

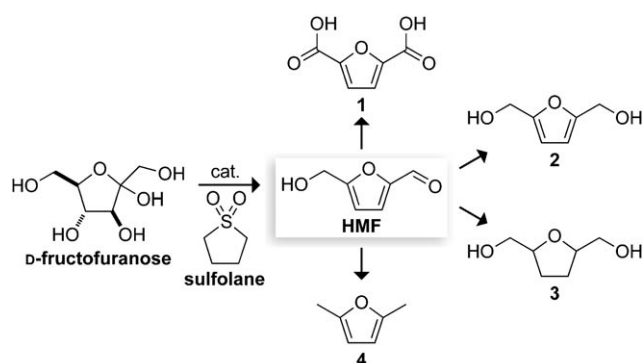
DOI: 10.1002/cssc.201000397

## Conversion of Fructose into 5-(Hydroxymethyl)furfural in Sulfolane

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Population growth has created an expanding gap between the supply and demand of both energy and chemicals. Nonrenewable fossil sources, such as coal, natural gas, and petroleum, are the source of nearly 86% of the world's energy and 96% of its organic chemicals.<sup>[1]</sup> Diminishing reserves of these sources, rising atmospheric CO<sub>2</sub> levels, and socioeconomic concerns require a reduction of our dependence on these sources.<sup>[2]</sup>

Furanics, such as 5-(hydroxymethyl)furfural (HMF), hold special promise because their carbon skeletons are identical to those in cellulose and hemicellulose, which are the most abundant organic molecules on our planet. HMF could serve as a sustainable source of liquid fuels and chemicals (Scheme 1).<sup>[3]</sup>



**Scheme 1.** Production of HMF from D-fructose. HMF serves as platform molecule for a range of other molecules.

For example, HMF is already a feedstock for common polyester building blocks, including 2,5-furandicarboxylic acid (**1**), 2,5-bis(hydroxymethyl)furan (**2**), and 2,5-bis(hydroxymethyl)tetrahydrofuran (**3**).<sup>[3b-d, f]</sup> In addition, HMF is a precursor to 2,5-dimethylfuran (**4**), which is a promising alternative liquid transportation fuel.<sup>[4]</sup> Obtaining HMF from biomass would help to bridge the growing gap between the supply and demand of energy and chemicals. Doing so requires processes to convert carbohydrates into HMF selectively and efficiently.<sup>[5]</sup>

Rapid progress has been made in the synthesis of HMF from simple sugars. Most notably, multiple conditions are now

known to enable the dehydration of D-fructose to HMF.<sup>[6]</sup> This reaction can be performed in acidified water<sup>[7]</sup> (including sub- and supercritical states<sup>[8]</sup>), organic solvents,<sup>[9]</sup> multicomponent mixtures,<sup>[3d, 5b, 10]</sup> and ionic liquids.<sup>[5a, 11]</sup> The aqueous reactions typically entail high temperatures or pressures that lead to energetic inefficiency and substantial degradation of HMF.

Organic solvents and ionic liquids provide advantages. First, they discourage the formation of acyclic fructose, which can polymerize along with HMF into an insoluble, amorphous polymer known as humin.<sup>[12]</sup> Second, they limit the water content in the reaction mixture, thereby diminishing HMF decomposition into levulinic and formic acids.<sup>[13]</sup> Nevertheless, the expense of ionic liquids and the limited industrial applicability of most organic solvents can be problematic. For example, dimethyl sulfoxide (DMSO; bp 189 °C) has been used to access high yields of HMF from fructose.<sup>[9a, 14a, b]</sup> Heating DMSO to > 150 °C, however, leads to its decomposition, as does exposure to acid.<sup>[15]</sup> This instability limits the utility of DMSO in industrial processes.

We envisioned that tetramethylene sulfone ("sulfolane") could be a superior solvent for HMF production. Sulfolane is a polar, aprotic solvent that is nonvolatile (bp 285 °C) and miscible with both water and hydrocarbons. Developed by the Shell Oil Company in the late 1950s, sulfolane is a preferred industrial solvent for the extraction of aromatics and purification of natural gas.<sup>[16]</sup> In addition, sulfolane has been used for the pyrolysis of cellulose to access HMF and furfural.<sup>[17]</sup> We view sulfolane as a robust congener of dimethyl sulfoxide. For example, unlike DMSO, sulfolane is stable at temperatures up to 240 °C and under acidic conditions. Herein, we report that sulfolane supports the high-yielding, energy-efficient transformation of D-fructose into HMF by using low loading of an inexpensive catalyst: HBr.

