher Scientific. D-[2-$^{13}$C]-Fructose (>99%), DMSO-$d_6$ (99.9%), and deuterium oxide ($D_2O$; 99.96%) were purchased from Cambridge Isotope Laboratories (Tewksbury, MA), and N,N-dimethylacetamide-$d_9$ (DMA-$d_9$; ≥99%) was obtained from CDN Isotopes (Pointe-Claire, QC). All chemicals were used without further purification.

**High-Throughput Procedure for Fructose Dehydration Studies.** Aqueous dipolar aprotic solutions (EMD Millipore Milli-Q) were prepared in a graduated flask with 25 g/L of fructose and 10 mM of acid, unless otherwise stated. Solutions were prepared in open air and loaded into 100 mL serum bottles (Supelco) that were sealed with a Teflon rubber stopper and crimped in position with an open-center aluminum crimp. As shown in Figure 1a, the serum bottles were then taken to a custom-made Schlenk line, where they were degassed and purged with $N_2$ for 25 cycles to remove excess air from the solutions. The serum bottles and the custom-made Hastelloy 96-well plate (Figure 1b) were loaded into a two-hand, nonsterile glovebag (Aldrich AtmosBag). The custom 96-well plate has the same dimensions as a standard well plate.[50] The individual wells are removable and made from Hastelloy bars cut to a length of 23.14 mm and the core was milled to a well volume of 640 μL. The glovebag was purged and degassed by $N_2$ for 25 cycles. Once oxygen was removed from the bag, the bottles were decrimped and desired solutions were loaded into the 96-well plate by pipet, under $N_2$ (see Figure 1c). The wells were then sealed by direct contact with Teflon PTFE film (0.012 in. thick, durometer hardness R58) and silicone gasket (thickness 1.5875 mm, durometer hardness A40), which were compressed onto the wells by two 304 stainless steel well plates using four 1/4 in. 20-threaded bolts (6.35 mm-20) placed in each corner of the plate together with spring washers (flat load 1500 N) and wing nuts. The 96-well plate was then sealed within the glovebag before being removed. The well plate was then placed in a custom-made high-pressure vertical chamber that was heated by saturated steam generated in a 75 kW boiler (FB-075-L Fulton Companies, Pulaski, NY) at the appropriate pressure and temperature (Figure 1d). When the desired reaction time was reached, the steam inlet valve was closed, steam was released from the chamber, and the chamber was filled with cool water to quench the reaction. The plates were then unsealed, and the reaction solution was pipetted into vials for high-pressure liquid chromatography (HPLC) analysis (Figure 1e). All similar experiments followed the same deaerating, loading, reaction, and analysis procedure. The

molar water content was determined by the volume of water added plus the water content within both the organic solvent and fructose added. Each experiment was run with four replicates, where 4 of the 96 wells were filled with identical sample solutions.

**Analytical Procedures.** The majority of the resulting mixtures formed a single phase and were analyzed without dilution. For samples in which insoluble humins production was observed, the samples were centrifuged at 5000 rpm for 10 min (Allegra X-15R Centrifuge, Beckman Coulter), and the solid-free supernatant was analyzed for sugars, organic acids, and furan concentrations using a Waters Alliance HPLC (Model e2695, Waters Co., Milford, MA) equipped with a Waters 2414 RI and PDA detector. The Aminex HPX-87H column (Bio-Rad Life Science, Hercules, CA) utilized in the HPLC was conditioned at 65 °C with a 5 mM sulfuric acid mobile phase at flow rate of 0.6 mL/min. The amounts of fructose, HMF, and DFA were determined by comparison to measurements with external standards. The fructose conversion and product yields and selectivity were calculated according to the equations

$$\text{conversion (mol \%)} = \left(1 - \frac{M_{RF}}{M_F}\right) \times 100\% \tag{1}$$

$$Y_{HMF} \text{ (mol \%)} = \left(\frac{M_{HMF}}{M_F}\right) \times 100\% \tag{2}$$

$$Y_{DFA} \text{ (mol \%)} = \left(\frac{2M_{DFA}}{M_F}\right) \times 100\% \tag{3}$$

in which $M_F$, $M_{RF}$, $M_{HMF}$, and $M_{DFA}$ represents the moles of initial fructose, remaining fructose, HMF, and DFA, respectively. Additionally, $Y_{HMF}$ and $Y_{DFA}$ are yields of HMF and DFA, respectively.

