5-Hydroxymethylfurfural Synthesis from Monosaccharides by a Biphasic Reaction–Extraction System Using a Microreactor and Extractor

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ABSTRACT: 5-Hydroxymethylfurfural (HMF) was synthesized from monosaccharides by a biphasic reaction system using a microreactor. The biphasic reaction system realized an immediate extraction and stabilization of product HMF, which further degrades under the reaction conditions. Segmented flow was utilized for an efficient reaction–extraction tool. The effect of extraction ability was evaluated based on the extraction phase/reaction phase partition coefficient of HMF. A Lewis acid catalyst was introduced to overcome the obstacle of the reaction, which was clarified as the isomerization of glucose to fructose, and improved the HMF yield to 85 mol % under the condition of T = 180 °C and τ = 47 min. The recovery of the product HMF was also examined using a constructed microextraction system, and HMF was selectively recovered from the extraction phase.

1. INTRODUCTION

HMF is one of the important and valuable biomass-derivative chemicals, which has applications such as in herbicides, food additives, or medical supplies. Especially, the use as a bioplastic material has gained attention because of worldwide urgent environmental issues such as fossil resource exhaustion and carbon dioxide emission. In addition, the importance of the bioplastics is perceived more commonly after "sustainability" had become one of the very important keywords for human life activities at the United Nations General Assembly in 2015. The practical utilization of HMF as a bioplastic material greatly contributes to the realization of a sustainable society. HMF is obtainable by an acidic aqueous conversion of hexose. Many previous studies developed novel catalysts to improve the HMF yield, and the yield reached approximately 50–60 mol %. However, under the acidic aqueous condition, HMF further converts into levulinic acid and formic acid or the undesirable byproduct humin. Levulinic acid is also one of the biomass-derivative important chemicals. On the other hand, humin has no applications at all, and it is regarded as a completely useless matter. To improve the selectivity of HMF, some previous studies introduced ionic liquids as solvents with a metal catalyst, which resulted in a 40–70 mol % HMF yield. However, most of them still employed high-price novel catalysts. In addition, they conducted experiments using batch reactors. In the prospects of process intensification, a continuous production system is desirable. To conduct a biphasic reaction continuously, a microreactor is one of the ideal tools. A microreactor can realize the unique flow state of "segmented flow", which is often employed for a biphasic extraction. When two or more kinds of immiscible fluids flow in a thin tube, each fluid flows alternately as a slug segment. Because of friction between the slug and tube wall, internal circulation occurs in each slug. This internal circulation thins down the boundary layer thickness and also prevents the accumulation of extracted objects near the reaction phase.
the phase boundary, which results in mass transfer improvement.\textsuperscript{19–23} Our previously reported study employed the segmented flow for the biphasic HMF production.\textsuperscript{24} Scheme 1 illustrates the conceptual diagram of the reaction. The system enabled the high HMF yield of 76 mol % from glucose using the simple experimental apparatus. On the other hand, the obstacle in the conversion pathways was revealed as the isomerization of glucose to fructose, and the use of a Lewis acid catalyst was suggested for HMF yield improvement. Therefore, this study reports the effect of Lewis acid use on the conversion. In addition, the product HMF was recovered as a solution in the organic phase in the previous study. Because HMF is not tolerant to heat, distillation is not suitable for HMF purification from solvents with high boiling points. This means that the recovery requires further HMF extraction to another kind of solvent or other operations such as crystallization or drying. Because a microreactor is an effective extraction tool, a microextraction apparatus was prepared and examined in this study.