We realized that the yield of HMF from the dehydration of fructose should depend on the catalyst identity, concentrations of the reacting species, and the reaction temperature and duration. We began our investigations by screening for an efficient catalyst. Previously, high yields of HMF from fructose have been reported by using CrCl<sub>2</sub> in ionic liquids (65%)<sup>[5a]</sup> and LiCl in dimethylacetamide (65%).<sup>[5a, b]</sup> Upon using these two metal chlorides as catalysts, we found that HMF yields with LiCl alone (67%) exceeded those with added CrCl<sub>2</sub> (53%). We tested other metal chlorides, both alone (Table 1) and with LiCl (Supporting Information, Table S1), but did not find an additive effect. Hence, we designated LiCl as a preferred catalyst.

Next, we investigated the effect of LiCl loading on HMF yields. Optimization of HMF yields with variable LiCl concentrations soon demonstrated that increasing the concentration of LiCl above a ratio of 1:1 w/w with fructose provided no improvement of either conversion rates or yields (Table S2). Conversely, decreasing the concentration of LiCl below a 1:1 w/w

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Supporting Information for this article is available on the WWW under <http://dx.doi.org/10.1002/cssc.201000397>.

Table 1. Effect of chloride salts on the conversion of D-fructose to HMF in sulfolane		
Catalyst	Amount <sup>[a]</sup> [wt %]	HMF yield <sup>[b]</sup> [%]
–	0	14
LiCl	100	67
CrCl <sub>2</sub>	100	5
CuCl	100	6
CuCl <sub>2</sub>	100	7
AlCl <sub>3</sub>	100	6
KCl	100	22
MgCl <sub>2</sub> ·6H <sub>2</sub> O	100	35
MnCl <sub>2</sub> ·4H <sub>2</sub> O	100	11
NaCl	100	19
RbCl	100	31
ZnCl <sub>2</sub>	100	1
BaCl <sub>2</sub> ·2H <sub>2</sub> O	100	17
CdCl <sub>2</sub> ·2.5H <sub>2</sub> O	100	2
CaCl <sub>2</sub> ·2H <sub>2</sub> O	100	8
CsCl	100	25
CoCl <sub>2</sub> ·6H <sub>2</sub> O	100	11
PdCl <sub>2</sub>	100	0
NiCl <sub>2</sub> ·6H <sub>2</sub> O	100	21
RuCl <sub>3</sub> (H <sub>2</sub> O) <sub>3</sub>	100	0
FeCl <sub>3</sub>	100	0
VaCl <sub>3</sub>	100	21
MoCl <sub>3</sub>	100	0
PtCl <sub>2</sub>	100	1
LaCl <sub>3</sub> ·7H <sub>2</sub> O	100	7

[a] Catalyst wt% is relative to fructose (83 mg g<sup>-1</sup>) in the reaction mixture.  
[b] Yields are based on HPLC analysis of reactions for 2 h at 90 °C.

ratio with fructose led to decreased HMF conversion rates and yields.

We then sought to identify the optimal fructose loading in sulfolane. We also varied the LiCl/fructose ratio during these trials. The effect of that ratio on HMF yield was negligible (Table S3). Hence, we employed a 1:1 w/w LiCl/fructose ratio in a wider range of fructose/sulfolane ratios. Again, changes in HMF yield were negligible (Table S4), indicating that the yield of fructose attainable from HMF in sulfolane is not highly sensitive to reagent concentrations.

Having explored the effects of catalyst type and concentration, we next sought to optimize the reaction temperature and duration. These reaction conditions are especially crucial, as HMF decomposes at elevated temperatures. Yet, high HMF yields are obtainable at short times only at elevated temperatures. Hence, a variety of temperatures was screened by taking aliquots at intervals of 30 or 60 min. At 90–100 °C, HMF reached a peak at 2 h (Figure 1). Achieving the same HMF yields at <90 °C required reaction times of at least 5 h, whereas temperatures >100 °C gave lower HMF yields, even at a reaction time of 1.5 h. Hence, we found that reactions were best performed at 90 or 100 °C for 1–2 h. The temperature and duration of this process provides a method for fructose to HMF conversion at a more energy-efficient temperature with a short reaction time, without any adverse effects on overall HMF yields.