**NMR Study of D-Fructose and DFA Tautomeric Distributions.** NMR spectra of the 2-[$^{13}$C]-fructose tautomeric distribution were recorded on a Bruker Avance 600 spectrometer equipped with a 5 mm BBO variable-temperature probe. The $^{13}$C NMR spectra were obtained over 128 scans with a standard gradient pulse sequence and a relaxation delay of 10 s. The percentage of each tautomer was calculated and normalized with respect to one another, using Bruker TopSpin software. All samples were loaded into pressure bottles and deaerated, via the custom-made Schlenk line described above. Within a deaerated glovebag, the samples were transferred into a Norell valved 5 mm NMR tube (thick walled). The fructose

tautomeric distribution in DMSO-$d_6$ (99.9%) was recorded at temperatures of 70, 80, 90, 105, 120, and 150 °C using the variable-temperature probe in situ. Dehydration studies analyzing the tautomeric distribution of DFAs were carried out at 80 °C in DMSO-$d_6$ with 10 mM $H_2SO_4$. The tautomeric distribution of 2-[$^{13}C$]-fructose (25 g/L) was also analyzed in DMA-$d_9$, NMP-$d_9$, and DMFA-$d_9$ at 120 °C.

## ■ RESULTS

**Influence of Environment on HMF Yield.** The role of DMSO oxidation and in situ production of acidic species was analyzed in aqueous−DMSO mixtures containing fructose over a range of water molar percent without an acid catalyst at a temperature of 150 °C for 30 min under aerated and deaerated conditions. Figure 2 reports the fructose conversion and HMF
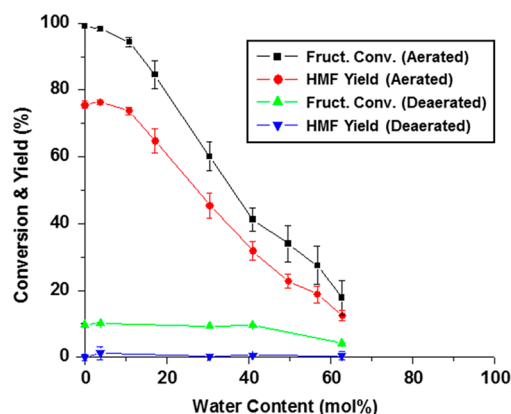


**Figure 2.** Conversion of fructose and yield of 5-HMF as a function of water content (mol %) in the DMSO mixture with a 25 g/L fructose loading and reaction volumes of 300 μL in 600 μL wells. Experiments were performed at 150 °C for 30 min after the solvent and headspace had been deaerated (green −▲−, fructose conversions; blue −▼−, 5-HMF yields) by nitrogen purging and with solvents and headspace without deaeration (black −■−, fructose conversions; red −●−, 5-HMF yields).

yields as a function of water molar percent under aerated and deaerated conditions. As shown, HMF was produced in significant yields for aerated conditions, while under deaerated

conditions little to no HMF production was observed. This result contrasts with previous reports which stated that DMSO acted as a catalyst that facilitated full fructose dehydration to reach high HMF yields.[33,48] This contradiction can be accounted for by the thermal decomposition of DMSO above 80 °C in the presence of oxygen[43] to produce acidic species, such as $H_2SO_4$, that can catalyze the reaction.[35,43] Additionally, it can be seen that under aerated conditions water content significantly hindered the conversion rates. However, water contents up to about 40 mol % had minimal effect on HMF selectivity, which remained roughly constant at 78%, in agreement with other reports of fructose dehydration in pure DMSO under aerated conditions.[35] The slight conversion of fructose under deaerated conditions can be accounted for by the caramelization of fructose, indicated by an observed light brown color. On the basis of these results, subsequent experiments were performed strictly under deaerated conditions to solely analyze the role of DMSO as a solvent.

**Influence of Acidity and Mineral Acid Type.** Fructose conversion and HMF selectivity were measured as a function of calculated pH (pH*) that was determined on the basis of $H_2SO_4$ concentration added to the solution. The experiments were executed by filling the 96-well plate reactor with 25 g/L of fructose over a range of pH and holding the reactor at 150 °C for 30 min. Figure 3a shows that the fructose conversion dropped with increasing pH, while the selectivity to HMF remained constant at between ∼80 and 85%. Only trace amounts of LA and FA were observed, as water is necessary for the conversion of HMF to LA and FA. Nonquantified products were mostly in the form of soluble humins, as evidenced by a deep dark color of the solution, and DFAs that are discussed further below. Importantly, it was observed that, while fructose conversion varied significantly as a function of acid loading, the HMF selectivity remained essentially constant. The constant HMF selectivity as a function of fructose conversion provides evidence that HMF selectivity was controlled by a thermodynamic equilibrium, rather than by competing kinetic pathways.