2. RESULTS AND DISCUSSION

2.1. HMF Synthesis Using Methylisobutyl Ketone (MIBK) as an Extraction Phase. Our previous study using 2-sec-butylphenol (SBP) as the extraction phase clarified that the rate-determining step in the conversion of glucose to HMF was the isomerization of glucose to fructose.\textsuperscript{25} The impact of the isomerization step was also evaluated using MIBK as the extraction phase. Figure 1 shows the results after converting 1 wt % glucose or fructose solution in 1.0 M PB-3.0 (see Section 4.1 for the definition) at $T = 180 \, ^\circ\text{C}$ at the ratio of the organic and aqueous phase flow rates, O/A = 2. The biphasic system using MIBK resulted in successful reaction–extraction synthesis as well, and in this system also, the isomerization step required long times judging from the differences between materials. However, the HMF yield was lower than that of the SBP case, for example, 5.5 min of conversion of fructose with SBP resulted in 77 mol % whereas with MIBK resulted in 43 mol %. One of the important causes of the yield difference was probably the difference in the extraction abilities between MIBK and SBP. Figure 1 indicates that the ratio of HMF in the organic phase did not depend on the residence time, which meant that the mass transfer was promoted by segmented flow and the extraction reached equilibrium. The organic phase/deionized water partition coefficient $K$ (see Section 4.3 for the definition) of HMF was calculated via batch extraction attempts, which resulted in $K$ for MIBK being 1.3 and $K$ for SBP being 8.7. Therefore, product HMF was efficiently extracted from the reaction phase when SBP was used as the extraction phase and resulted in a higher HMF yield. Because the extraction capacity could improve by increasing O/A, the effect of O/A on the HMF yield was evaluated. Figure 2 shows the results when 1 wt % glucose in 1.0 M PB-3.0 was converted at $T = 180 \, ^\circ\text{C}$ and $\tau = 10.3 \, \text{min}$. Increasing O/A resulted in the higher HMF ratio in the organic phase and the higher HMF yield, which clarified that the higher extraction capacity resulted in a higher HMF yield. However, the HMF concentration in the extraction phase decreased with increasing O/A, which is a disadvantage for the recovery of HMF. In addition, the HMF ratio in the organic phase almost reached a plateau when O/A was over 4, and the HMF yield was still much lower than that of the SBP extraction case. Therefore, further HMF synthesis examinations were conducted using SBP as the extraction phase.

2.2. HMF Synthesis Using SBP as an Extraction Phase. As mentioned in the previous section, it was clarified that the

![Scheme 1. Conceptual Diagram of the Reaction in a Microreactor (Glu. = Glucose, Fru. = Fructose, LA = Levulinic Acid, and FA = Formic Acid)](Image 123x121 to 238x221)

![Figure 1. Monosaccharide conversions using MIBK as an extraction phase; 1 wt % saccharide solution, 1.0 M PB-3.0, $T = 180 \, ^\circ\text{C}$, an O/A = 2. Solid line - glucose, broken line - fructose, square - saccharide conversion, circle - HMF yield, triangle - HMF selectivity, and cross - HMF ratio in the organic phase.](Image 123x620 to 502x722)

![Figure 2. Effect of O/A on glucose conversion using MIBK as an extraction phase; 1 wt % glucose, 1.0 M PB-3.0, $\tau = 10.3 \, \text{min}$, and $T = 180 \, ^\circ\text{C}$. Square - glucose conversion, circle - HMF yield, cross - HMF ratio in the organic phase, and triangle - HMF concentration in the product MIBK.](Image 375x282 to 514x395)

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SBP/deionized water partition coefficient of HMF was much higher than that of MIBK via batch extraction attempts. According to $K = 1.3$ for MIBK, the maximum value of the HMF ratio in the organic phase was calculated as 71% at O/A = 2. However, the results shown in Figures 1 and 2 indicated that the ratio was approximately 80%. This fact implied that the use of phosphate buffer saline (PB) as the aqueous phase increased the partition coefficient. Thus, the SBP/PB partition coefficients of HMF were calculated using different concentrations and pH values of PBs. The results are shown in Figure 3. The higher pH and especially the higher concentration of PB showed the higher partition coefficient. Because the concentration of PB changed the partition coefficient, the difference between 1 wt % glucose conversions using 1.0 M PB-2.0 and 2.0 M PB-2.0 at $T = 180 \degree C$ and O/A = 3 was compared, and the results are shown in Figure 4. As expected, the HMF ratio significantly increased by the biphase reaction system by preventing an overreaction with the extraction phase.

Next, the effect of the catalyst was examined. In our previous study, the use of a Lewis acid was predicted to be efficient on this reaction system because a Lewis acid was known to promote the glucose isomerization to fructose, which was the rate-determining step. As the Lewis acid, cheap and common AlCl$_3$·6H$_2$O was employed. An amount of 0.05 g/g glucose of AlCl$_3$·6H$_2$O was added to 1 wt % glucose solution in 1.0 M PB-2.0, and it was converted at $T = 180 \degree C$ and O/A = 3. Figure 5 shows the glucose conversion and HMF yield.

