Solvent System for Effective Near-term Production of Hydroxymethylfurfural (HMF) with Potential for Long-term Process Improvement

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ARTICLE

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Production of renewable chemicals to mitigate the deleterious effects of greenhouse gas emissions requires technologies that are cost-competitive with the fossil-fuel industry, require low capital investment, and produce high value products. We report production of 5-hydroxymethylfurfural (HMF), a valuable platform molecule from biomass-derived carbohydrates at high yields (>90%) and with excellent carbon balance (>95%) using an inexpensive solvent system composed of acetone and water. We demonstrate that HMF, a thermally unstable molecule, can be separated from this low boiling solvent system with high recovery (96%) and purity (~99%). We show that fructose is selectively dehydrated in this solvent system from a mixture of glucose and fructose, a property that can be leveraged to integrate the proposed process with current processes for production of high fructose corn syrup. Techno-economic analysis indicates that utilizing fructose as feedstock leads to low investment (16 MM$) and produces HMF at a minimum selling price (MSP) of $ 1710/ton. The MSP can be further reduced to $ 1460/ton by changing the feedstock to glucose.

Broader context:
It is essential to develop and implement technologies to produce renewable fuels and chemicals to limit the net carbon emission and thereby limit global warming to 1.5 °C above pre-industrial levels. This formidable task requires development of new technologies and processes that are compatible with the current infrastructure as well as have the potential to be intergrated in bio-refineries. Commercialization of new processes for production of renewable fuels and chemicals has faced significant challenges mainly due to the large capital investment required to build these facilities and the associated risk with unproven technologies. Thus, there is a need to develop processes that not only have low risk and require low investment for near-term implementation, but that also have potential for long term significant improvement. In this article, we demonstrate that using a solvent system comprised of acetone and water is remarkably effective for the conversion of biomass-derived carbohydrates to a versatile platform molecule, 5-hydroxy-methylfurfural (HMF). HMF can be used for the production of high value renewable chemicals, polymers and biofuels. For example, HMF is a precursor in the production of 2,5-furandicarboxylic acid (a renewable replacement for terephthalic acid); levulinic acid (for production of bio-based fuels) and 2,5-diformylfuran (used in production of organic conductors, furan-urea resin, functional polymers and polyesters). As such, HMF has been identified by US-DOE as a priority chemical required for a successful renewable economy. The simplicity and low capital investment of our approach make it an ideal process for integration with the current high fructose corn syrup process for near-term implementation. This near-term implementation provides the opportunity to de-risk the technology, and we show that the process can be modified to use glucose as feedstock for longer-term implementation.

I. Introduction

Emerging changes in climate caused by continued emissions of carbon dioxide into the environment require the development of new processes for conversion of renewable resources to fuels, chemicals, and/or materials that have (i) low risk for near-term implementation and (ii) potential for significant long-term improvement. In this context, the past two decades have seen an increased interest in developing technologies and processes for the conversion of biomass-derived feedstocks, especially biomass-derived carbohydrates, into renewable fuels and chemicals[1-3]. Commercialization of new processes in this area has faced significant challenges due to high capital investment (e.g., hundreds of millions of dollars) required to build the facilities to convert biomass and biomass-derived carbohydrates to platform and/or commodity chemicals[4]. Even with subsidies, tax credits and loan guarantees from the government, many start-up companies working on biomass upgrading have failed and some have filed for bankruptcy[4]. Thus, technologies which require low capital investment and can be integrated with current facilities to reduce risk are required. Additionally, it is required that the target product has high market value and a sizable market to generate revenue in the short term to cover the start-up cost and provide cash flow for future plants.

Conversion of biomass-derived carbohydrates to 5-hydroxymethylfurfural (HMF), a versatile platform molecule produced by selective dehydration of sugars, has gained considerable attention in recent years as an important precursor to produce high value renewable chemicals, polymers and biofuels[5-8]. For example, complete oxidation of HMF leads to the formation of 2,5-furandicarboxylic acid (FDCA), which can be used as a replacement for terephthalic acid in the production

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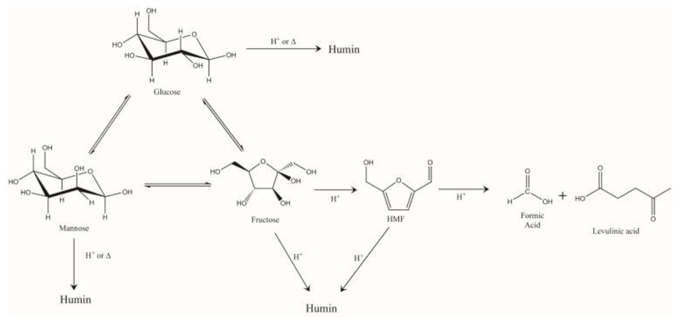

Fig. 1. Reaction network for production of HMF from mono-saccharides.

of polyethylene therephthalate (PET)[9]. Coupled with biomass-derived ethylene glycol, FDCA can lead to 100% biomass-derived polymers. Selective oxidation of HMF forms 2,5-diformylfuran which is used in production of organic conductors, furan-urea resin and functional polymers[10]. HMF can be reduced to produce chemicals such as 2,5-Bis(hydroxymethyl)furan or 2,5-Bis(hydroxymethyl)-tetrahydrofuran which are used for the synthesis of polyesters and functional polymers[10]. Additionally, HMF can serve as a precursor in the production of diesel and jet range liquid fuels[11,12]. Thus, HMF is a platform chemical with potentially large market size, and it has been identified by US-DOE as a priority chemical required for a successful bio-refinery[13].

Economical production of HMF must address technological challenges, such as the instability of HMF due to undesirable condensation reactions leading to formation of humins (Fig. 1) and also the separation of HMF from the solvents and byproducts[5,14]. Dehydration of fructose, the most amenable sugar for production of HMF, in water is nonselective and forms byproducts leading to poor HMF yield (ca ~20-25 %)[15].

HMF can be produced in high yields, ~90%, using high-boiling organic solvents such as dimethylsulfoxide and dimethylformamide; however, HMF separation from these solvents must be carried out under high vacuum and low temperatures to minimize thermal degradation, and even under these conditions (e.g., 1.3 mbar and 343 K), ~30% HMF loss is reported[14,16]. Recent advances have shown improved HMF yield in water-miscible organic solvents, such as acetonitrile[17], lactones[18], furans[18] and 1,4-dioxane[19]. Bicker et al. reported the dehydration of fructose in supercritical acetone and achieved HMF yield of 77 %[20]. High HMF yields (~90 %) were also obtained using ionic liquids, however, the separation and recycle of expensive ionic liquids is challenging[21-23]. Biphasic reaction systems have been utilized to extract HMF from the aqueous phase into the organic phase where it is protected from acid-catalyzed condensation as well as rehydration reactions[24]. Roman-Leshkov et al. reported a biphasic system where fructose was dehydrated to HMF with 77% selectivity at 92% conversion[14]. Many studies using bi-phasic solvent systems have been reported[25-29], however, HMF yields of ~60-70% are achieved. Additionally, separation of HMF from the solvent system remains a formidable challenge. Furthermore, most studies have focused on the conversion of fructose to HMF but using glucose as the feedstock is desirable due to its abundance and lower price. Low HMF yield and thereby poor carbon balance are generally reported when glucose is used as the feedstock.