In addition to the influence of acid loading, the effect of acid type was examined to determine if the weak base pair of the acid catalyst influenced the fructose dehydration reaction. In particular, the mineral acids HI, HBr, HCl, $HNO_3$, and $H_2SO_4$ were applied to catalyze fructose dehydration in DMSO
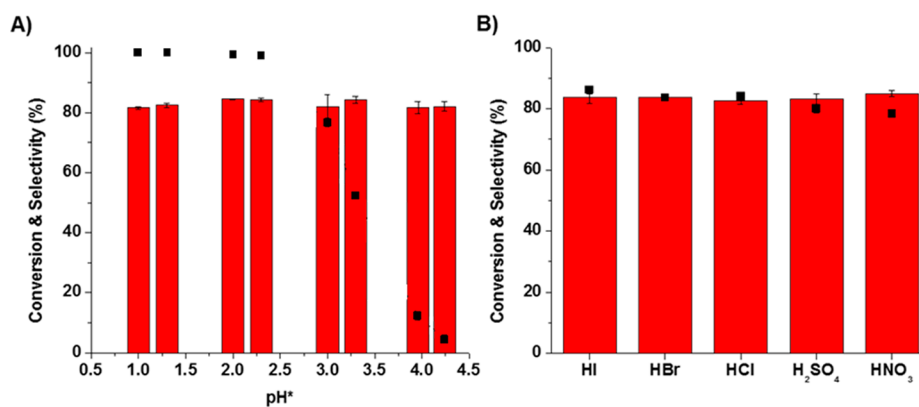


**Figure 3.** (A) Fructose conversion (black dots) and HMF selectivity (red bars) vs the calculated pH (pH*) based on initial $H_2SO_4$ concentration for acid-catalyzed dehydration of fructose in anhydrous DMSO under deaerated conditions. (B) Effect of acid type on fructose conversion and HMF selectivity. For (A), $H_2SO_4$ concentrations were varied from 0.01 to 100 mM and reactions were performed at 150 °C for 30 min. For (B), reactions were performed with 10 mM HI, HBr, HCl, $H_2SO_4$, and $HNO_3$ at 120 °C for 12.5 min. All reactions were run with 25 g/L fructose in DMSO for reaction volumes of 300 μL in 600 μL wells, deaerated with nitrogen gas.

mixtures at an acid loading of 10 mM, a temperature of 120 °C, and a reaction time of 12.5 min. The results in Figure 3b show that the selectivity to HMF was ~83% for all five acids. Fructose conversion increased slightly from about 78% to 84% as the acid strength was increased. Because HI has a $K_a$ value over 9 orders of magnitude higher than that of $HNO_3$ (3.9 × $10^9$ versus 2.4, respectively), the very small increase in conversion with significant variation in acid strength demonstrated that the initial protonation of fructose by a Brønsted acid is not the rate-limiting step in the reaction.

**Influence of Temperature.** Next, the influence of reaction temperature on the fructose dehydration rate and selectivity was analyzed. Fructose was dehydrated for 30 min in DMSO at temperatures of 70, 80, 90, 105, and 120 °C at a fructose loading of 25 g/L and catalyst loading of 10 mM $H_2SO_4$. Two major products were identified and quantified by HPLC: DFAs and HMF, as shown in Figure 4. It was observed that selectivity
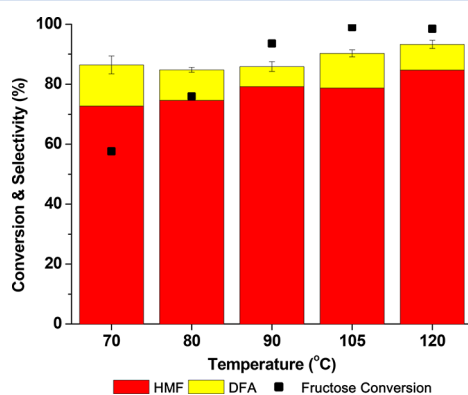


**Figure 4.** Fructose conversion (black dots), HMF selectivity (red bars), and DFA selectivity (yellow bars) for acid-catalyzed dehydration of fructose in anhydrous DMSO under deaerated conditions. Reactions were performed at 70, 80, 90, 105, and 120 °C. All reactions were performed with 25 g/L fructose in DMSO with reaction volumes of 300 µL in 600 µL wells, deaerated with nitrogen gas.

to HMF increased from 74% to 84% as the temperature was increased from 70 to 120 °C. In contrast, DFA selectivity dropped with increasing temperature from 70 to 120 °C but more directly decreased with increasing HMF selectivity, suggesting that DFAs serve as intermediates for HMF formation. Fructose conversion also increased with temperature. Unlike the effect of increasing acid loading, which did not change HMF selectivity, the selectivity to HMF increased with temperature. This result again suggests that HMF selectivity is thermodynamically controlled in aqueous DMSO mixtures.

