### DOI: 10.1002/cssc.201100489 The Production of 5-Hydroxymethylfurfural from Fructose in Isopropyl Alcohol: A Green and Efficient System

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Fossil fuels are still the primary carbon feedstock for a wide variety of commodity and specialty chemicals, as well as thermal energy and transportation fuels. However, after one century of heavy industrial consumption hydrocarbon reserves are diminishing and concerns regarding their future scarcity of are wellfounded. Biomass-derived carbohydrates are a promising carbon-based alternative, both as energy source and as sustainable feedstock for chemicals.<sup>[1,2]</sup> Recently much effort has been devoted to the conversion of biomass into 5-hydroxymethylfurfural (HMF), a versatile and key intermediate in the biofuel and petrochemical industries.<sup>[3,4]</sup> However, the large-scale application of biomass-sourced HMF is still limited due to

some critical challenges, such as costs, supply, and the environmental impact of industrial activity. Low efficiency in synthesis and high solubility in water pose difficulties in HMF mass production processes, especially for isolation and purification.<sup>[5]</sup> In most reported methods for the transformation of biomass or derivatives into HMF, the HMF is obtained in solution and the yield is reported by using HPLC or GC. However, developing efficient separation methods is very important in order to make the industrial-scale production of HMF economically viable.

Reaction media used for the synthesis of HMF from biomass include water,<sup>[6]</sup> polar organic solvents such as dimethyl sulfoxide (DMSO) or dimethylformamide (DMF),<sup>[7]</sup> ionic liquids,<sup>[8]</sup> or mixtures.<sup>[9]</sup> HMF can be isolated by extraction with various organic solvents, such as methyl isobutyl ketone (MIBK),<sup>[9a,b]</sup> dichloromethane (DCM),<sup>[9c]</sup> ethyl acetate,<sup>[10]</sup> tetrahydrofuran (THF),<sup>[10]</sup> diethyl ether,<sup>[11]</sup> and acetone.<sup>[6c]</sup> Due to the high polarity of HMF, its isolation typically requires multiple runs of vigorous extraction processes. In this context, aqueous-organic and ionic liquid-organic biphasic solvent systems are great improvements,<sup>[9,10]</sup> however, they still suffer from inefficient extraction. The use of large volumes of organic solvent is costly and has negative impacts on the environment.<sup>[12]</sup> Other challenges faced by biphasic systems are complex plant designs and the difficulty of recycling the reaction system (e.g., ionic liquids and catalyst).

In an effort to develop an economically viable HMF synthesis process, we disclose herein an isopropyl alcohol-mediated reaction system for the production of HMF from fructose.<sup>[13]</sup> The

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Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201100489. new system avoids the use of large volumes of organic solvent and has a minimal environmental impact. It enables a simple production and isolation of HMF, and offers a new opportunity for a large-scale economically viable process.

Our reasoning for using an alcohol as solvent for the transformation of sugars into HMF was two-fold: Firstly, alcohols are environmentally friendly, cost efficient, and easy-to-use reaction media. Their capacity to dissolve sugars is also high. Secondly, alcohols may further react with HMF to form HMF ethers, which could prevent decomposition or oligomerization of HMF (Scheme 1). Thus, methanol was first tested as a medium for the transformation of fructose to HMF, with HCl as



Scheme 1. Equilibria between HMF and its alcohol derivatives.

catalyst. Fructose (0.45 g) and HCl (12.5 M aqueous solution, 10 mol%) were added into methanol (5 mL). The mixture was stirred at 80°C for 8 h. NMR analysis showed that products A-D in Scheme 1 were formed in a ratio of 1:3:4:17 (Table 1, entry 8). The formation of products B, C, and D was not surprising because the reaction conditions are suitable for acetalization and ether formation. However, the total yield of furfural products was only 25%. With these results in hand, other alcohols were also tested. In ethanol (entry 8), only HMF (A) and ether (B) were produced in yields of 24% and 14%, respectively. When isopropyl alcohol and tert-butanol were used as solvent, HMF was produced as sole furfural product in yields of 67% and 62%, respectively. The high selectivity towards HMF in isopropyl alcohol and tert-butanol is likely due to their bulkiness. Mixed solvents of methanol and isopropyl alcohol improved neither the selectivity nor the yield of the reaction (Supporting Information, Table S1). These results suggest that isopropyl alcohol could be a suitable solvent for the dehydration of fructose to HMF.