In this paper, we outline a process which utilizes an inexpensive solvent system, composed of acetone and water, for the conversion of fructose to HMF and its subsequent separation. We show through techno-economic analysis (TEA) that the proposed process involves low initial capital investment and can be integrated into the current high fructose corn syrup production process. Additionally, we show that the same solvent system can be used to convert glucose, the most abundant and the least expensive carbohydrate, to HMF in a two-step process, wherein glucose is isomerized to fructose, and fructose is further dehydrated to HMF. Importantly, this process eliminates one of the most expensive unit operations in the current production of fructose, namely, simulated moving bed chromatography required to separate fructose from glucose, by leveraging the exceptional property of the solvent system wherein fructose is selectively dehydrated to HMF while glucose remains unreacted. We propose that initial chemical plants can be constructed to operate using fructose as feedstock, where low capital is required. Thereafter, as the process generates revenue, future chemical plants can be developed to change the feedstock to glucose to increase overall revenue. Additionally, we note that the process described herein can be integrated with bio-refineries which produce a stream of glucose from cellulosic and/or lignocellulosic biomass.

Results and discussion

Dehydration of fructose to HMF

The results in Fig. 2a show the fructose conversion and HMF yield during dehydration of 1 wt% fructose in a solvent system composed of 80/20 (v/v) acetone/water containing 15 mM hydrochloric acid at 393 K. High HMF selectivity (97%) and excellent carbon balance (~97%) are achieved even at high fructose conversion (98%) under these reaction conditions. The extent of formation of humins is minimal during dehydration of fructose in this acetone/water solvent system, as can be observed in Fig. 2a and Fig. S1, ESI†. Specifically, the solution after dehydration of fructose is clear, whereas dehydration of fructose in water produces a black opaque solution due to the formation of humins (Fig. S2, ESI†).

The rate constant for fructose dehydration increases with an increase in acetone concentration in the solvent system (Fig. 2b). While it is desirable to perform dehydration at high acetone concentration, the solubility of fructose in the solvent system decreases with increasing acetone concentration. However, we found that the solubility of fructose is 7.9 wt% at 303 K in a solvent system containing 80 vol% acetone (Fig. S10). Thus, 80 vol% acetone solution is capable of dissolving fructose produced in a high fructose corn syrup production plant[30] and this solvent system also has a high dehydration rate. Accordingly, a solvent system containing 80 vol% acetone was chosen for further study. The activation energy for fructose

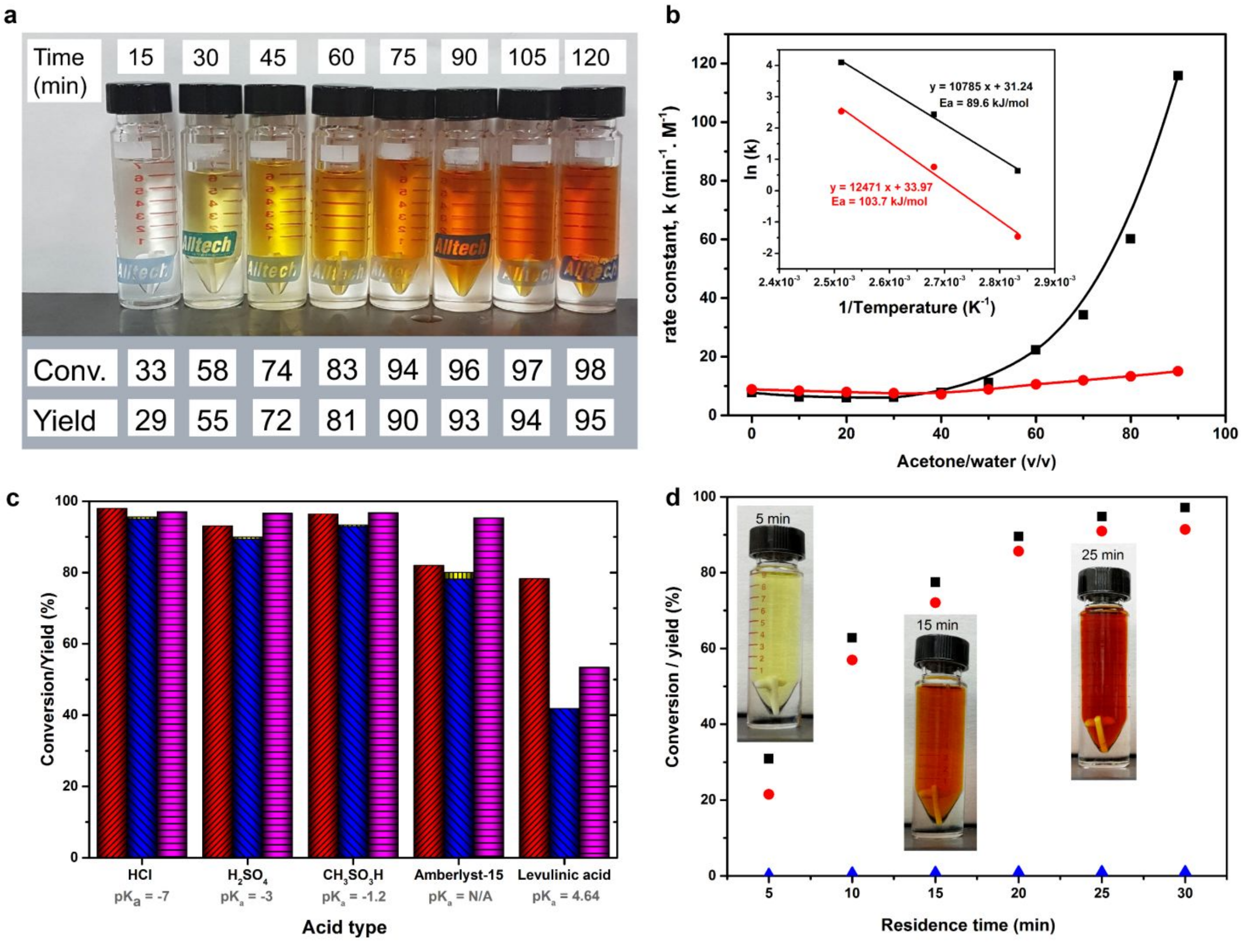

Fig. 2. Dehydration of fructose in acetone/water solvent system. (A) Dehydration of fructose (1 wt%) in 80/20 (v/v) acetone/water solvent system at 393 K with 15 mM HCl as dehydration catalyst. (B) Rate constants for fructose and glucose dehydration as a function of acetone concentration in the solvent system at 393 K with 15 mM HCl as dehydration catalyst. Black square for fructose dehydration. Red circle for glucose dehydration. (B, inset) Activation energy for fructose and glucose dehydration in 80/20 (v/v) acetone/water solvent system with 15 mM HCl as dehydration catalyst. Black square for fructose dehydration. Red circle for glucose dehydration. (C) Effect of acid type on the dehydration of fructose in acetone/water solvent system. Red bars for fructose conversion, blue bars for HMF yield, yellow bars for Levulinic acid yield and pink bars for HMF selectivity. Reaction condition: Feed – 1 wt% fructose; solvent – acetone:H_2O = 80:20; reaction temperature – 393 K; acid concentration – 15 mM. (D) Dehydration of high concentration of fructose in 80/20 (v/v) acetone/water solvent system at 393 K with 50 mM HCl as dehydration catalyst. Inset picture shows the change in solution color with reaction time.