**Influence of Water Content.** To determine how water content plays a role in HMF production, aqueous DMSO mixtures of 25 g/L fructose with 10 mM $H_2SO_4$ were prepared in combination with water amounts from ~0 to 80 mol % and heated at 105 °C for 30 min. The results in Figure 5 show that both DFA and HMF selectivity stayed roughly constant (~10% and ~80%, respectively) up to water contents of 40 mol %. Above 40 mol % water content HMF selectivity began to drop until it reached ~60% at a water content of 80%, at which point the DFA selectivity had increased to ~15%. Increasing water content was observed to also hinder fructose conversion. These results demonstrate that water content influences both HMF selectivity and yields.

**Effect of Solvent.** To further understand the influence of the solvent environment, fructose dehydration reactions were
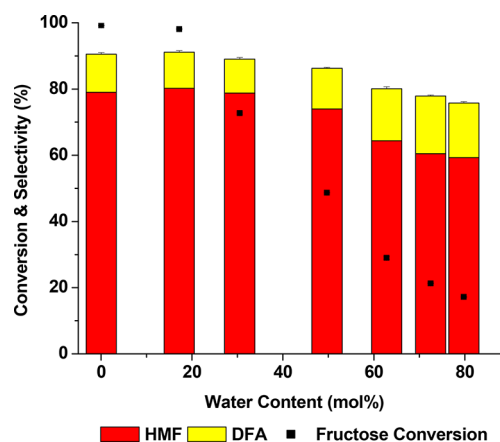


**Figure 5.** Fructose conversion (black dots), DFA selectivity (yellow bars), and HMF selectivity (red bars) for acid-catalyzed dehydration of fructose with increasing water content (mol %) in DMSO mixtures under deaerated conditions. Reaction conditions: 25 g/L fructose in DMSO with 10 mM $H_2SO_4$ at 105 °C for 30 min. A 300 µL portion of the solution was added to 600 µL wells that were then deaerated with nitrogen gas.

performed in different aqueous dipolar aprotic mixtures with varying water content. A 25 g/L amount of fructose was loaded into aqueous mixtures of DMSO, NMP, DMA, and DMF and heated to 120 °C for 10 min with 10 mM HCl as the acid catalyst. Figure 6a shows fructose conversion as a function of water content (mol %) for each solvent, as the water content was varied from ~0 to 30 mol %. In DMSO and NMP nearly identical fructose conversions were observed over a range of water contents, whereas fructose conversion in DMFA and DMA followed similar dependences on water content. In Figure 6b, HMF selectivity is plotted as a function of fructose conversion for each of the aqueous solvent mixtures. Fructose conversion in DMSO was greatest at the lowest water content and exhibited the highest HMF selectivity (~84%), followed by DMA (~78%), NMP (~77%), and DMFA (~74%). For DMA, NMP, and DMSO, the HMF selectivity did not change with fructose conversion, consistent with the observation that, below ~40% water content, solvent composition had little influence on HMF selectivity. The drop in HMF selectivity in DMFA with increasing water content will be discussed in more detail later.

To summarize the observations from these studies

(1) Operating in deaerated DMSO solutions without additional acid resulted in minimal observable fructose conversion. This outcome demonstrated that DMSO is itself not a catalyst that can drive fructose conversion and further that the primary influence of DMSO on HMF production must be a solvent effect.

(2) Acid loading and acid strength (type) had no measurable influence on HMF selectivity, whereas variations in reaction temperature and solvent composition (type of solvent and aqueous dilution above 40%) influenced HMF selectivity.

(3) DFA formed and its selectivity tended to drop as HMF selectivity increased, suggesting that DFA is an intermediate to HMF formation.

In the following discussion, a unifying mechanism will be developed to explain how the experimentally observed rate and selectivity of fructose dehydration to HMF are controlled.
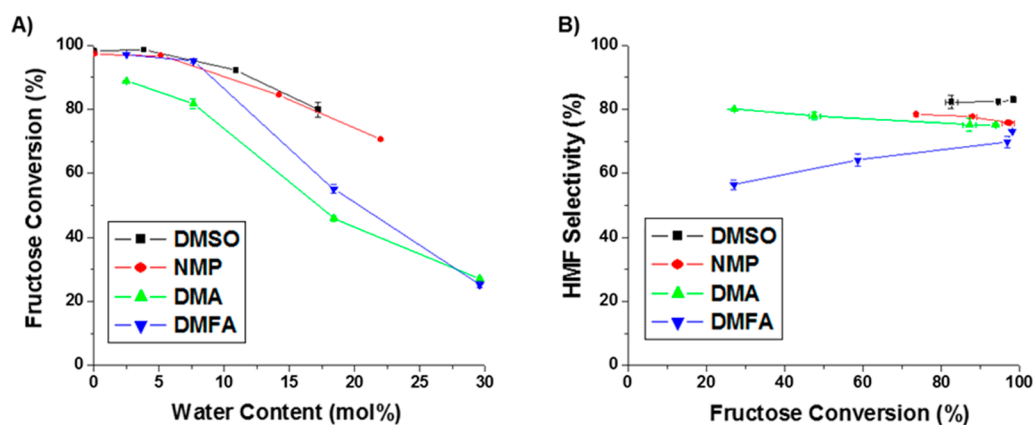
**Figure 6.** (A) Conversion of fructose as a function of water content (mol %) and (B) 5-HMF selectivity as a function of fructose conversion for DMSO (black), NMP (red), DMA (green), and DMFA (blue). Experiments were performed in 10 mM HCl catalyst for 10 min with deaerated solvent and headspace.

