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# Mechanism of the dehydration of D-fructose to 5-hydroxymethylfurfural in dimethyl sulfoxide at 150 °C: an NMR study

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#### ABSTRACT

The anomeric composition of D-fructose in dimethyl sulfoxide changes when the solution is heated from room temperature to 150 °C, with a small increase in the  $\alpha$ -furanose form at the expense of the  $\beta$ -pyranose tautomer. Additionally, a small amount of  $\alpha$ -pyranose form was also observed at 150 °C. A mechanism is proposed for the dehydration of D-fructose to 5-hydroxymethylfurfural in DMSO at 150 °C, where the solvent acts as the catalyst. A key intermediate in the reaction was identified as (4*R*,5*R*)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde by using <sup>1</sup>H and <sup>13</sup>C NMR spectra of the sample during the reaction.

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#### 1. Introduction

Acid-catalyzed hydrolysis, followed by dehydration of most of the abundant biomass polysaccharides, produces furan derivatives such as furfural and 5-hydroxymethylfurfural (HMF) as the major products. These furans can be considered as practical renewable resources-based feedstock materials useful in the replacement of some fossil raw materials.<sup>1,2</sup> 5-Hydroxymethylfurfural is expected to play a major role in this new generation of chemicals as it can be used as a precursor for polymers and a number of useful materials. As testimony to the importance of HMF, several extensive reviews are reported in the literature about the preparation and applications of this versatile compound.<sup>3-5</sup> The acid-catalyzed dehydration of hexoses in aqueous medium at elevated temperatures produces levulinic acid in significant amounts in addition to HMF. Ketohexoses are known to produce HMF more efficiently and selectively than aldohexoses, and this may be due to the fact that aldohexoses enolize to a much lower degree than ketohexoses. In these reactions levulinic and formic acid formation is primarily due to further hydrolysis of HMF in the aqueous acidic medium, and this can be virtually suppressed by using a non-aqueous solvent such as dimethyl sulfoxide (DMSO) and using certain Lewis acid catalysts. In recent years, a number of methods have been developed for the efficient high-yield dehydration of D-fructose to HMF. These include the acidic ion-exchange resins<sup>6</sup> in DMSO, vanadium,<sup>7</sup> niobium<sup>8</sup> and zirconium<sup>9</sup> phosphate catalysts, supercritical fluids,<sup>10,11</sup> and ionic liquid<sup>12,13</sup> media.

The dehydration of D-fructose is a complex multistep process, and there are several reports on the mechanistic investigations on this industrially significant reaction.<sup>14-18</sup> All these studies were carried out on the aqueous media reaction with an added mineral acid, which usually leads to further hydrolysis of HMF to levulinic acid, lowering the yield of HMF. On the other hand, dehydration in DMSO gives a cleaner reaction, and at a higher temperature, this occurs without an added mineral or Lewis acid catalyst.<sup>19</sup> All the earlier mechanistic studies<sup>14-18</sup> were carried out by measuring the rate of disappearance of D-fructose, which did not yield insight into the intermediates involved in the reaction. In a kinetic investigation, Kuster and van der Baan showed<sup>17</sup> that the rate of disappearance of D-fructose and formation of HMF are essentially first order in D-fructose concentration for reactions carried out in 0.5-2 M aq HCl at 95 °C. Further, their studies suggested the role of an unprotonated (uncharged) intermediate in the two-step reaction sequence. Antal et al.<sup>20</sup> later reported the reaction in 2 mM aq H<sub>2</sub>SO<sub>4</sub> medium at different temperatures and pressures by monitoring the concentrations of p-fructose and the key products, levulinic acid, formic acid, furfural and HMF, and proposed a mechanism involving a fructofuranosyl cation as a key intermediate. The mechanism of the dehydration reaction in DMSO has not been investigated, and we have undertaken to study this reaction using NMR methods, which give a better insight into the structures of the intermediates. In this communication, we report our study on the dehydration of Dfructose in DMSO at 150 °C without any added mineral or Lewis acid catalyst by monitoring the <sup>1</sup>H and <sup>13</sup>C NMR spectra, and the identification of a key intermediate involved in the reaction using spectroscopic data.