A time-dependent analysis indicated that the reaction in isopropyl alcohol generally proceeded fast in the first few hours and then slowly ran to completion (Figure 1). The reaction conditions were then further optimized. The reaction was found to quickly reach a yield of more than 82% at 120 °C (less than 1 h). The yield slowly decreased after 4 h, possibly due to the HMF decomposition/oligomerization. At 100 °C, it took 3 h to reach a yield of 82%. A yield of 85% was achieved in 5–6 h

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Table 1. The transformation of fructose to HMF in alcohols with HCI. <sup>[a]</sup>										
Entry	t [h]	Methanol Yield <sup>[b]</sup> [%]	Ratio <sup>[c]</sup> A/B/C/D	Ethanol Yield <sup>[b]</sup> [%]	Ratio <sup>[c]</sup> A/B/C/D	lsopropy Yield <sup>[b]</sup> [%]	'l alcohol Ratio <sup>[c]</sup> <b>A/B/C/D</b>	<i>tert-</i> Buta Yield <sup>[b]</sup> [%]	nol Ratio <sup>[c]</sup> <b>A/B/C/D</b>	
1	1	7	0.7:0.2:4:2	14	12:2:0:0	30	30:0:0:0	43	43:0:0:0	
2	2	11	1:1:4:5	22	17:5:0:0	39	39:0:0:0	53	53:0:0:0	
3	3	14	1:1:4:8	28	21:7:0:0	44	44:0:0:0	55	55:0:0:0	
4	4	19	1:2:5:11	29	21:8:0:0	50	50:0:0:0	60	60:0:0:0	
5	5	20	1:2:5:12	33	23:10:0:0	56	56:0:0:0	60	60:0:0:0	
6	6	23	2:3:4:14	35	23:12:0:0	59	59:0:0:0	61	61:0:0:0	
7	7	23	1:3:4:15	37	24:13:0:0	63	63:0:0:0	62	62:0:0:0	
8	8	25	1:3:4:17	38	24:14:0:0	67	67:0:0:0	61	61:0:0:0	
9 <sup>[d]</sup>	4	50	8:10:11:21	57	15:42:0:0	61	21:40:0:0	59	29:30:0:0	

[a] Reaction conditions: fructose (0.45 g), ROH (5 mL), HCl (10 mol%), T=80 °C. [b] Total furfural yields (isolated). [c] The structures of **A**, **B**, **C**, and **D** are shown in Scheme 1. The ratios were determined by NMR with internal standard. [d] With Amberlyst 15 as catalyst (20 mol%), T=100 °C.



Figure 1. Influence of temperature on HMF yield at different reaction times. ▲: 80 °C; ■: 100 °C; ●: 120 °C. Reaction conditions: fructose (0.45 g), HCI (5 mol%), isopropyl alcohol (5 mL).

(Figure 1). When lowering the HCl catalyst loadings to 5 mol% and 2.5 mol%, the reactions took 2 h and 5 h, respectively, to reach maximum HMF yields (81% and 82%) at 120°C (Table 2). With these optimized reaction conditions, other alcohols were tested again as solvents for fructose dehydration. Under the same conditions (T=120°C, t=2 h), methanol, ethanol, 1-propanol, and 1-butanol gave yields of a mixture of products **A** (HMF) and **B** (ether) of 40%, 64%, 69% and 65%, respectively, while isopropyl alcohol and *tert*-butanol gave yields of HMF (**A**) of 83% and 70%, respectively (Figure 2). A larger-scale reaction (with 13.5 g fructose) was carried out under the same conditions in isopropyl alcohol and 7.6 g of HMF (80.4%, purified by flash column chromatography, EtOAc/hexane = 1:1) was obtained.