![Figure 3](image3.png)

**Figure 3.** Effect of the pH and concentration of PB on the partition coefficient of HMF. Circle - 0.1 M PB, square - 1.0 M PB, and triangle - 2.0 M PB.

![Figure 4](image4.png)

**Figure 4.** Effect of the PB concentration on glucose conversion using SBP as an extraction phase; 1 wt % glucose solution, $T = 180 \degree C$, and O/A = 3. Solid line - with a Lewis acid, broken line - without a Lewis acid, square - glucose conversion, and circle - HMF yield by the monophasic reaction.

![Figure 5](image5.png)

**Figure 5.** Effect of Lewis acid on glucose conversion using SBP as an extraction phase; 1 wt % glucose solution, 1.0 M PB-2.0, $T = 180 \degree C$, and O/A = 3. Solid line - with a Lewis acid, broken line - without a Lewis acid, square - glucose conversion, and circle - HMF yield.

AlCl$_3$ significantly improved the HMF yield, and it reached 84.9 mol % after 47 min of conversion. The partition coefficient change due to the catalyst being little where $K = 12.1$ with AlCl$_3$ and $K = 11.7$ without AlCl$_3$. The HMF ratio in SBP after catalytic conversion was 97%, which was at approximately the equilibrium with $K = 12.1$ and O/A = 3. In addition, the undesirable byproduct formic acid was suppressed to less than 2 mol %. In summary, the use of segmented flow realized that the extraction reached equilibrium, and the use of a Lewis acid significantly reduced the obstacle of the isomerization step, resulting in the high HMF yield of 84.9 mol % with the simple reaction setups and the simple operation.

Scheme 2 illustrates the sequential reaction mechanisms of glucose to fructose, HMF, and levulinic acid (LA) + formic acid (FA) via isomerization, dehydration, and hydrolysis, respectively. Basically, fructose conversion to HMF and HMF conversion to LA are promoted by a Brønsted acid, and HMF conversion obviously favors the aqueous phase with a Brønsted acid according to Scheme 2. Without a Lewis acid, the employed reaction-phase PB contained only the Brønsted acid. Therefore, the isomerization step was the rate-determining step. Glucose isomerization to fructose was promoted by the Lewis acid. According to Zhang et al., even fructose conversion to HMF is promoted by the Lewis acid, which probably helped the HMF yield improve in this study. The partition coefficients of the chemicals involved in the reaction were examined using deionized water or 1.0 M PB-2.0 as the aqueous phase and SBP as the organic phase. Among the chemicals, glucose, fructose, and acid catalysts of AlCl$_3$ and the phosphoric ion were completely hydrophilic in that all the dissolved amounts were recovered in the aqueous phases. FA was also strongly hydrophilic, and it was slightly extracted to SBP with the partition coefficients of $2.5 \times 10^{-2}$ and $2.4 \times 10^{-3}$ for deionized water and 1.0 M PB-2.0, respectively. LA, on the other hand, favored SBP with the partition coefficients.
of 2.3 and 3.3 for deionized water and 1.0 M PB-2.0, respectively. Because all the catalysts and upstream chemicals were completely hydrophilic, the reactions proceeded in the aqueous phase. Ideally, the reactions except for the over-reaction of HMF occur in the organic phase because water inhibits dehydration and Lewis acid activity. The HMF yield possibly increases by selecting the organic solvent that has the high value of the partition coefficient of HMF and capable of dissolving sugars and Lewis acids. In the examined system in this study, nevertheless, the HMF yield was highly improved by promoting isomerization with the Lewis acid and preventing an overreaction of HMF with the extraction phase. It should be noted that the solubility of SBP in water was very low (1.4 g/L) and favorably even lower in 1.0 M PB-2.0 (0.4 g/L).

