

University of Groningen

Selective fructose dehydration to 5-hydroxymethylfurfural from a fructose-glucose mixture over a sulfuric acid catalyst in a biphasic system: Experimental study and kinetic modelling

Guo, Wenze; Zhang, Zheng; Hacking, Jasper; Heeres, Hero; Yue, Jun

Published in:
Chemical Engineering Journal

DOI:
[10.1016/j.cej.2020.128182](https://doi.org/10.1016/j.cej.2020.128182)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Guo, W., Zhang, Z., Hacking, J., Heeres, H., & Yue, J. (2020). Selective fructose dehydration to 5-hydroxymethylfurfural from a fructose-glucose mixture over a sulfuric acid catalyst in a biphasic system: Experimental study and kinetic modelling. *Chemical Engineering Journal*, 409, [128182]. <https://doi.org/10.1016/j.cej.2020.128182>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Selective fructose dehydration to 5-hydroxymethylfurfural from a fructose-glucose mixture over a sulfuric acid catalyst in a biphasic system: Experimental study and kinetic modelling

Wenze Guo, Zheng Zhang, Jasper Hacking, Hero Jan Heeres, Jun Yue*

Department of Chemical Engineering, Engineering and Technology Institute Groningen, University of Groningen, 9747 AG Groningen, The Netherlands

ARTICLE INFO

Keywords:

Brønsted acid
Fructose
Glucose
5-hydroxymethylfurfural
Kinetics
Microreactor

ABSTRACT

A two-step process combining the (equilibrium) glucose isomerization to fructose with selective dehydration of fructose in the obtained sugar mixture to 5-hydroxymethylfurfural (HMF), where glucose is largely unconverted and recycled, represents an attractive concept to increase the overall efficiency for HMF synthesis. This work presents experimental and modelling studies on the conversion of such fructose-glucose mixture to HMF using the sulfuric acid catalyst in a water-methyl isobutyl ketone biphasic system under a wide range of conditions (e. g., temperature, catalyst and sugar concentrations). Through detailed product analyses and ESI-MS spectroscopy, the excess formation of formic acid (together with humins) by the direct sugar/HMF degradation was confirmed and included in the reaction network (neglected in most literatures). The kinetic modelling based on batch experiments in monophasic water well describes the measurements thereof, whereas distinct deviations were found in the prediction of typical literature kinetic models. The incorporation of HMF equilibrium extraction into the developed kinetic model, with consideration of phase volume change as a function of temperature and partial phase miscibility, enables to predict reaction results in the biphasic system in batch. This kinetic model allows to optimize conditions for HMF synthesis that are favored in continuous reactors with minimized back mixing. Based on the model implications, the biphasic system was optimized with slug flow microreactors to better address process intensification and scale-up aspects. Using a simulated fructose-glucose mixture feedstock to represent commercially available high fructose corn syrups, a maximum HMF yield of 81% was obtained at 155 °C over 0.05 M H₂SO₄ at a residence time of 16 min in the microreactor, with 96% fructose conversion and over 95% of glucose remaining unconverted.

1. Introduction

The steadily depleting fossil resource and growing environmental concern over CO₂ emission have promoted worldwide research attentions on utilizing lignocellulosic biomass as a green and sustainable feedstock for chemical industry. Lignocellulosic biomass is an abundant source for pentose and hexose that can be converted to several versatile platform chemicals [1-3]. 5-Hydroxymethylfurfural (HMF) has been identified as such an important bio-based platform chemical that can be further transformed into a wide range of derivatives with broad applications [4,5]. For instance, the oxidation of HMF yields 2,5-furandicarboxylic acid, the monomer of polyethylene furanoate (PEF) that is a promising alternative for petroleum-based polyethylene terephthalate (PET) [6,7]. The reduction of HMF yields 2,5-dimethylfuran and 2-

methylfuran as the promising liquid transportation fuel additives [8-10]. The rehydration of HMF yields levulinic acid which can be hydrogenated to γ -valerolactone as a green solvent and fuel additive [11-13].

HMF is typically produced in good yields by the acid catalyzed dehydration of hexoses such as glucose and fructose [14]. The HMF yield depends strongly on the hexose used, with fructose giving by far better yields than glucose. However, the techno-economic analysis indicates that glucose is a more attractive feedstock due to its higher abundance and much cheaper price compared with fructose [15]. In this context, a two-step process integrating the (equilibrium) isomerization of glucose to fructose and the subsequent selective fructose dehydration to HMF, with glucose remaining (largely) unconverted and recycled, represents an attractive concept to increase the overall HMF yield from glucose or glucose-rich cellulosic biomass, as illustrated in Fig. 1.