dehydration in the acetone/water solvent system containing 80 vol% acetone is determined to be 90 kJ/mol (Fig. 2b, inset), which is lower than the activation energy reported for fructose dehydration in water (130-140 kJ/mol)[15,31]. These results are in agreement with our previous report which suggest that an aprotic organic solvent affects the reaction kinetics by changing the stabilization of the acidic proton relative to the protonated transition state thereby decreasing the activation energy of the reaction[32]. Additionally, fructose exists in at least five tautomer forms in solution, and the relative abundance of the furanose form can improve HMF selectivity based on the structural similarities between the furanose form of fructose and HMF. We note here that addition of acetone to water may change the relative composition of the tautomeric forms leading to a reduced activation energy for fructose dehydration. It was also observed that the addition of NaCl to the solvent system increases the rate of dehydration (Fig. S3, ESI†), which is in agreement with the literature[33]. Fig. 2c shows the fructose conversion, HMF yield and selectivity for fructose dehydration using various acid catalysts. It is seen that strong acids (e.g., HCl, H_2SO_4 and CH_3SO_3H) are effective catalysts for fructose dehydration, whereas, weak acids (e.g., levulinic acid) are not. This behaviour is in agreement with literature wherein the lowering of the activation energy is only observed for strong acids as the conjugate base of the strong acid has no effect on the protonstability[32]. It is clear from Fig. 2c that a non-corrosive organic acid, such as methanesulfonic acid, can be used to effectively dehydrate fructose to HMF. A heterogeneous acid catalyst is desired due to ease of separation from the product solution. Fructose dehydration using an acidic ion-exchange resin catalyst was conducted with 1 wt% fructose in 80/20 (v/v) acetone/water solvent at 398 K using Amberlyst-15® as the solid acid catalyst. Fig. 2c shows that high HMF yield (78%) and selectivity (96%) are obtained using Amberlyst-15® as dehydration catalyst.

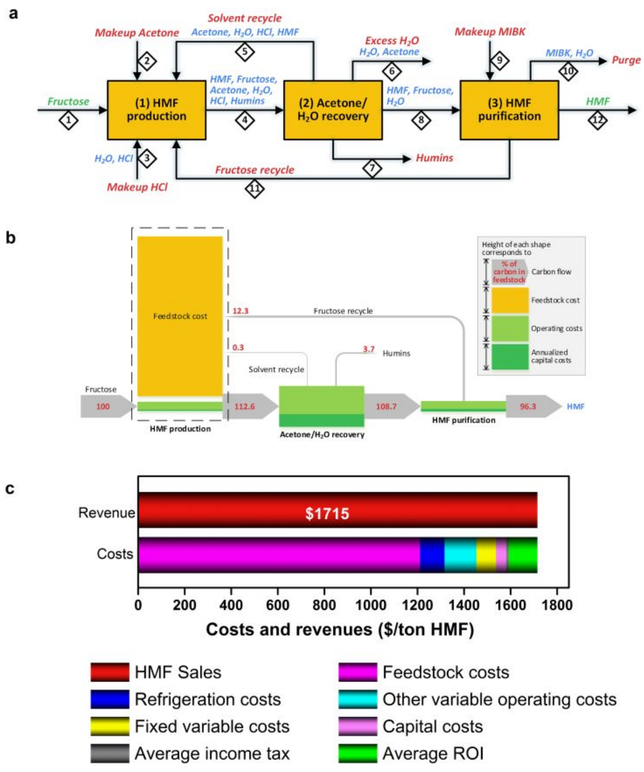

Fig. 3. Process economics for the production of HMF from fructose. (a) Process model (b) Sankey diagram for HMF production processes and (c) costs and revenues. ROI, return on investment.

The stability of Amberlyst-15® was investigated in a continuous tubular fixed bed reactor with 1 wt% fructose feed in 80/20 acetone water solvent system at 383 K. Under these reaction conditions, 96% fructose conversion and 92% yield of HMF were achieved (Fig. S4, ESI†). We also note that the number of acid sites per gram catalyst remained constant before and after continuous dehydration in a packed bed reactor, which shows that leaching of sulfonic acid groups from the resin is negligible under these mild operating conditions (Table. 1, ESI†). Thus, HMF can be selectively produced with high selectivity from fructose using a stable heterogeneous acid catalyst in the acetone water solvent system.

For economical production of HMF, it is desirable to integrate the fructose dehydration with the current process for production of fructose, where a simulated moving bed separation step produces a stream containing 25 wt% fructose in water[34]. Acetone was added to a solution containing 25 wt% fructose to achieve a solution containing 80 vol% acetone and 5 wt% fructose. Dehydration of this solution with 15 mM HCl for 20 min resulted in 89% fructose conversion and 85% HMF yield, leading to 95% HMF selectivity (Fig. 2d). The separation of HMF from the solvent system was achieved by evaporating the solvent under reduced pressure (50 mbar) at 313 K to obtain a mixture of HMF and unreacted fructose. HMF was extracted from the mixture using a solvent in which fructose solubility is low and HMF solubility is high, such as methyl isobutyl ketone (MIBK). Afterextraction, HMF was separated from MIBK by vacuum evaporation at 313 K and 50 mbar to obtain a light orange liquid (Fig.S5, ESI†). The purity of HMF was determined to be 99% based on HPLC analysis (Fig. S5, ESI†).

Based on our experimental data, we developed a process model (see Fig. 3a) and performed techno-economic analysis (TEA) of the process. Assuming a fructose price of $816 per ton, a preliminary TEA suggests that the process could produce HMF at a minimum selling price (MSP) of $1,715/ton (Fig. 3 b-c). A detailed description of the model and further explanation is available in the methods section. The low MSP for the approach described in the present paper is due to the improved yield of HMF in the acetone/water solvent system and the ease of HMF separation from the solvent system. Our TEA, in agreement with the previous study by Tsapatsis et al.[39], shows that the largest contributor to the MSP of HMF is the feedstock cost, whereas the operating and capital cost are low (Fig. 3). Additionally, if fructose is available at $300/ton (as predicted by Avantium) the MSP of HMF is reduced to $949/ton (Fig. S6, ESI†).