### 2.3. HMF Extraction from the Organic Phase.

Because the introduced organic solvents (MIBK and SBP) are toxic reagents, the recovery of HMF from the extraction solvents is essential. The synthesis experiments revealed that the extraction ability of MIBK was inferior to that of SBP. However, the inferior extraction ability might be the advantage when the whole process was taken into account. Because HMF is not tolerant to heat, distillation is not suitable for HMF purification from solvents with high boiling points. This means that the recovery requires operations such as back extraction, crystallization, or drying. The inferior extraction ability works as an advantage in these processes. Because the partition coefficient was revealed to be highly dependent on the aqueous solution, the back extraction of HMF to deionized water using a constructed counter-current flow microextractor was examined in this study. First, the back extraction of the product HMF in MIBK after the synthesis reaction was examined. The synthesis conditions were as follows: 1 wt% glucose, 1.0 M PB-3.0, $\tau = 16.8$ min, $T = 180$ °C, and $O/A = 2$. After the examination, the chromatogram of the obtained MIBK decreased the intensity of HMF only. In addition, the obtained water phase only delivered the peak of HMF. Thus, using the constructed microextraction apparatus, HMF was selectively extracted from the product organic phase to deionized water. Next, the extraction efficiency of the constructed system was examined. The HMF solution in MIBK was prepared, and then dissolved HMF was extracted to deionized water using the constructed microextractor. Figure 6 shows the extraction results with the equilibrium line. In average, 50% or 95% equilibrium was achieved after 3.8 min or 19 min of extraction, respectively. The 19 min operation enabled us to extract 79% initial HMF in MIBK to the deionized water phase. In summary, it was confirmed that the counter-current microextractor enabled rapid and selective HMF extraction from MIBK to deionized water. However, when HMF was extracted from SBP to deionized water, the extracted rate was only 11% equilibrium after 19 min of extraction (the initial HMF concentration in SBP was 5.86 g/L, and the HMF concentration in deionized water after extraction was 0.0760 g/L). The back extraction from SBP was
The HMF yield reached 85 mol % under the condition of 1 wt step in the reaction, and improved the HMF yield significantly. The extraction rate was not high because of the high triangle - A/O = 3, and broken lines - equilibrium lines. To produce pure HMF from monosaccharides, the balance of sugar material to pure HMF production method including all the processes from the into account. Our future work will develop the HMF also could be a part of the efficient mass transfer. Therefore, the HMF extraction from SBP was examined using segmented flow (co-current with the PFA tube of i.d. = 2.18 mm, o.d. = 3.18 mm, and length = 100 cm). Figure 7 shows the extraction results with the equilibrium line. The extraction rate was not high because of the high partition coefficient \( K = 8.7 \). However, segmented flow enabled the rapid HMF extraction reaching equilibrium. This process also could be a part of the efficient HMF purification method. To produce pure HMF from monosaccharides, the balance of efficiency both at the reaction and the extraction must be taken into account. Our future work will develop the HMF production method including all the processes from the sugar material to pure HMF.

3. CONCLUSIONS

The liquid–liquid biphasic reaction and extraction was applied to HMF production from monosaccharides. Segmented flow enabled the rapid extraction of the product HMF from the reaction phase and prevented the further conversion of product HMF. The extraction ability of the extraction phase was clarified as an important factor for the HMF yield improvement, and the higher partition coefficient and O/A resulted in the higher yield. The acid concentration of the reaction phase also affected the partition coefficient; however, it also changed the reactivity, and the yield improvement was not expected. The use of the Lewis acid had less effect on the partition coefficient. Nevertheless, the Lewis acid promoted the isomerization of glucose, which was the rate-determining step in the reaction, and improved the HMF yield significantly. The HMF yield reached 85 mol % under the condition of 1 wt % glucose solution in 1.0 M PB-2.0, 0.05 g/g-glucose AlCl₃- 6H₂O, and O/A = 3 using SBP, \( T = 180 \, ^{\circ}C \), and \( \tau = 47 \, \text{min} \). Product HMF was selectively extracted from the organic phase to deionized water. Counter-current extraction using a microextractor and co-current extraction by segmented flow enabled rapid HMF extraction from MIBK and SBP, respectively. Thus, a high-yield HMF production method from glucose and selective HMF recovery method were developed.