In the dehydration process, three water molecules are generated during the reaction. The effect of traces of water in the reaction system was further investigated. Notably, the reaction system did not require strict water-free conditions. With traces of water (6 vol%) present in the system, the yield of HMF increased to 87%, but more than 10 vol% of water resulted in a low HMF yield (Figure 3). Under optimized reaction conditions, an HMF yield of up to 87% and a conversion of 99% were achieved. This result is comparable to the efficiency of other solvent systems.<sup>[4]</sup> High-boiling-point humin was the main by-product of this process, and could be removed by filtration of the reaction mixture.

Recycling experiments for this homogeneous system were carried out with 4.5 g of fructose. To a 150 mL flask equipped with stirrer bars were added fructose, isopropyl alcohol (50 mL), and hydrochloric acid (5 mol%). The reaction flask was heated on an oil bath to 120 °C with stirring



**Figure 2.** Effects of different alcohol solvents on HMF production from fructose. Reaction conditions: fructose (0.45 g), HCI (5 mol%), ROH (5 mL), T = 120 °C, t = 2 h.

for 4 h. Raw HMF product was obtained simply by filtration and evaporation. Evaporated isopropyl alcohol and HCl catalyst were collected and used for the next batch reaction. The water content of the reaction system could also be adjusted by azeotropic evaporation of the solvent. As shown in Figure 4, using recycled solvent directly for the reaction caused the HMF yield to decrease slightly in subsequent runs. This is due to the partial loss of HCl catalyst during the evaporation process. After correcting the amount of HCl catalyst in the recycled solvent, the HMF yield was successfully maintained at a high level. This simple product isolation and solvent recycling process makes the reaction system particularly suitable for large-scale operation (see Supporting Information).

Other Brønsted-acidic catalysts were also screened, and HCl proved the best catalyst for fructose dehydration in isopropyl alcohol. Under standard conditions (T = 120 °C, 10% catalyst loading, t = 2 h), H<sub>2</sub>SO<sub>4</sub> gave 68% yield (57% **A** and 17% **B**), while other acids, such as HNO<sub>3</sub>, H<sub>3</sub>PO<sub>4</sub>, HCOOH, CH<sub>3</sub>COOH, and B(OH)<sub>3</sub>, gave trace or zero yields of HMF. Accounting for the different catalyst recycling pathways for a large-scale process, a solid acid catalyst (Amberlyst 15) was also evaluated. The reaction was tested in methanol, ethanol, isopropyl alcohol, and *tert*-butanol (Table 1, entry 9). Reaction in methanol gave a 50% yield of a mixture of **A**, **B**, **C**, and **D**. Reactions in



**Figure 3.** Effects of water content on HMF yield. Reaction conditions: fructose (0.45 g), HCl (5 mol%), isopropyl alcohol (5 mL), T=120 °C, t=2 h.



**Figure 4.** Recycling experiments.  $\bullet$ : Evaporated solvent was directly used for the next reaction run;  $\bullet$ : an additional 2 mol% of HCl was added to the recycled solvent for subsequent run. Reaction conditions: fructose (4.5 g), HCl (5 mol%), isopropyl alcohol (50 mL), T = 120 °C, t = 4 h.

ethanol, isopropyl alcohol, and tert-butanol gave a yield of ca. 60% of a mixture of A and B. The reactions in bulky alcohols had a better selectivity to HMF. These results indicate that using Amberlyst 15 as catalyst (in different alcohols) leads to the formation of more ether or acetalization products (B, C,  $\mathbf{D}_{t}^{[13]}$  compared to HCl catalyst systems. This may be due to the stronger acidity of Amberlyst 15. For comparison, the reaction conditions with Amberlyst 15 as catalyst in isopropyl alcohol were further optimized (see Table 2 and the Supporting Information, which also includes the results of catalyst recycling tests). For the first run, at 120°C, the total furfural yield reached 40% in 1 h and increased to a maximum of 60% in 4 h. The ratio of products A/B/C/D was 24:28:5:3. The second run with recycled catalyst gave slightly better results: 62% of furfural yield was achieved in 4 h with an A/B/C/D product ratio of 39:22:1:0. More HMF was produced in the second run, with recycled catalyst. This change indicated that the acidity of recycled catalyst had decreased, which was reflected in a sub-