Industrially, liquefaction and saccharification of corn kernels yields a 25 wt% glucose (DE 94) solution, which is processed over xylose isomerase (EC 5.3.1.5) at 333 K to yield corn syrup containing 42% fructose and 52% glucose and 6% oligosaccharides. Acetone was added to a solution containing 25 wt% sugars to achieve a solution containing 80 vol% acetone and 5 wt% sugar. Dehydration of this solution (58% glucose and 42% fructose) over Amberlyst-15® at 398 K for 60 min in 80/20 (v/v) acetone/water solvent system resulted in 82% fructose conversion and HMF yield of 77% based on the initial fructose concentration. Glucose conversion to oligosaccharides and anhydrous sugars was 7% (Fig. S7, ESI†). Importantly, the overall carbon balance was greater than 94%. Since, xylose isomerase can efficiently isomerize glucose to fructose in the presence of oligosaccharides and anhydro-sugars[32], this catalyst eliminates the need for separating glucose from oligosaccharides and anhydro-sugars for recycle of the unreacted carbohydrates to the isomerization unit. Thus, the present strategy for production of a value-added platform molecule, HMF, can be integrated with the current infrastructure used for the production of high fructose corn syrup.

Dehydration of glucose to HMF

Glucose is the most abundant and the least expensive carbohydrate, and because our TEA shows that the MSP of HMF is dependent on the feedstock cost, it is desirable to convert glucose to HMF. For this transformation, glucose is first isomerized to fructose over a Lewis acid catalyst and fructose is subsequently converted to HMF over a Brønsted acid catalyst (Fig. 1).

One pot conversion of glucose to HMF in 80/20 acetone/water solvent system with Sn-β as isomerization catalyst and Amberlyst-15 as Brønsted acid catalyst resulted in poor HMF yield (36%) at 95% glucose conversion (Fig. S8, ESI†). This result is in agreement with literature wherein condensation is proposed to occur between HMF and an intermediate formed during glucose isomerization and/or fructose dehydration[35,36]. Importantly, we observed that in the acetone/water solvent

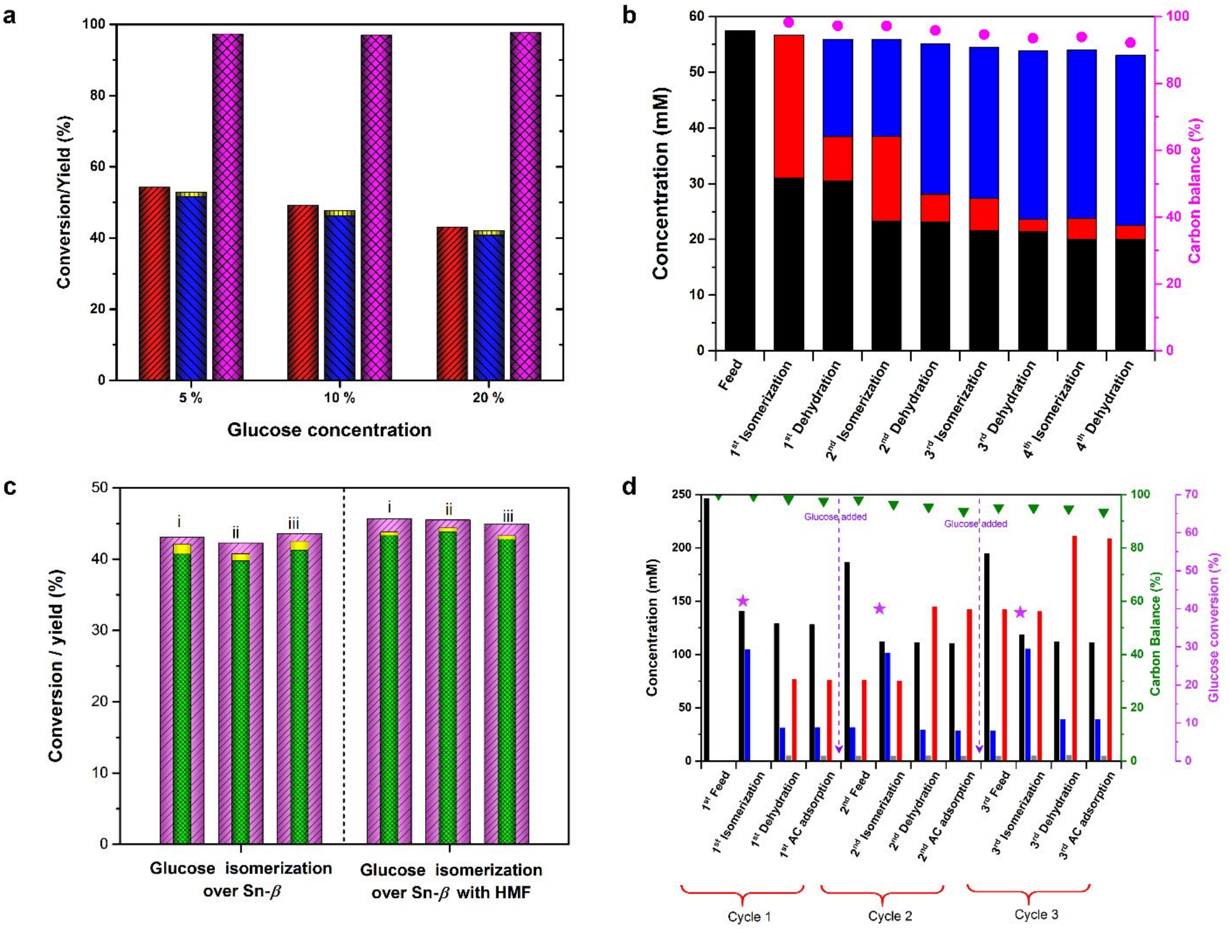

Fig. 4. Glucose conversion to HMF in acetone/water solvent system. (A) Effect of glucose concentration (aqueous basis) on isomerization over Sn-β in acetone/water (80/20) solvent system with glucose/Sn-β = 4 (g/g). Red, blue, yellow and pink represent glucose conversion, fructose yield, mannose yield and carbon balance, respectively. (B) Deactivation of Sn-β during subsequent isomerization. Reaction condition: Glucose concentration – 5 wt% (aqueous basis), Sn-β – 12.5 mg/mL feed, Amberlyst-15® – 12.5 mg/mL feed. Black, red and blue represent glucose, fructose and HMF concentration, respectively. Pink circles represent the overall carbon balance. (C) Stability of Sn-β during isomerization in the presence and absence of HMF. Reaction condition: Glucose concentration – 5 wt% (aqueous basis), Sn-β – 12.5 mg/mL feed. (i), (ii) and (iii) represent subsequent isomerization after product removal without catalyst regeneration. Pink, green and yellow represent glucose conversion, fructose yield and mannose yield, respectively. **(**D) Glucose conversion to HMF in acetone/water solvent system. Reaction condition: Glucose concentration – 20 wt% (aqueous basis), Sn-β – 6.25 mg/mL feed, Amberlyst-15® – 6.25 mg/mL feed. Black, blue, gray and red represent glucose, fructose, oligomer, and HMF concentration, respectively. Solvent system for all reactions was acetone/water (80/20). All isomerization reactions were conducted at 353 K for 180 minutes and all dehydration reactions were conducted at 393 K for 120 minutes.