Knowing that the dehydration of fructose is acid-catalyzed in aqueous systems,<sup>[7]</sup> we sought benefits from acid catalysts.

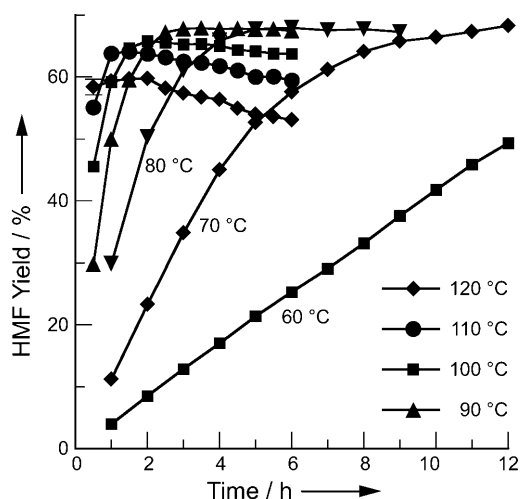


Figure 1. Effect of temperature on the production of HMF from D-fructose in sulfolane containing LiCl (100 wt%). Yields are based on HPLC analysis.

Hence, we tested HCl, HNO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>, and HOAc as additives to the LiCl catalyst. Of these four, HCl and HOAc provided HMF yields over 60% (Table S5). Interestingly, these two were the strongest and weakest, respectively, of the four acids. The high HMF yields from these two acids led us to vary their molar concentrations in the absence of LiCl. Interestingly, only HCl availed HMF yields comparable to those obtained using LiCl alone. The conversion of fructose to HMF appeared to benefit from the presence of a halide ion. Using LiBr as the halide source increased HMF yields by ca. 10% (Table 2). Remarkably, the analogous bromide source, HBr, provided HMF with a yield of 93%. A likely byproduct was humin, as evidenced by the

Table 2. Effect of bromide and iodide on the conversion of D-fructose to HMF in sulfolane.			
Catalyst	Amount <sup>[a]</sup> [wt %]	Time [h]	HMF yield <sup>[b]</sup> [%]
LiBr	100	2	78
LiBr	100	4	79
HBr	2	1	80
HBr	2	2	91
HBr	5	1	93
HBr	5	2	82
HBr	7	1	86
HBr	7	2	81
HBr	9	0.5	90
HBr	9	1	79
HBr	28	0.5	66
HBr	28	1	64
LiI	100	2	8
LiI	100	4	18
LiI	100	6	30
NaI	100	2	34
NaI	100	4	45
HI	3.75	0.5	28
HI	3.75	1	28
HI	7.5	0.5	29
HI	7.5	1	22

[a] Catalyst wt% is relative to fructose (67 mg g<sup>-1</sup>) in the reaction mixture.  
[b] Yields are based on HPLC analysis of reactions at 100 °C.

formation of insoluble material in the reaction vessel. To our knowledge, this HMF yield is the highest for a conversion at ambient pressure and  $\leq 100^\circ\text{C}$ . To complete this analysis, we tested the iodide sources HI, LiI, and NaI as catalysts, and obtained yields of  $\leq 30\%$ .

What is the basis for the superior catalytic activity of HBr? We suspect that the Brønsted acid facilitates formation of a fructofuranosyl oxocarbenium ion that suffers nucleophilic attack by a bromide ion to form a 2-deoxy-2-bromo intermediate.<sup>[5b]</sup> This intermediate, which would have a lower tendency ion to undergo deleterious side reactions than the oxocarbenium, then loses HBr to form an enol. Two subsequent dehydration steps catalyzed by the Brønsted acid and bromide base would lead to HMF.

Next, we explored the breadth of our conversion process. Only ketohexoses gave appreciable furanic yields (Table S6). In addition, HBr in DMSO did support the conversion of fructose into HMF (Table S7), but at lower yields than obtainable in sulfolane (Table 2).