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# 2. Experimental

# 2.1. Instrumentation and materials

<sup>1</sup>H NMR spectra were recorded in DMSO- $d_6$  on a Varian Mercury Plus spectrometer operating at 400 MHz. Chemical shifts are given in ppm downfield from TMS ( $\delta = 0.00$ ). <sup>13</sup>C NMR spectra in DMSO $d_6$  were recorded on the same spectrometer operating at 100 MHz. Chemical shifts are reported relative to DMSO- $d_6$  and converted to  $\delta$  (TMS) using  $\delta$  (DMSO) = 39.51. Anhyd DMSO- $d_6$  (99.9% atom D) was used as the reaction medium. (–)-D-Fructose (>99.9%) and biphenyl (99.5%) from Sigma–Aldrich were used without further purification.

# 2.2. NMR kinetic investigation

A solution of p-fructose (45.0 mg, 0.25 mmol) in 0.60 mL of anhyd DMSO- $d_6$  was prepared in a 5-mm NMR tube. Biphenyl (15.4 mg, 0.10 mmol) was added as an internal standard. The sample was allowed to stabilize at room temperature for 24 h, then, <sup>1</sup>H (rd = 2 s, NS = 8) and  ${}^{13}C$  (rd = 2 s, NS = 256) NMR spectra were recorded as the initial baseline data. Afterward the NMR tube was heated in a thermostated oil bath at  $150 \pm 1 \,^{\circ}$ C for 1.0 min. and then the reaction was guenched by immersing the NMR tube in an ice-water bath. The tube was immediately transferred to the NMR spectrometer, <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using conditions identical to the first t = 0 spectra. Further spectra were recorded after heating 3.0, 6.0, 12.0, 18.0, 24.0, 30.0 and 36.0 min of total heating time at 150 ± 1 °C. p-Fructose, reaction intermediate, and HMF amounts at different time intervals were measured by manual integration of the <sup>1</sup>H NMR peaks and comparison of these areas with the area of the biphenyl internal standard. The variations in the amounts of D-Fructose, reaction intermediate, and HMF during the 36.0-min reaction period are shown in Figure 3. The changes in the <sup>1</sup>H NMR spectra during the course of the reaction are shown in Figure 1, and this set of spectra were recorded using an identical experiment without adding biphenyl internal standard in order to maintain the clarity of the spectra in the low-field region.

# 2.3. Anomeric compositions of D-fructose at 23 °C and 150 °C

The anomeric compositions of D-fructose at 23 °C (room temperature) and 150 °C were determined by the reported method<sup>21,22</sup> of integrating the anomeric 2-OH <sup>1</sup>H NMR signals of furanose and pyranose tautomers in the t = 0.0, 1.0 and 3.0 min samples. These results are shown in Table 1. All the D-fructose anomers are negligibly small in the t = 6.0 spectra and completely disappeared at later stages of the reaction.

#### 3. Results and discussion

#### 3.1. Anomeric composition of p-fructose in DMSO

The anomeric compositions of D-fructose in DMSO at 23 °C and 150 °C from this work and selected 20 and 50 °C data from published results are shown in Table 1. The results obtained at 23 °C are comparable to the published<sup>22,23</sup> anomeric compositions at 20 °C. The anomeric compositions at 150 °C show a small increase in the  $\alpha$ -furanose form at the expense of the  $\beta$ -pyranose tautomer. Interestingly, a small amount of  $\alpha$ -pyranose form was also observed at 150 °C.

# **3.2.** Characterization of the intermediate and the mechanism of the reaction

Figure 1 shows a time-progression stack of <sup>1</sup>H NMR spectra, illustrating the course of the dehydration of p-fructose to HMF. The spectra recorded after 1.0 min at 150 °C (t = 1.0 min) showed only the four tautomers of fructose and no intermediates or products, whereas the t = 6.0 min, sample showed two new peaks in the low-field region at 6.23 (d, J = 3.2 Hz) and 9.46 (s) ppm, indicating



Figure 1. <sup>1</sup>H NMR spectra of the D-fructose sample (0.25 mmol in 0.6 mL of DMSO-d<sub>6</sub>) after 1.0, 6.0, 12.0, 18.0, 24.0, and 30.0 min of heating at 150 °C.