## ■ MECHANISM OF FRUCTOSE DEHYDRATION

The dehydration of fructose to HMF has been previously reported for DMSO systems with and without an added acid catalyst.[6] Previous reports suggested that DMSO acts as both a catalyst and a solvent.[33] However, it is known that DMSO undergoes radical decomposition in the presence of oxygen at elevated temperatures to form acidic species.[34,43] To determine the effect of DMSO decomposition on HMF production, fructose dehydration in aqueous DMSO mixtures was compared for aerated and deaerated conditions without adding an acid catalyst. HMF production was only observed under aerated conditions in all aqueous mixtures while minimal fructose conversion (<10%) was observed, likely due to sugar degradation. This result demonstrates that DMSO does not act as a catalyst by itself. HMF production can be attributed to in situ production of acidic species (e.g., $H_2SO_4$ and $CH_3SO_3H$) that then catalyze fructose dehydration to HMF. These results demonstrate conclusively that obtaining an accurate kinetic and mechanistic understanding of fructose conversion in DMSO solvent mixtures requires deaerated conditions.

Several mechanistic pathways have been proposed for acid-catalyzed dehydration of fructose to HMF in aqueous and aprotic systems in attempts to identify the selectivity-controlling factors. For example, Akien et al.[35] on the basis of application of $^{13}C$ NMR to fructose dehydration in DMSO suggested that the homogeneous acid catalyzed dehydration of fructose has two irreversible pathways: (1) fructofuranose to HMF and (2) fructopyranose to humins. It was proposed that these pathways could be linked by a secondary equilibrium formed after protonation between the fuctosyl cation intermediates. This equilibrium was justified by the observed formation of 2,6-anhydro-*b*-D-fructofuranose that was thought to be reversibly formed between the carbocation intermediates.[35] Additionally, it has been proposed by both Zhang et al.[34] and Binder et al.[9] that the carbocation intermediates or charged nucleophiles could form complexes with a dipolar aprotic solvent. This complexation can possibly lower energy barriers and stabilize intermediates from unwanted side reactions, promoting HMF production and selectivity.[34] While various assertions have been made regarding factors that could control HMF selectivity, such as the tautomeric distribution controlling selectivity,[35] no previous direct quantified analysis has demonstrated how reaction pathways control HMF selectivity

or the direct influence of reaction conditions (e.g., temperature, solvent composition).

In this study, increasing sulfuric acid concentration primarily affected the rate of HMF production, but not HMF selectivity. Over a range of sulfuric acid loadings at 150 °C for 30 min, the selectivity to HMF held steady at roughly 80% over all fructose conversions (Figure 3a). This result suggests that HMF selectivity is independent of the acid-catalyzed rate-limiting step. Additionally, comparison of several strong mineral acids in aqueous−DMSO mixtures (Figure 3b) showed minor variations in HMF selectivity—from 81 to 85% over a range of fructose conversions. If the anions of these mineral acids played a role in stabilizing intermediates, then HMF selectivity would be expected to change significantly with acid catalyst type. Thus, the mineral acid catalyst had a minor effect on the selectivity to HMF in aqueous DMSO mixtures. The differences in the conversion of the dehydration reactions can be accounted for by the strength of the acid. However, even though the strength of the acids varied by several orders of magnitude, the type of acid had minimal effect on conversion. This result demonstrates that the initial protonation step for fructose conversion to a cation intermediate is not rate-limiting. Furthermore, the fact that HMF selectivity remained constant as fructose conversion increased with acid loading demonstrated that selectivity is controlled by a thermodynamic equilibrium prior to the rate-limiting step. Overall, our results clarify that mineral acid catalysts control the rate of fructose dehydration to HMF but do not control selectivity to HMF.