system, the rate of fructose dehydration is higher than the rate of glucose dehydration/degradation, and the enhancement in the rate of fructose dehydration relative to glucose degradation increases with increasing acetone concentration in the solvent system (Fig. 2b). Furthermore, glucose dehydration has a higher activation energy compared to fructose dehydration (Fig. 2b, inset), and thus lower temperatures are preferred for selective fructose conversion to HMF. Isomerization of glucose over Sn-β in 80/20 acetone/water solvent system at 353 K resulted in an equilibrium mixture of glucose, fructose and mannose with excellent carbon balance for various initial glucose concentrations (Fig. 4a). Additionally, the equilibrium is shifted towards the fructose due to higher solubility of fructose in acetone/water solvent system, leading to improved conversion of glucose. Based on these results, we designed a two-step process for production and separation of HMF from glucose using acetone/water (80/20) as solvent. In this process, glucose is isomerized to fructose in the first step, and the product of the isomerization step is subjected to dehydration over a Brønsted acid catalyst where fructose is selectively dehydrated to HMF and glucose remains unreacted under the dehydration condition (Fig. 4b, 1st isomerization and 1st dehydration). It is observed, however, that the activity of the isomerization catalyst decreases during further isomerization of unreacted glucose (Fig. 4b, 3rd and 4th isomerization). This behavior implies that the isomerization catalyst (Sn-β) is deactivating during subsequent cycles of isomerization and dehydration. To identify the source of catalyst deactivation, two studies were performed. First, glucose isomerization was carried out over Sn-β in three consecutive cycles. Fig. 4c shows that Sn-β was stable during consecutive isomerization experiments, thereby

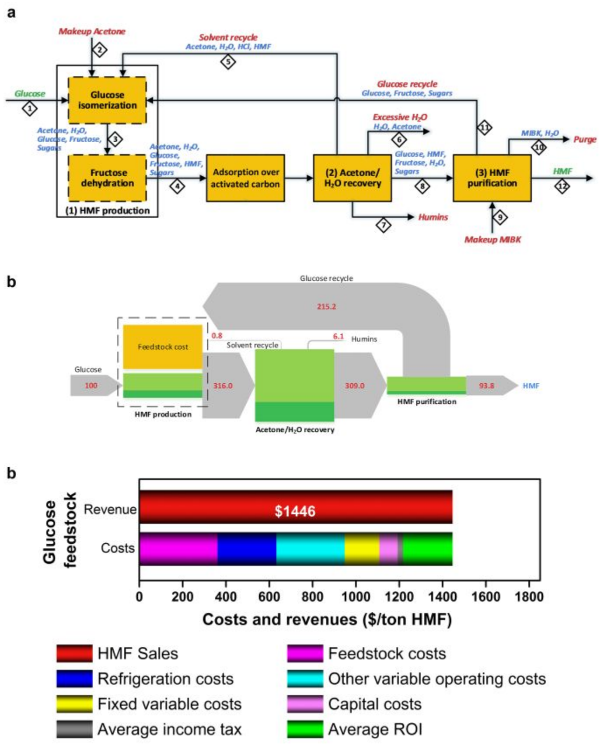

Fig. 5. Process economics for the production of HMF from glucose. (a) Process model (b) Sankey diagram for HMF production processes and (c) costs and revenues. ROI, return on investment.

eliminating the possibility that catalyst deactivation occurred during the isomerization reaction. Next, glucose isomerization was carried out over Sn-β in the presence of HMF. Fig. 4c shows that Sn-β is stable in the presence of HMF, thereby eliminating the possibility of irreversible adsorption of HMF on Sn-β. Thus, it appears that a by-product produced during dehydration reaction leads to deactivation of Sn-β. These results are in agreement with results reported by Hammond et al. [40], wherein the stability of Sn-β was evaluated for glucose isomerization in methanol/water solvent system, and catalyst deactivation was attributed to adsorption of by-products onto the catalyst surface. Attempts to regenerate Sn-β by oxidation in air at elevated temperature and by hydrogen peroxide treatment proved to be ineffective (Fig. S9, ESI†). We found, however, that the by-product leading to catalyst deactivation could be completely removed by adsorption on activated carbon. Moreover, we also show that sugars and HMF did not adsorb on the activated carbon (Table S2). It is observed from Fig 4d that the glucose conversion, after adsorption of the by-product of the dehydration reaction on activated carbon, for each cycle is stable at 40%. Thus, Sn-β was remains stable during subsequent isomerization runs. Additionally, we show that the concentration of HMF increases with each cycle (Fig. 4d). We note here that integration of this process with a biorefinery would require a sufficiently pure glucose stream, and such glucose streams have been reported previously, wherein a stream of fermentable sugar is obtained by chemical hydrolysis of lignocellulosic biomass[37,38]. We also note that the sugar stream obtained from a biorefinery can be further purified by passing the sugar stream over a bed of activated carbon wherein the by-products formed during hydrolysis of lignocellulosic biomass are adsorbed, producing a clean glucose stream for downstream processing. Moreover, our process would be ideal of coupling with a biorefinery that coverts glucose to high fructose corn syrup.

Fig. 5a shows a process schematic for the conversion of glucose to HMF. In this proposed process, the outlet of the dehydration reactor is passed through an adsorption column containing activated carbon to adsorb by-products of the dehydration reaction. The stream from the adsorption column enters vacuum evaporators to obtain a solid stream containing unreacted glucose, oligosaccharides, anhydrous sugars and HMF; and a vapor stream composed of acetone and water. HMF is extracted from the solid phase using MIBK, and this stream is subsequently subjected to another vacuum evaporation to yield pure HMF. The sugars retained after HMF extraction is recycled back to the isomerization unit. We stress here that with the limited number of experimental cycles, the catalyst stability can not be ascertained, and as such, we include a 20% refurbishment of Sn-β, Amberlyst-15®, and activated carbon every 3 months.

Using the results of this study and assuming a glucose price of $236 per ton, a preliminary techno-economic model suggests that HMF could be produced at a minimum selling price (MSP) of $1,446/ton (Fig. 5b-c). A detailed description of the model and further explanation is available in the methods section. The most substantial savings in this process are from the reduced feedstock cost, while transition from fructose to glucose increases the capital and operating costs. The process with glucose feedstock has high capital and operating costs, compared to the process starting with fructose, due to longer residence time and large recycle stream.

Finally, we note that the process outlined here for production of HMF could use fructose from an upstream fructose production process (containing 25 wt% fructose in water). An analysis of the sensitivity of the MSP of HMF to the fructose price demonstrates that the MSP of HMF can decrease to $1,097/ton if the fructose is purchased at $400/ton (Fig. S6, ESI†). Thus, we envision an economically viable way to back integrate our proposed process with current industrial fructose production because of its relatively low capital investment ($16.2MM in Table S6). In addition, our proposed process using glucose as the feedstock, while requiring a higher capital investment ($31.0MM in Table S6), could be an economically viable alternative for mitigating the fructose price fluctuations on HMF production if the glucose price remains $395/ton lower than the fructose price (Fig. S6, ESI†).