* Corresponding author.

E-mail address: yue.jun@rug.nl (J. Yue).

<https://doi.org/10.1016/j.cej.2020.128182>

Received 28 August 2020; Received in revised form 23 November 2020; Accepted 15 December 2020

Available online 26 December 2020

1385-8947/© 2020 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

The isomerization step is typically catalyzed by the enzyme (glucose isomerase), base or Lewis acid catalyst [16-21] and produces a proportional mixture of glucose and fructose (typically in 1:1 ratio over enzyme at temperatures below 80 °C) due to the thermodynamic equilibrium limitation depending on the reaction temperature [22]. Additionally, the fructose-glucose mixture can be produced directly from raw cellulosic biomass such as cellulose and starch via the combined hydrolysis and isomerization reactions (Fig. 1). One typical example is the well-established industrial process for the production of high fructose corn syrup (HFCS), the cheapest commercially available fructose-glucose mixture which has been marketed since 1970s and widely used as a sweetener in food industry [23]. In its typical production process, corn starch as the feedstock is firstly converted to corn syrup by breaking down long chains into glucose over enzymes such as alpha-amylase and glucoamylase. Then, the fructose-glucose mixture (HFCS) is produced by further processing the corn syrup over glucose isomerase to convert some of its glucose into fructose [24,25]. To meet the requirements of different applications, the typical content of fructose in the HFCS can be tuned from 42 wt% to 90 wt% by adjusting process conditions. Nowadays, due to the cheap price and high availability, the application of HFCS in chemical industry, e.g., its conversion to HMF, 5-(chloromethyl)furfural (CMF) and 2,5-furandicarboxylic acid, has attracted increasing attention [26-29], and this perfectly falls in the scope of the concept proposed in this work (Fig. 1).

The dehydration step is typically conducted over a Brønsted acid catalyst and using water as the reaction medium. The latter is more environmentally and economically desirable compared to organic solvents and ionic liquids [30]. However, side reactions involving HMF and/or sugars occur in water to produce formic acid, levulinic acid and humins (soluble or insoluble polymerized carbonaceous species). To increase the HMF yield, a biphasic system with an additional organic phase to extract HMF from water and thus prevent its degradation, has been experimentally proved effective [30,31]. In the proposed concept (Fig. 1), due to the difficulty and high cost of the direct separation of glucose from the fructose-glucose mixture, the separation and recycling

of glucose (to the isomerization step) is performed after the fructose dehydration step in a biphasic system, where the majority of HMF is extracted to the organic phase and glucose remains in water. Thus, it is important to operate such that the dehydration of fructose is much favored over glucose, so that glucose is (largely) unconverted. In the product separation step, HMF can be purified by vacuum distillation if the boiling point of the organic solvent used in the biphasic system is much lower than that of HMF. A typical example is the use of methyl isobutyl ketone (MIBK) as a cheap extraction solvent with low toxicity and acceptable HMF partition capacity compared to other common organic solvents. It has a boiling point of 117 °C at 101.3 kPa and 25 °C at 2.66 kPa [32]. Therefore, it is feasible to separate HMF (boiling point: 291 °C at 101.3 kPa and 114–116 °C at 133.3 Pa [4]) from MIBK by vacuum distillation at relatively lower temperatures (<80 °C) to avoid the thermal degradation of HMF which usually occurs at temperatures over 100 °C [33]. In the less favored case of using organic solvents with high boiling points, it is more difficult to separate HMF by distillation without incurring its thermal degradation. In such case, other separation techniques such as adsorption and crystallization might be considered [34]. After HMF separation, the organic solvent can be recycled and reused in the dehydration step. Currently, the synthesis of value-added chemicals such as HMF and gluconic acid by the selective conversion of fructose or glucose from the cheap and commercially available fructose-glucose mixture feedstock (e.g., HFCS, sucrose or sucrose-rich raw materials like crude sugar beet thick juice, as sucrose can be fast hydrolyzed to equimolar glucose and fructose), represents an important research hotspot for the upgrading of the current biorefinery [26-29,35-37]. Apparently, to ensure the high feasibility of the overall concept (Fig. 1), the process especially regarding the preferential dehydration of fructose over glucose in the aqueous-organic biphasic system should be optimized to obtain a sufficiently high HMF (space time) yield. Consequently, an in-depth kinetic and process understanding thereof is required.