Table 1Anomeric compositions of D-fructose in DMSO-d6 at different temperatures

Temperature (°C)	α-Pyranose (α-p)	β-Pyranose (β-p)	α-Furanose (α-f)	β-Furanose (β-f)	Reference
20	_	26	20	55	23
20	_	29	20	46	22
50	_	21	23.5	51	22
23	_	27.7	20.7	51.6	This work
150 (1.0 min)	4.5	16.1	24.9	54.5	This work
150 (3.0 min)	4.0	21.9	25.9	48.9	This work

the formation of a reaction intermediate. The <sup>13</sup>C NMR spectra of this sample (not shown in the figures) showed two new alkene peaks at 122.8 and 156.9 ppm and a peak in the carbonyl region at 184.9 ppm corresponding to an  $\alpha$ , $\beta$ -unsaturated aldehyde functional group. These new peaks in the <sup>1</sup>H and <sup>13</sup>C NMR spectra can be explained as the formation of a dihydrofuran-2-aldehyde intermediate in the dehydration reaction. The proposed mechanism for the dehydration reaction in DMSO at 150 °C without any added acid is shown in Figure 2. The dihydrofuran-2-aldehyde intermediate identified in the NMR study can be recognized as (4R,5R)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde (4) in the proposed mechanism. The <sup>1</sup>H NMR signal at 6.23 ppm in the spectra of the intermediate 4 was assigned to the C-3 olefinic hydrogen, and this signal appears as a doublet (J 3.3 Hz) with coupling to the C-4 hydrogen. <sup>13</sup>C NMR signals of the dihydrofuran-2aldehyde intermediate 4 were observed at 122.8, 156.8, and 184.9 ppm, and these values are comparable to the chemical shifts of a similar intermediate, 5-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde, where the corresponding peaks were reported<sup>24</sup> at 125.4, 153.5, and 192.2 ppm. In the proposed mechanism both furanose forms  $(\alpha - f/\beta - f)$  can undergo DMSO-catalyzed initial dehydration (Fig. 2  $1 \rightarrow 2$ ). The <sup>1</sup>H NMR spectra of the sample after 12.0 min of reaction at 150 °C (Fig. 1) showed further increase in the peaks corresponding to intermediate 4. Furthermore, this sample showed another new set of small peaks at 6.57 (d, J 3.6 Hz), 7.46 (d, J 3.6 Hz), and 9.51 (s) ppm corresponding to the final product HMF. The <sup>13</sup>C NMR spectra of this sample further confirmed the production of HMF with the peaks at 58.6, 110.4, 125.0, 152.4, 162.8, and 178.7 ppm, identical to the reported <sup>13</sup>C resonance values.<sup>24</sup> At t = 18.0 min, a further increase in the amounts of intermediate **4** and HMF is observed, whereas beyond t = 24.0 min it shows a decrease in **4** with an increase in HMF (Fig. 1). Finally, the intermediate **4** completely disappeared to give HMF as the final product. Figure 3 shows the changes in the amounts of D-fructose, intermediate 4, and HMF during the course of the reaction, where the amounts were determined using a sample with a biphenyl internal standard. Furthermore, no direct NMR



**Figure 3.** Changes in the amounts of D-fructose, (4R,5R)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde (**4**) and 5-hydroxymethylfurfural (HMF) during the reaction (0.25 mmol of D-fructose in 0.6 mL of DMSO- $d_6$  at 150 °C).

evidence was seen for the intermediate 2 or the enol intermediate 3 (Fig. 2), probably because these compounds rapidly dehydrate to give 4, which was identified by spectroscopic data. Attempts to isolate this important intermediate were not successful showing the facile dehydration of 4 to HMF.

# 4. Conclusion

We have shown that the anomeric composition of p-fructose in DMSO changes when heated from room temperature to 150 °C, with a small increase in the  $\alpha$ -furanose ( $\alpha$ -f) form at the expense of  $\beta$ -pyranose ( $\beta$ -p) tautomer. Additionally, a small amount of  $\alpha$ -pyranose ( $\alpha$ -p) form was also observed at 150 °C. We have proposed a mechanism to explain the dehydration of the two furanose forms of p-fructose to HMF through the elimination of three water molecules, where DMSO acts as the catalyst, and we identified a key intermediate in the reaction based on spectroscopic methods. The structure of this intermediate was established as (4*R*,5*R*)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde (**4**) by using a combination of <sup>1</sup>H and <sup>13</sup>C NMR data. This is the first direct identification of an intermediate involved in the important dehydration process of p-fructose.



Figure 2. Proposed mechanism for the dehydration of D-fructose furanose forms 1 ( $\alpha$ -f/ $\beta$ -f) to 5-hydroxymethylfurfural (5) in dimethyl sulfoxide at 150 °C.

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