Conclusions

We have developed a process for production of HMF, a versatile platform molecule, from biomass derived carbohydrates using an inexpensive solvent system composed of acetone and water. The rate of fructose dehydration increases with increasing fraction of acetone in the solvent system, balanced by decreased solubility of fructose with increasing acetone fraction. We demonstrate that a solvent system composed of 80 vol% acetone has high fructose dehydration rate and can be used to integrate HMF production with the current process for high fructose corn syrup (HFCS) production. The fructose stream obtained from HFCS production, containing 25 wt% fructose, can be converted to HMF with 95% HMF selectivity at 90% fructose conversion. Additionally, we show that the HMF obtained can be easily separated from the low boiling point solvent and unreacted fructose. Moreover, we show that an acidic ion-exchange resin is an active and stable catalyst for fructose dehydration in the acetone/water solvent system, eliminating the need for utilization of mineral acids, thereby making the process environmentally friendly. Furthermore, it is shown that the rate of fructose dehydration is higher than the rate of glucose dehydration/degradation, and the enhancement in the rate of fructose dehydration relative to glucose degradation increases with increasing acetone concentration in the solvent system. This desirable property of the solvent system was used to selectively dehydrate fructose from an equimolar mixture of glucose and fructose obtained after glucose isomerization. Using Sn-β as isomerization catalyst and Amberlyst-15 as dehydration catalyst, we show that HMF can be produced in a carbon efficient manner from glucose. Thus, a process which can be integrated with the current HFCS production process and future bio-refineries is designed. Finally, techno-economic analyses indicate that utilizing fructose as feedstock leads to low investment (16 MM$) and produces HMF at an MSP of $ 1710/ton. The MSP of HMF can be further reduced to $ 1460/ton by changing the feedstock to glucose.

Experimental Section

Materials

Fructose (>99%, Sigma-Aldrich), Glucose (>99%, Sigma-Aldrich), acetone (HPLC grade, Fisher Scientific), HCl (0.5 M, Sigma-Aldrich), sulfuric acid (0.5 M, Sigma-Aldrich), methanesulfonic acid (Sigma-Aldrich) were used as received. Amberlyst-15® (Sigma-Aldrich) was crushed and sieved to obtain particle size between 45–150 μm. Sn-β (Si/Sn = 125) was a gift from Haldor-Topsøe. Milli-Q water (~18 MΩ-cm) was used in all experiments.

Impurity removal over activated carbon

Activated carbon (Norit SX-Ultra) was received from Cabot Corporation and was used as received. By-products generated during fructose dehydration were responsible for the deactivation of isomerization catalyst Sn-β. These contaminants were adsorbed on activated carbon at 303 K. In a typical experiment, 10 mg of activated carbon was added for each gram of product solution generated by fructose dehydration. The above solution was stirred at 500 rpm for 30 min. After adsorption, the solution was centrifuged at 5000 rpm for 10 min to remove the activated carbon. An aliquot of the solution after adsorption was diluted 10 times with Milli-Q water and was analysed using HPLC. It was confirmed that neither sugars nor HMF were adsorbed on activated carbon. Table S2 shows the typical product composition before and after contaminant removal on activated carbon.

Product analysis

The concentrations of the products were measured by High Performance Liquid Chromatography (HPLC) using a Bio-Rad Aminex HPX-87H column on a Waters 2695 system equipped with RI-2414 and PDA-2998 detectors in series. An aliquot of the product mixture was filtered with a 0.2 μm PTFE filter before analysis. The temperature of the HPLC column was maintained at 338 K, and the flow rate of the mobile phase (pH=2 water, acidified by sulfuric acid) was 0.6 mL/min. Fructose, anydro-sugars, oligomers and levulinic acid were analysed with the RI detector, while hydroxymethylfurfural (HMF) concentration was measured with the PDA detector at 320 nm. Fructose conversion and HMF yields acid were calculated as follows:

$$\text{Fructose conversion (\%)} = \frac{n^{o}_{\text{fructose}} - n_{\text{fructose}}}{n^{o}_{\text{fructose}}} \times 100$$

$$\text{HMF yield (\%)} = \frac{n_{\text{HMF}}}{n^{o}_{\text{fructose}}} \times 100$$

where, n^{o}_{fructose}, n_{fructose} and n_{HMF} are the moles of fructose in the feed, moles of fructose in the product and moles of HMF in the product, respectively.

Fructose dehydration in water

Feed was prepared by dissolving 100 mg fructose in 10 mL Milli-Q water containing 15 mM HCl. 8 mL volume of feed was added to a thick-walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K for 120 min. Reaction was stopped by cooling the reactor in an ice bath. 2 ml volume of liquid product was diluted with Milli-Q water to the final volume of 20 mL and was analysed using HPLC. HMF yield was determined to be 19% at complete fructose conversion. Fig. S2 shows the product after dehydration reaction. It is observed from Fig. S2 that black tarry product (humin) is produced in water. Comparison of Fig. S2 with Fig. 2a shows that the acetone/water (80/20) solvent system eliminates the degradation of HMF to insoluble humins during fructose dehydration.

Fructose dehydration in acetone/water (low fructose concentration)

The solvent system was prepared by mixing 6.8 mL Milli-Q water, 32 mL acetone and 1.2 mL 0.5 M HCl. The feed solution was prepared by dissolving 400 mg fructose in the solvent system. 8 mL volume of feed was added to a thick-walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K. The reaction was stopped at 15 minute interval by cooling the reactor in an ice bath. 500 μl liquid product was diluted with Milli-Q water to the final volume of 5 mL and was analysed using HPLC as described above. Results are reported in Fig. 2a.

Effect of solvent composition in Fructose dehydration

Results reported in Fig. 2b were obtained by changing the solvent composition. The solvent system was prepared by mixing Milli-Q water, acetone and 0.5 M HCl in the amounts shown in Table 1. The feed solution was prepared by dissolving 400 mg fructose in the solvent system. 8 mL volume of feed was added to a thick-walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K. The reaction was stopped at 15 minutes. 500 μl liquid product was diluted with Milli-Q water to the final volume of 5 mL and was analysed using HPLC, as described above.

Table 1. Amounts of solvent used to prepare various solvent composition containing 15 mM HCl.

Solvent composition (acetone/water)	Milli-Q water added (ml)	Acetone added (ml)	0.5 M HCl added (ml)
0/100	38.8	0	1.2
10/90	34.8	4	1.2
20/80	30.8	8	1.2
30/70	26.8	12	1.2
40/60	22.8	16	1.2
50/50	18.8	20	1.2
60/40	14.8	24	1.2
70/30	10.8	28	1.2
80/20	6.8	32	1.2
90/10	2.8	36	1.2

For the result reported in inset of Fig 2b, the solvent composition was fixed at 80/20 and the reaction temperature was changed to 353 K, 373 K and 398 K.

Fructose dehydration with various acids.