4. EXPERIMENTAL SECTION

4.1. Materials. As a material, glucose (FUJIFILM Wako Pure Chemical, Japan) or fructose (KISHIDA CHEMICAL, Japan) was solubilized into PB. PB was prepared at three different pH values (2.0, 2.5, and 3.0) by mixing the same concentrations of dilute phosphoric acid (0.1, 1.0, and 2.0 M) and NaH₂PO₄·2H₂O solution (0.1, 1.0, and 2.0 M), which resulted in nine different types of PB. Hereafter, the prepared PB is denoted as "concentration PB-pH", for example, 0.1 M PB at pH 3.0 is "0.1 M PB-3.0". A dilute phosphoric acid was prepared by diluting 85% phosphoric acid (Nacalai Tesque, Japan) with deionized water, and NaH₂PO₄·2H₂O solution was prepared by dissolving NaH₂PO₄·2H₂O (Nacalai Tesque) into deionized water. AlCl₃·6H₂O (Nacalai Tesque) was also dissolved into PB when catalytic conversion was examined. As an extraction phase, MIBK (FUJIFILM Wako Pure Chemical) or SBP (Tokyo Chemical Industry, Japan) was used. All the chemicals were used as purchased without any further purification.

4.2. HMF Synthesis Using a Microreactor. The experimental apparatus consisted of two high-pressure pumps, SUS 316 tubes, a PTFE tube, a hastelloy tube, a SUS 316 union tee, and a back pressure regulator. The 1 wt % sugar solution in PB and the organic phase (MIBK or SBP) were fed by the high-performance liquid chromatography (HPLC) pumps (LC-20 AD, Shimadzu Corporation, Japan) and mixed at the union tee with an internal diameter of 1.3 mm (i.d. = 1.3 mm), which was connected in sequence to a PTFE tube (i.D. = 2 mm) and hastelloy tube (i.d. = 2 mm). The PTFE section was prepared for the visualization of the flow states, and all of the biphasic experiments were guaranteed to be conducted under segmented flow. The hastelloy section with the length of 1.6 or 19.7 m was employed as the reactor section, which was cooled and soaked into an oil bath to maintain the reaction temperature at 160–190 °C. At the reactor outlet, 1 m of the SUS 316 tube (i.d. = 2 mm) was soaked into an ice bath to quench the reaction. The quenching section was followed by a back pressure regulator (IDEX Health & Science, U.S.A.), which pressurized the entire channel to 3.45 MPa to prevent fluid evaporation in the reactor. The depressurized product was collected at the ambient sampling section. The reaction temperature \( T \, [^\circ C] \), residence time \( \tau \, [\text{min}] \), sugar type, pH and concentration of PB, and the ratio of the organic and aqueous phase flow rates O/A [—] were varied to evaluate the effects on the HMF yield. In addition, the effect of the Lewis-acidic catalyst was examined using the sugar solution prepared with AlCl₃·6H₂O (5 wt % sugar). The product HMF concentration in each phase was analyzed by HPLC.

4.3. HMF Extraction from the Organic Phase. A double-pipe counter-current flow extractor was constructed for the HMF extraction from the product organic phase to deionized water. Scheme 3 illustrates the setups. The outer tube was the PFA tube with the outer diameter of 1.6 mm (o.d. 9388

Figure 6. HMF extraction from MIBK to deionized water by a counter-current microextraction system. Circle - 19 min, square - 3.8 min, and line - equilibrium line.

Figure 7. HMF extraction from SBP to deionized water by co-current segmented flow extraction. Circle - A/O = 1, square - A/O = 2, triangle - A/O = 3, and broken lines - equilibrium lines.
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Notes

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ABBREVIATIONS

HMF, 5-hydroxymethylfurfural; MIBK, methyisobutyl ketone; SBP, 2-sec-butylphenol; PB, phosphate buffer saline; LA, levulinic acid; FA, formic acid; HPLC, high-performance liquid chromatography

REFERENCES

(1) De Jong, E.; Dam, M. A.; Sipos, L.; Gruter, G.-J. M. Furandicarboxylic Acid (FDCA), A Versatile Building Block for a Very Interesting Class of Polymers. ACS Symp. Ser. 2012, 1105, 1.

(2) Thiyagarajan, S.; Vogelzang, W.; J. J. Knoop, R.; Frissen, A. E.; van Haveren, J.; van Es, D. S. Biobased Furandicarboxylic Acids (FDCA)s: Effects of Isomeric Substitution on Polyester Synthesis and Properties. Green Chem. 2014, 16, 1957.