The temperature-dependent analysis of fructose dehydration in DMSO shown in Figure 4 resulted in two important observations. First, both the rate of fructose conversion and selectivity to HMF increased with temperature, further supporting the hypothesis that HMF selectivity is thermodynamically controlled by an equilibrium before the rate-limiting step. Second, selectivity to DFAs decreased with increasing temperature, and the decrease in DFA selectivity was roughly compensated by an increase in HMF selectivity. This result indicates that DFA is a secondary pathway intermediate to form HMF.

To elucidate the relationship between fructose tautomeric distribution and HMF selectivity, we proposed that the fraction of fructose existing in the furanose form controls HMF selectivity, whereas the pyranose form of fructose degrades to humins. Furthermore, because the equilibration among the

furanose, pyranose, and open-chain forms of fructose is very rapid, we also proposed that the fraction of open-chain fructose which ultimately converts to HMF or humins is dictated by the existing furanose/pyranose ratio. On the basis of this hypothesis eq 4 was developed, in which $\theta_{HMF}$ represents the predicted HMF selectivity based on the tautomeric percentages of furanose ($\theta_F$), open chain ($\theta_{OC}$), and pyranose forms of fructose ($\theta_P$):

$$\theta_{HMF} = \theta_F + \theta_{OC} \frac{\theta_F}{\theta_F + \theta_P} \tag{4}$$

To understand whether variations in HMF selectivity as a function of reaction temperature could be explained on the basis of variations in equilibrated fructose tautomeric distributions, in situ $^{13}C$ NMR spectroscopy was carried out for solutions containing D-[2-$^{13}C$]-fructose dissolved in DMSO at temperatures of 70, 80, 90, 120, and 150 °C and the fractions of fructose existing in the furanose, pyranose, and open-chain tautomers were quantified. A parity plot of the predicted selectivity ($\theta_{HMF}$) measured by NMR versus the actual selectivity from the dehydration experiments is shown in Figure 7 for fructose dehydration in DMSO at several different
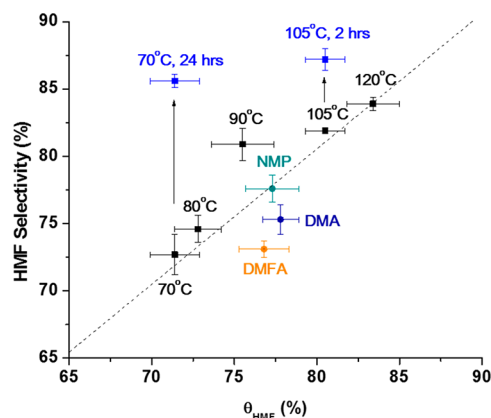


**Figure 7.** Experimentally observed HMF selectivity plotted as a function of $\theta_{HMF}$, the HMF selectivity predicted from the NMR measurements. Black squares represent experiments performed in DMSO with 10 mM $H_2SO_4$ at a reaction time of 30 min at temperatures of 70, 80, 90, 105, and 120 °C. Blue squares represent experiments in DMSO with 10 mM $H_2SO_4$ over longer durations: 24 h for 70 °C and 2 h for 105 °C. Fructose dehydrations in 10 mM HCl in NMP (green), DMA (navy blue), and DMFA (orange) were run at 120 °C for 10 min. All reactions and NMR experiments were carried out with 25 g/L fructose under deaerated conditions.

temperatures and a reaction time of 30 min (black dots). There is an excellent agreement between the predicted and measured HMF selectivity, with the parity plot showing a slope of close to 1. The NMR predicted selectivity and experimentally measured selectivity both increased with temperature due to shifting of the fructose tautomeric equilibrium toward the fructofuranose form. The strong correlation between NMR predicted and measured HMF selectivities provides direct evidence that selectivity is controlled by the branching ratio of the furanose and pyranose forms of fructose, which are in equilibrium, and dehydration of the fructopyranose form leads to humins while dehydration of the fructofuranose form directly converts to HMF.

To determine whether the dependence of HMF selectivity on solvent composition could also be quantitatively predicted

by the tautomeric distribution, fructose dehydration catalyzed by HCl was compared in DMSO, NMP, DMA, and DMFA, and $\theta_{HMF}$ was measured in each solvent at 120 °C. As shown in Figure 6, HMF selectivity was the highest in DMSO followed by NMP, DMA, and DMFA. Correlation between the measured HMF selectivity and NMR-predicted HMF selectivity at 120 °C in each solvent is also included on the parity plot in Figure 7. Figure 7 shows that the measured solvent-dependent HMF selectivity is predicted quite well by $\theta_{HMF}$ from NMR measurements. The agreement between the predicted HMF selectivity from the tautomeric distribution and the measured selectivity as a function of reaction temperature and solvent composition is strong evidence that HMF selectivity is primarily controlled by the fraction of fructose existing in the furanose form under the reaction conditions. Differences in the tautomeric distribution between solvents can be attributed to the solvent interactiona with fructose. NMP, DMA, and DMFA have similar solvent properties, each including an amide group, and their polarity indexes are similar: 6.7, 6.5, and 6.4, respectively. However, DMSO contains a sulfoxide group rather than an amide and has a higher polarity index of 7.2. This suggests that either the polarity of DMSO or specific interactions between the sulfoxide group and fructose promote enhanced stabilization of the furanose form by DMSO and thus higher HMF selectivity.[48,52]