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Table 2. Transformation of fructose to HMF in isopropyl alcohol with Amberlyst  ${\rm 15.}^{\rm [a]}$ 

Entry	<i>t</i> [h]	Yield <sup>(b)</sup> [%]	Ratio <sup>[c]</sup> A/B/C/D
1	1	40	31:9:0:0
2	4	60	24:28:5:3
3 <sup>[d]</sup>	1	46	35:11:0:0
4 <sup>[d]</sup>	4	62	39:22:1:0
5 <sup>[e]</sup>	1	50	27:7:12:5
6 <sup>[e]</sup>	4	57	45:12:0:0

[a] Reaction conditions: fructose (0.45 g), Amberlyst 15 (20 mol%), isopropyl alcohol (5 mL), T = 120 °C. [b] Total furfural yield. [c] Structures of product **A**, **B**, **C**, **D** as shown in Scheme 1, composition was determined by NMR. [d] First run recycled catalyst; [e] Second run recycled catalyst.

sequent run: for the third run, a 57% furfural yield was achieved in 4 h with an A/B/C/D product ratio 45:12:0:0.

In conclusion, an isopropyl alcohol-mediated reaction system for the production of HMF from fructose is reported. Using isopropyl alcohol as solvent and HCl as catalyst, an HMF yield of up to 87% from fructose is achieved. The solvent and catalyst can be easily recycled by evaporation, giving the HMF product. The new system avoids the use of large amounts of organic solvent and has a minimal impact on the environment. It allows for efficient and convenient HMF production and isolation, and provides a new opportunity for a large-scale economically viable process. A recyclable solid acid catalyst (Amberlyst 15) was also used, but a lower yield and lower selectivity to HMF were found.

#### **Experimental Section**

HCI-catalyzed conversion of fructose to HMF and HMF derivatives in alcohols: To a 15 mL sealed tube equipped with stirrer bars, fructose (0.45 g, 2.5 mmol), alcohol (5 mL), and hydrochloric acid (12.5  $\,$ m aqueous solution, 0.01 mL) were added. The sealed tube was heated on an oil bath to 100 °C with stirring. The reaction was stopped at the desired reaction time. For product isolation, the reaction mixture was cooled in an ice/water bath and addition of sodium hydroxide (6.25  $\,$ m, 0.04 mL) to neutralize the catalyst. Solvents in the reaction mixtures were removed under vacuum. 1 mL of distilled water was then added to the residue and the product was extracted with 10 mL of ethyl acetate. The organic layer was collected and evaporated to obtain the crude product to which mesitylene (0.1 g, 0.83 mmol) was added as internal standard. The composition of the samples was then analyzed by NMR.

HCI-catalyzed conversion of fructose to HMF in isopropyl alcohol (recycle and larger scale): To a 150 mL flask equipped with stirrer bars, fructose (4.5 g, 25 mmol), isopropyl alcohol (50 mL), and hydrochloric acid (12.5 M aqueous solution, 0.1 mL) were added. The reaction flask was heated on an oil bath to  $120 \,^{\circ}$ C with stirring. For larger-scale experiments, fructose (13.5 g, 75 mmol), isopropyl alcohol (150 mL) and hydrochloric acid (12.5 M aqueous solution, 0.3 mL) were added in a 500 mL flask. The reaction was stopped after 4 h. The reaction mixture was filtrated to remove insoluble humin by-product. Solvent in the reaction mixture was then distilled to give the crude HMF product. The recycled solvent was either directly used or used with additional 2 mol% HCl for next

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run. The crude HMF product was purified by flash column chromatography, EtOAc/hexane = 1:1.

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