(3) Gandini, A.; Silvestre, A. J. D.; Neto, C. P.; Sousa, A. F.; Gomes, M. The Furan Counterpart of Poly(ethylene Terephthalate): An Alternative Material Based on Renewable Resources. J. Polym. Sci., Part A: Polym. Chem. 2009, 47, 295.

(4) Ravasco, J. M. M.; Coelho, J. A. S.; Simeonov, S. P.; Afonso, C. A. M. Bifunctional Cr(III) Modified Ion Exchange Resins as Efficient Reusables Catalysts for the Production and Isolation of 5-Hydroxymethylfurfural from Glucose. RSC Adv. 2017, 7, 7555.

(5) Lu, Y.; Mi, L.; Li, H.; He, J.; Liu, Y.-X.; Wu, Z.-B.; Hu, D.-Y.; Yang, S. Efficient Conversion of Glucose to 5-Hydroxymethylfurfural Using Bifunctional Partially Hydroxylated AlF3. RSC Adv. 2016, 6, 12782.

(6) Parveen, F.; Upadhyayula, S. Efficient Conversion of Glucose to HMF Using Organocatalysts with Dual Acidic and Basic Functionalities - A Mechanistic and Experimental Study. Fuel Process. Technol. 2017, 162, 30.

(7) Schüth, F.; Rinaldi, R.; Meine, N.; Kaldström, M.; Hilgert, J.; Rechulski, M. D. K. Mechanocatalytic Depolymerization of Cellulose and Raw Biomass and Downstream Processing of the Products. Catal. Today 2014, 234, 24.

(8) Kuster, B. F. M. 5-Hydroxymethylfurfural (HMF). A Review Focussing on Its Manufacture. Starch-Stärke 1990, 42, 314.

(9) Girisuta, B.; Janssen, L. P. B. M.; Heeres, H. J. Kinetic Study on the Acid-Catalyzed Hydrolysis of Cellulose to Levulinic Acid. Ind. Eng. Chem. Res. 2007, 46, 1696.

(10) Zhang, Z.; Zhao, Z. K. Production of 5-Hydroxymethylfurfural from Glucose Catalyzed by Hydroxyapatite Supported Chromium Chloride. Biosour. Technol. 2011, 102, 3970.

(11) Zhou, J.; Tang, Z.; Jiang, X.; Jiang, R.; Shao, J.; Han, F.; Xu, Q. Catalytic Conversion of Glucose into 5-Hydroxymethyl-Furfural Over Chromium-Exchanged Bentonite in Ionic Liquid-Dimethyl Sulfoxide Mixtures. Waste Biomass Valorization 2016, 1357.

(12) Cui, S.; Tofanelli, M. A.; Ernst, R. D.; Eyring, E. M. Chromium(III) Catalysts in Ionic Liquids for the Conversion of Glucose to 5-(Hydroxymethyl)furfural (HMF): Insight into Metal
Catalystonic Liquid Mediated Conversion of Cellulosic Biomass to Biofuels and Chemicals. *Biomass Bioenergy* 2012, 42, 224.

(13) Peniston, Q. P. Manufacture of 5-Hydroxymethyl-2-Furfural. US2750394A, 1956.

(14) Cope, A. C. Production and Recovery of Furans. US2917520A, 1959.

(15) Román-Leshkov, Y.; Chheda, J. N.; Dumesic, J. A. Phase Modifiers Promote Efficient Production of Hydroxymethylfurfural from Fructose. *Science* 2006, 312, 1933.

(16) Wang, T.; Pagán-Torres, Y. J.; Combs, E. J.; Dumesic, J. A.; Shanks, B. H. Water-Compatible Lewis Acid-Catalyzed Conversion of Carbohydrates to 5-Hydroxymethylfurfural in a Biphasic Solvent System. *Top. Catal.* 2012, 55, 657.

(17) Mamo, W.; Chebude, Y.; Márquez-Álvarez, C.; Díaz, I.; Sastre, E. Comparison of Glucose Conversion to 5-HMF Using Different Modified Mordenites in Ionic Liquid and Biphasic Media. *Catal. Sci. Technol.* 2016, 6, 2766.