Additionally, water content was observed to play a significant role in HMF production, as seen in Figure 5. It was observed that selectivity to HMF remained roughly constant (~80%) up to water contents of around 40 mol % and then decreased with further increase in water content. It is likely that DMSO is able to preferentially solvate fructose molecules, creating a solvation shell, which hinders interaction of the fructose with surrounding water molecules.[51] This could prevent the tautomeric distribution of fructose from shifting toward fructopyranose due to increasing water. However, once a significant amount of water was added, the DMSO solvation shell weakens, allowing for water to interact with fructose. This would shift the tautomeric equilibrium toward the pyranose forms of fructose, lowering HMF selectivity.

While $\theta_{HMF}$ based on the NMR-measured fructose tautomer distribution was an excellent predictor of the influence of solvent composition and reaction temperature at short reaction times, this correlation could not account for DFAs produced during fructose dehydration or the conversion of DFAs to HMF over long reaction times. It was observed that DFAs were consumed at longer reaction times, and as a result the selectivity to HMF increased proportionally. Results in Figure 7 show that HMF selectivity increased for longer reaction times, which was not predicted by the NMR measurements of the fructose tautomer distribution. This outcome suggests either that all DFAs are in the furanose form or that DFAs are protective intermediates to HMF production by blocking the humins pathway.

It has been proposed that DFA production occurs after the first dehydration step of fructose.[30] In that mechanism, fructose is first dehydrated to a fructosyl cation intermediate, which can then react through a parallel and reversible pathway with another fructose molecule. The result is a strong six-membered ring between the two fructose tautomers. Two primary DFA tautomers can form from fructose: (1) fructofuranose−fructofuranose anhydride or (2) fructofuranose−fructopyranose anhydride. Due to the stable six-membered-ring structure of DFAs, hydrolysis of DFAs back to fructose tends to be
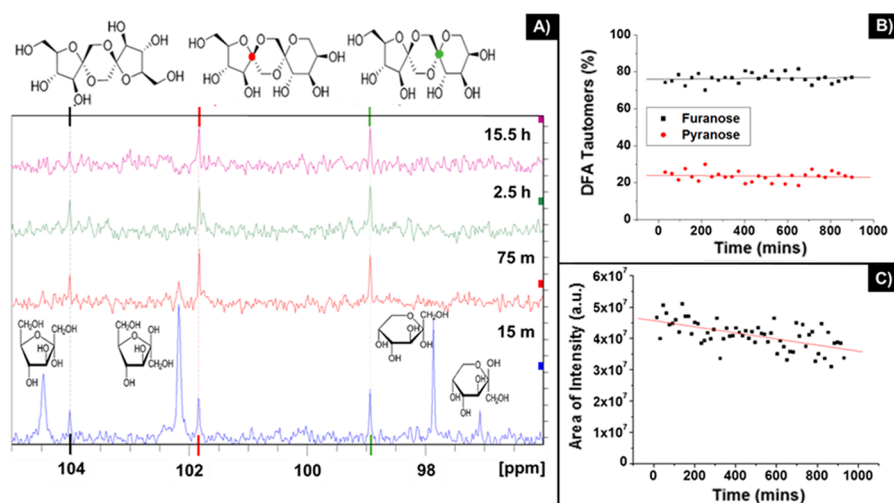
**Figure 8.** (A) Selected $^{13}$C NMR spectra for times of 15 min, 75 min, 2.5 h, and 15.5 h. (B) Furanose and pyranose DFA tautomeric percentages over time from 0 to 900 min. (C) Total $^{13}$C NMR area of DFA peaks over time from 0 to 900 min. For $^{13}$C NMR, the dehydration of 2-[$^{13}$C]-fructose was performed in 10 mM $H_2SO_4$ in deaerated DMSO-$d_6$ solution at 80 °C.