Results reported in Fig. 2c were obtained by changing the acid type. The solvent system was prepared by mixing Milli-Q water, acetone and acid in the amounts shown in Table 2. The feed solution was prepared by dissolving 400 mg fructose in the solvent system. 8 mL volume of feed was added to a thick-walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K. The reaction was stopped at 120 minutes. 500 μl liquid product was diluted with Milli-Q water to the final volume of 5 mL and was analysed using HPLC, as described above.

Table 2. Amounts of solvent used to prepare feed for studying different acids.

Acid type (acetone/water)	Milli-Q water added (mL)	Acetone added (mL)	Acid added
0.5 M HCl	6.8	32	1.20 mL
0.5 M H_2SO_4	6.8	32	1.20 mL
CH_3SO_3H	19.85	80	0.15 mL
Amberlyst-15[a]	20	80	--
Levulinic acid	20	16	0.17 mL

[a] 50 mg Amberlyst-15 was added to each reactor containing 8 mL feed.

Fructose dehydration in acetone/water (high fructose concentration)

Aqueous feed was prepared by mixing 5 g fructose in 15 mL Milli-Q water containing 250 mM HCl (25 wt. % fructose). 2.13 g of aqueous feed along with 6.4 mL of acetone was added to a 10 mL thick walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K. The reaction was stopped at 5 minute interval by cooling the reactor in an ice bath. Reaction was stopped by cooling the reactor in an ice bath. 500 μl liquid product was diluted with Milli-Q water to the final volume of 5 mL and was analysed using HPLC as described above. The results obtained using this procedure are reported in Fig. 2d.

Effect of salt in fructose dehydration

Two different feed solutions were prepared to test the effect of salt on dehydration rate. For reaction without salt, feed was prepared by adding 1 gram fructose in a solution containing acetone (80 mL), methanesulfonic acid (0.15 mL) and Milli-Q water (20 mL). For reaction with salt, feed was prepared by adding 1 gram fructose in a solution containing acetone (80 mL), methanesulfonic acid (0.15 mL), NaCl (340 mg) and Milli-Q water (20 mL). For both reactions, 8 mL volume of feed was added to a thick walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K. The reaction was stopped at 15 minute interval by cooling the reactor in an ice bath. An aliquot of the product was diluted 10 times with Milli-Q water and was analysed using HPLC as described above. Fig. S3 shows the effect of the addition of NaCl on fructose dehydration. It is observed that fructose dehydration rate is enhanced in the presence of NaCl; however, addition of salt has no effect on the final HMF yield.

Stability of Amberlyst-15® during fructose dehydration:

A schematic representation of the flow-through reaction system used to study the stability of Amberlyst-15® is shown in Fig. S4a. 250 mg crushed Amberlyst-15® (45-150 μm) was mixed with 1.5 g carbon black (Black-pearl 1300) and placed in heated zone of the flow-through reactor between two beds of silica granules separated by quartz wool plugs (Ohio Valley Specialty Company). The flow-through reactor was comprised of a glass lined stainless steel tube (2 mm inner diameter, Trajan Scientific) with corresponding stainless steel valves and fittings (Swagelok). The heated zone of the reactor was fitted between two aluminum blocks placed within an insulated furnace (Applied Test Systems). A type-K thermocouple (Omega) was placed at the reactor wall and was used to monitor and control the reactor temperature using a 16A series controller (Love). Reactor temperature was maintained at 383 K throughout the reaction. Pressure was maintained constant at 300 psi by flowing helium (Airgas) in the headspace of the liquid collector through a back-pressure regulator (1500 PSI, Tescom). A feed solution containing, acetone (600 mL), water (150 mL), and fructose (7.5 g) was prepared and was flowed through the system using an HPLC pump (Series 1, Lab Alliances). Flow rate was maintained at 0.1 ml/min. The resulting flow-through liquid was sampled periodically by draining the liquid collector. An aliquot of the product was diluted 10 times with Milli-Q water and was analysed using HPLC as described above. Fig. S4b shows the fructose conversion and HMF yield as a function of time on stream. It is observed that the catalyst remain stable for over 100 hours on stream. Additionally, after 100 hour reaction, the catalyst was recovered from the flow-through reactor and the total number of acid sites was determined. Catalyst was stirred in 4.0 mL of saturated NaCl solution for 30 min to exchange H+ in the Amberlyst-15® with Na+. The quantity of H+ was determined by titration with 0.1 M NaOH solution. Table S1 shows the amount of H^+ ion exchanged in the fresh catalyst and the used catalyst. The number of acid sites per gram catalyst before and after continuous dehydration in a packed bed reactor remain constant, which shows that the leaching of sulfonic acid groups from the resin is negligible under these mild operating conditions.

Separation of HMF from solvent system:

The solvent was removed from the product of dehydration reaction under reduced pressure using a rotary evaporator (Heidolph). Pressure was maintained at 50 mbar and temperature was kept constant at 313 K. Water and acetone were removed to obtain HMF and unreacted fructose. HMF was subsequently separated from fructose using MIBK. MIBK (equal to volume of acetone and water removed) was added to selectively solubilize HMF from the mixture of HMF and unreacted fructose. MIBK was removed under reduced pressure (50 mbar) and 313 K using a rotary evaporator to obtain HMF as a light orange liquid. Fig. S5 shows the final product after MIBK removal. A small fraction (~100 mg) of light orange liquid was dissolved in water (5 mL) and analysed by HPLC. Fig. S5 shows the chromatogram of HMF obtained after separation. The purity of HMF was ascertained to be 99 %.

Glucose conversion to HMF (One pot):

One pot conversion of glucose to HMF was performed as follows: 400 mg glucose was dissolved in 8 mL water. Acetone (32 mL) was added to the glucose solution to obtain the feed solution for one pot conversion. 8 mL feed, 50 mg Amberlyst-15® and 50 mg Sn-β were added to a thick walled glass reactor. A triangular stir bar was added for stirring at 750 rpm. The reactor was placed in an oil bath at 398 K. The reaction was stopped at 20 minute interval by cooling the reactor in an ice bath. 100 μl liquid product was diluted with Milli-Q water to the final volume of 1 mL and was analysed for glucose, fructose, oligomers and HMF using HPLC. Fig. S8 shows the product distribution as a function of reaction time. HMF yield of 36% is achieved at 96% glucose conversion with a carbon balance of 74% at 120 min.

Glucose conversion to HMF:

Isomerization: 1.2 gram of glucose was dissolved in 6 mL water. Acetone (24 mL) was added to the glucose solution to obtain the feed solution. The feed solution was kept at a constant temperature of 323 K. In a typical experiment, 8 mL of feed solution and 50 mg Sn-β were loaded into the glass reactor. The reactor was placed in an oil bath set at 353 K. The mixture was stirred by a magnetic stir bar in the reactor at 750 rpm. After 3 hours, reaction was stopped by cooling the reactor in an ice bath. An aliquot of the product was diluted 10 times with Milli-Q water and was analysed using HPLC. Sn-β was separated by centrifugation at 5000 rpm for 5 minutes. Liquid product was obtained after decanting the solution. The liquid obtained after decanting was filtered through 0.2 μm filter to remove residual isomerization catalyst before dehydration.