In addition, we sought to isolate HMF from sulfolane by adapting a known extraction procedure.<sup>[3d]</sup> Our results were encouraging in that the organic and aqueous phases can be modified such that HMF favors the organic layer of methylisobutylketone (MIBK) and 2-butanol over the aqueous layer of water and sulfolane, while sulfolane favors the aqueous phase (Table S8). We achieved the best partitioning by using a  $\text{H}_2\text{O}/\text{sulfolane}$  9:1 aqueous phase and MIBK/2-butanol 8:2 organic phase. Optimization of a continuous extraction process could lead to even greater partitioning of HMF into the organic layer.

Finally, we tested the scalability of our optimized conditions for HMF production by performing reactions on 5 g of fructose. These conditions (sulfolane containing 5 wt% HBr, 1 h,  $100^\circ\text{C}$ ) consistently provided HMF in yields near 90%, instilling optimism for their utility in an industrial-scale process.

In conclusion, we have developed a high-yielding process to access HMF from D-fructose in sulfolane. The use of an inexpensive catalyst (HBr) at a low concentration (5 wt%), low temperature ( $100^\circ\text{C}$ ), and short reaction time (1 h) makes our process amenable for large-scale access to HMF. We propose that transformation of the nascent HMF in sulfolane, which is among the most versatile of solvents, could be the basis for an advantageous route to liquid fuels and chemicals (Scheme 1).

## Experimental Section

Commercial chemicals were reagent-grade or better, obtained from Sigma-Aldrich (Milwaukee, WI) and were used without further purification. Reactions were performed in 4 mL glass vials heated in a temperature-controlled oil bath with magnetic stirring or in a temperature-controlled VWR Mini Shaker at 600 rpm.

At known times, reaction mixtures were diluted with a known mass of deionized water, subjected to centrifugation at 12000 rpm for 5 min to remove insoluble products, and analyzed by HPLC. Product concentrations were calculated from HPLC-peak integrations, which were then used to calculate yields. HPLC was performed by using either a Waters system equipped with two 515 pumps, a 717 Plus autosampler, and a 996 photodiode array detector, or an Agilent 1200 system equipped with refractive index and

photodiode array detectors. HMF was analyzed by either reversed-phase chromatography with a Varian Microsorb-MV 100-5-C18 column ( $250 \times 4.6$  mm) using a 93:7 water/acetonitrile mobile phase at a flow rate of  $1 \text{ mL min}^{-1}$  and  $25^\circ\text{C}$ , or by ion-exclusion chromatography with a Bio-Rad Aminex HPX-87H column ( $300 \times 7.8$  mm) using a 5 mM  $\text{H}_2\text{SO}_4$  mobile phase at a flow rate of  $0.6 \text{ mL min}^{-1}$  at  $65^\circ\text{C}$ .

D-Fructose (0.10 g, 0.563 mmol) was dissolved in sulfolane (1.40 g, 11.7 mmol). Hydrobromic acid (4.7 mg, 0.058 mmol) was added, and the reaction mixture was heated at  $100^\circ\text{C}$  for 2 h. At 30 min intervals, aliquots were removed, quenched with deionized water, and analyzed by HPLC. Any humins were removed prior to HPLC analysis. Only low levels of colored products, other than HMF, were detected by HPLC. For reaction mixtures containing salts rather than acid, the salts and fructose were dissolved in sulfolane prior to heating.

Experiments to isolate HMF were done after using the optimized reaction conditions (67  $\text{mg g}^{-1}$  fructose in sulfolane containing 5 wt% HBr for 1 h at  $100^\circ\text{C}$ ). Water was added to the reaction mixture, followed by the MIBK and 2-butanol. Aliquots of the organic and aqueous layers were analyzed by HPLC to determine values of  $R_{\text{org/aq}}$ .

## Acknowledgements

This work was supported by the Great Lakes Bioenergy Research Center, a DOE Bioenergy Research Center. We are grateful to J. B. Binder and A. Choudhary for insightful discussions.

**Keywords:** biofuels • homogeneous catalysis • renewable resources • solvent effects • sulfur heterocycles

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Received: November 17, 2010

Revised: December 26, 2010

Published online on February 10, 2011