comparatively slower than fructose conversion to HMF.[53] This slower reverse reaction is evidenced by our observations of the presence of significant quantities of DFAs (∼10% yields) at near-quantitative conversions of fructose. Thus, DFAs can possibly isolate fructose tautomers from equilibrating in solution and slowly release fructose through reversible acid-catalyzed hydrolysis. Therefore, it has been suggested that DFAs could act as a protective intermediate, preventing sugar degradation and increasing selectivity to HMF more than expected, on the basis of the estimated tautomeric distribution.[30] It may also be possible that HMF is formed directly from DFAs as an intermediate. However, this process would likely be far slower than direct conversion from fructose.[53]

To examine how DFAs increase HMF selectivity, NMR studies were employed to measure the tautomeric distribution within DFAs for acid-catalyzed dehydration of 2-[$^{13}$C]-fructose in DMSO-$d_6$ at 80 °C. Figure 8a shows in situ $^{13}$C NMR spectra for 15 min, 75 min, 2.5 h, and 15.5 h of reaction. At 15 min, fructose tautomers were still seen and had not been fully consumed, consistent with the data in Figure 4. However, after 75 min, all of the fructose had been converted into either HMF or DFAs. The DFA signals for the two 2-[$^{13}$C]-carbons can be seen for fructofuranose−fructofuranose dianhydride, and the two distinct 2-[$^{13}$C]-carbon signals for the fructofuranose−fructopyranose dianhydride are observed. These signals were seen throughout the reaction due to the stable structure of DFA, slowly undergoing hydrolysis to fructose or directly converting to HMF instead of fructose. Figure 8b shows that the tautomeric distribution of the fructose monomers in DFAs over time is roughly constant at ∼78% fructofuranose and 22% fructopyranose, a result consistent with the tautomeric distribution of fructose in solution under these reaction conditions. Additionally, the slow consumption of DFAs in Figure 8c suggests that DFAs acted as a protective intermediate to HMF formation, while those containing the fructopyranose form seem to hinder their degradation to humins.

Our results suggest that the main factors controlling HMF selectivity are the fructose tautomeric distribution and the protective nature of DFAs. Scheme 1 highlights our proposed simplified mechanism controlling selectivity to HMF. A fast equilibrium exists between the fructose tautomers in solution

**Scheme 1. Proposed Simplified Mechanism of the Acid-Catalyzed Dehydration of Fructose**
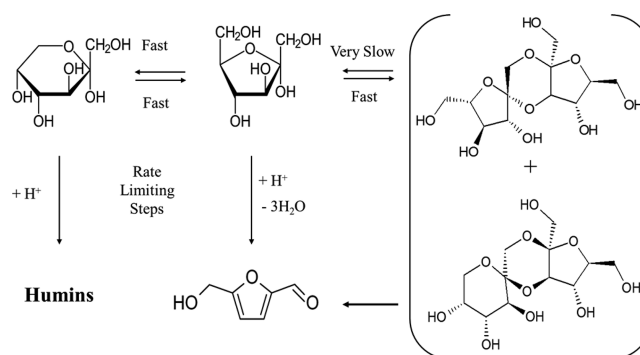


that can be shifted toward the furanose form of fructose by increasing temperature or changing the solvent environment to dipolar aprotic solvents. The dehydration of fructopyranose leads to humins formation, while fructofuranose leads to HMF. Several past studies have proposed that HMF can form through the acyclic pathway. However, our results suggest that the open-chain form remains relatively unreactive, as the ratios between the furanose and pyranose forms were the primary controllers of HMF selectivity. This is likely due to a faster rate of tautomerization between the acyclic tautomer and the cyclic tautomers than to any acyclic conversion pathway.[29] Additionally, a secondary pathway to HMF involves the formation of DFAs, which act as protective intermediates. While it is not clear how DFAs convert to HMF, either by hydrolyzing back to fructose or by directly converting to HMF, it is clear that DFAs increase selectivity to HMF at longer reaction times.

## ■ CONCLUSIONS

In this study, the influence of reaction conditions (deaeration, acid type/loading, water concentration, temperature, time, and solvent composition) on acid-catalyzed fructose dehydration to HMF was systematically analyzed. The reactivity results, along with in situ NMR analysis, suggest that the primary factor controlling selectivity in this reaction is the fructose tautomer distribution under the reaction conditions, which was most effectively controlled by varying the reaction temperature and

solvent composition. Furthermore, it was demonstrated that elucidation of the role of environmental conditions on fructose dehydration in DMSO requires application of deaerated conditions to mitigate in situ oxidation of DMSO to form acids. Additionally, it was shown that selectivity is controlled secondarily by the formation of DFAs that slowly convert to HMF under the reaction conditions, acting as protective intermediates. By understanding the primary factors that control selectivity, the development of higher-yielding processes and conditions can be developed for conversion of fructose to HMF.

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**Notes**
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## ■ ACKNOWLEDGMENTS

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