Dehydration: The product of the isomerization reaction and 50 mg Amberlyst-15® were loaded into the glass reactor. The reactor was placed in an oil bath set at 393 K for 2 hours. The mixture was stirred by a magnetic stir bar in the reactor at 750 rpm. The reaction was stopped by cooling the reactor in an ice bath. An aliquot of the product was diluted 10 times with Milli-Q water and was analysed using HPLC. Solid acid catalyst was separated using the method discussed for Sn-β.

Sn-β stability and regeneration:

Fig.S9 shows the change in color of the Sn-β catalyst from white to light brown after isomerization of feed that has been previously subjected to dehydration. The following methods were employed to regenerate Sn-β.

High temperature calcination: Sn-β was separated by centrifugation (5000 rpm, 15 min) and the product was decanted. The catalyst was washed twice with Milli-Q water (5 mL) and was dried in oven at 383 K. The dried catalyst was transferred to a ceramic crucible and was calcined at 773 K for 4 hours. Fig. S9 shows the calcined catalyst. The catalyst after calcination becomes white again; however, the catalyst does not recover activity for glucose isomerization, as shown in Fig. S9.

Hydrogen peroxide treatment: Sn-β was separated from the solvent system by centrifugation (5000 rpm, 15 min) and the solvent was decanted. The catalyst was washed twice with Milli-Q water (5 mL). 5 mL hydrogen peroxide (Sigma Aldrich, 30 wt. % H_2O_2 in water) was added to the catalyst and stirred at room temperature (~303 K) for 30 min. After peroxide treatment, the catalyst was washed with water three times. The activity of the catalyst did not improve after peroxide treatment, as shown in Fig. S9.

Dehydration of simulated feed from enzymatic isomerization process:

Aqueous feed was prepared by mixing 5.8 g glucose, 4.2 g fructose in 30 mL Milli-Q water (25 wt. % sugar). 2.13 g of aqueous feed along with 6.4 mL of acetone was added to a 10 mL thick walled reactor (Chromatography Research Supplies). A triangular stir bar was added to the reactor for stirring at 750 rpm. The reactor was placed in an oil bath at 393 K. The reaction was stopped at 10 minute interval by cooling the reactor in an ice bath. 500 μl liquid product was diluted with Milli-Q water to the final volume of 5 mL and was analysed using HPLC. The result obtained using this procedure are reported in Fig. S7.

Techno-economic analysis:

Our techno-economic analyses of the two approaches for HMF production from fructose and glucose respectively follow five steps. First, a process block diagram of the process with fructose feedstock was developed, as shown in Fig. 3a. The corresponding process models were developed using Aspen Plus Process Simulator (V8.8 Aspen Technology) based on the experimental data (Table S3). In the HMF production section, fructose is converted to HMF in 85.8% molar yield. Acetone/H_2O solvent is then recovered via throttling flash and vacuum evaporation in the acetone/H_2O recovery section. Here we assume a refrigerant at 248 K is available to purchase and use to liquefy the acetone/H_2O solvent before pumping it back to the dehydration reactor. Since fructose dehydration produces H_2O as a by-product, the excessive H_2O in the recycling acetone/H_2O solvent is removed by a molecular sieve to maintain 25 wt% fructose concentration in reaction feed. In the subsequent HMF purification section, HMF is first extracted by MIBK (1:1 on mass basis) from its mixture with fructose. The insoluble portion, mainly unreacted fructose, is then taken for recycle to dehydration reactor, while the remaining soluble portion is sent to the vacuum evaporation to recover the MIBK solvent and purify HMF. Here, again we assume a refrigerant at 233 K is available to purchase and use to liquefy the MIBK solvent before pumping it back for the HMF extraction. The MIBK rich gas stream from the vacuum evaporation is cooled and recycled back for the HMF extraction after purging a fraction (1%) to mitigate build-up of impurities. The liquid stream from the vacuum evaporation forms the HMF product at 99 wt% purity. Second, a process block diagram for the process with glucose feedstock (Fig. 5a) was developed using the experimental data (Table S3). In this process, the glucose feed is first isomerized to fructose, whose equilibrium conversion is maintained at 42.9% leading to a product stream with an equilibrium fraction of glucose to fructose (48:52 on mass basis). The resulting product stream is then fed to the dehydration reactor, in which 66.1% fructose is converted to HMF. Subsequently, the reactor product stream passes through the acetone/H_2O recovery section and HMF purification section, which are similar to the aforementioned process in Fig. 3a, to purify and recover HMF product, as well as to recycle acetone/H_2O and MIBK solvents. The purity of HMF product from the HMF purification section is 98.7 wt%. Table S4 shows the mass and energy balances of both processes based on the same HMF production rate of 11 kilotons per year. Third, we performed heat integration to optimize energy utilization using Aspen Energy Analyzer (V8.6 Aspen Technology). Both approaches require refrigeration to liquefy the solvents for recycle after vacuum evaporation. The process with glucose feedstock consumes approximately 2 times more energy than the process with fructose feedstock since it recovers HMF from a more diluted solution (4.5 wt% HMF vs. 1.4 wt%). After heat integration, we obtained energy recovery of 171 kW and 1,570 kW for the process with fructose feedstock and the process with glucose feedstock, respectively. The electricity requirement of the two processes are estimated to be 18 kW and 36 kW, respectively (Table S5). The heating, cooling and electricity requirements after heat integration are satisfied by external sources. Fourth, we performed equipment sizing and cost analysis using Aspen Process Economic Analyse (V8.8 Aspen Technology) based on simulation results. All equipment and material costs were adjusted to a common basis year of 2017. Table S6 shows the capital costs and operating costs for all processing equipment (using economic parameters and assumptions in Table S7). The total capital investment is estimated to be $16.2 million for the process with fructose feedstock, which is nearly 2 times lower because of a smaller separation subsystem resulting from higher HMF concentration (4.5 wt%) in the solvent, compared to that of the process with glucose feedstock (1.4 wt%) requiring a large recycle ratio. However, the total variable operating costs of the process with glucose feedstock decrease to $10.8 million yr-1 compared with those of the process with fructose feedstock ($16.5 million yr-1) because the glucose feedstock cost ($4.1 million yr-1), is over 3 times lower than the fructose feedstock cost ($13.8 million yr-1). Finally, we determined the MSP of HMF (using a discounted cash flow analysis (7), economic parameters and assumptions in Table S7) based on the capital and operating costs. The MSP of HMF from glucose feedstock is estimated to be $1,446/ton compared to $1,715/ton for the process with fructose feedstock. While feedstock is the primary cost drive to the MSP for the process with fructose feedstock, lower residence time and recovery of HMF product from a more concentrated solution ultimately lead to a less expensive and more efficient process with lower capital and operating costs (reduction factor of 2, excluding the feedstock contribution).

Conflicts of interest

J.A.D. and A.H.M. are authors on a patent related to this work filed by the Wisconsin Alumni Research Foundation (application no. 16/050522). All other authors declare that they have no competing interests.

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