(18) Yang, F.; Liu, Q.; Bai, X.; Du, Y. Conversion of Biomass into 5-Hydroxymethylfurfural Using Solid Acid Catalyst. *Bioresour. Technol.* 2011, 102, 3424.

(19) Ahmed-Omer, B.; Barrow, D.; Wirth, T. Effect of Segmented Fluid Flow, Sonication and Phase Transfer Catalysis on Fructose. *Ind. Eng. Chem. Res.* 2008, 47, 4346.

(20) Kühler, J. M.; Henkel, T.; Grodrian, A.; Kirner, T.; Roth, M.; Martin, K.; Metze, J. Digital Reaction Technology by Micro Segmented Flow - Components, Concepts and Applications. *Chem. Eng. J.* 2004, 101, 201.

(21) Van Steijn, V.; Kreutzer, M. T.; Kleijn, C. R. Velocity Fluctuations of Segmented Flow in Microchannels. *Chem. Eng. J.* 2008, 135, S159.

(22) Knauer, A.; Thete, A.; Li, S.; Romanus, H.; Csáki, A.; Fritzche, W.; Kühler, J. M. Au/Ag/Au Double Shell Nanoparticles with Narrow Size Distribution Obtained by Continuous Micro Segmented Flow Synthesis. *Chem. Eng. J.* 2011, 166, 1164.

(23) Henkel, T.; Bermig, T.; Kielpinski, M.; Grodrian, A.; Metze, J.; Kühler, J. M. Chip Modules for Generation and Manipulation of Fluid Segments for Micro Serial Flow Processes. *Chem. Eng. J.* 2004, 101, 439.

(24) Muranaka, Y.; Nakagawa, H.; Masaki, R.; Maki, T.; Mae, K. Continuous 5-Hydroxymethylfurfural Production from Monosaccharides in a Microreactor. *Ind. Eng. Chem. Res.* 2017, 56, 10998.

(25) Román-Leshkov, Y.; Moliner, M.; Labinger, J. A.; Davis, M. E. Mechanism of Glucose Isomerization Using a Solid Lewis Acid Catalyst in Water. *Angew. Chem., Int. Ed.* 2010, 49, 8954.

(26) Bermejo-Deval, R.; Assary, R. S.; Nikolla, E.; Moliner, M.; Roman-Leshkov, Y.; Hwang, S.-J.; Palsdottir, A.; Silverman, D.; Lobo, R. F.; Curtiss, L. A.; Davis, M. E. Metalloenzyme-like Catalyzed Isomerizations of Sugars by Lewis Acid Zeolites. *Proc. Natl. Acad. Sci.* 2012, 109, 9727.

(27) Gounder, R.; Davis, M. E. Monosaccharide and Disaccharide Isomerization over Lewis Acid Sites in Hydrophobic and Hydrophilic Molecular Sieves. *J. Catal.* 2013, 308, 176.

(28) Corma, A.; Iborra, S.; Velty, A. Chemical Routes for the Transformation of Biomass into Chemicals. *Chem. Rev.* 2007, 107, 2411.

(29) Zhang, Z.; Liu, B.; Zhao, Z. K. Conversion of Fructose into 5-HMF Catalyzed by GeCl4 in DMSO and [Bmim]Cl System at Room Temperature. *Carbohydr. Polym.* 2012, 88, 891.

(30) Caratzoulas, S.; Vlachos, D. G. Converting Fructose to 5-Hydroxymethylfurfural: A Quantum Mechanics/molecular Mechanics Study of the Mechanism and Energetics. *Carbohydr. Res.* 2011, 346, 664.

(31) Kreissl, H. T.; Nakagawa, K.; Peng, Y. K.; Koito, Y.; Zheng, J.; Tsang, S. C. E. Niobium Oxides: Correlation of Acidity with Structure and Catalytic Performance in Sucrose Conversion to 5-Hydroxymethylfurfural. *J. Catal.* 2016, 338, 329.

(32) Horvat, J.; Klaić, B.; Metelko, B.; Šunić, V. Mechanism of Levulinic Acid Formation. *Tetrahedron Lett.* 1985, 26, 2111.