Usually, heterogeneous catalysis is preferred over homogeneous one due to the ease of catalyst separation and reuse. However, the long-term

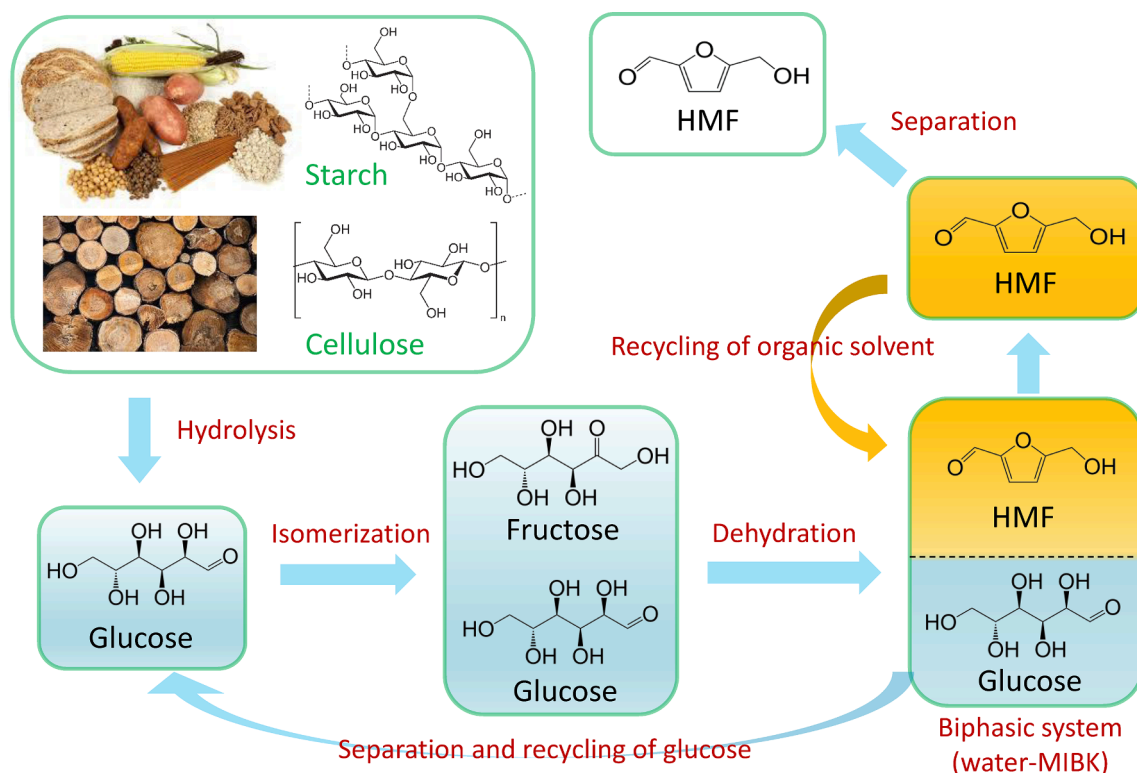


Fig. 1. Concept of the integrated process for HMF production from glucose or glucose-rich cellulosic biomass.

stability of solid catalysts under hydrothermal reaction conditions for sugar dehydration is still an issue to be well addressed, and the byproduct humins may deposit on the catalyst surface blocking active sites, requiring frequent catalyst regeneration [38]. Therefore, an efficient and stable homogeneous acid catalyst system is also attractive from the perspective of industrial HMF production. It is worth mentioning that such homogeneous acid catalysts (e.g., hydrochloric acid, sulfuric acid and phosphoric acid, as well as organic acids like formic acid and acetic acid) can be recycled from the remaining glucose solution in the proposed concept (Fig. 1), e.g., by extraction using organic diluents/solvents such as amines, amides, fatty acids and C5-C9 alcohols [39-43], if they interfere with the glucose isomerization step. Kinetics of dehydration of individual fructose or glucose in water has been extensively studied over the above-mentioned homogeneous mineral or organic acid catalysts [44-53] (cf. an overview in Table S1). Typical reaction networks proposed so far involve the direct dehydration of glucose or fructose to HMF, followed by HMF rehydration to equimolar formic acid (FA) and levulinic acid (LA), and simultaneously all HMF, fructose or glucose react directly to humins. However, a stoichiometric excess of FA (relative to LA) has been frequently observed, indicative of possibly new reaction pathways for the additional FA formation [21,49,54-56]. Noteworthy, most reported kinetic models (as shown in Table S1) simply assume the formation of an equimolar amount of FA and LA [11,36,44-48,57]. Despite the acceptable or satisfactory accuracy of these models in describing the experimental data (especially regarding the HMF yield) in the literature, reactions forming the excess FA are not described by the model. Such pitfall possibly becomes significant under certain conditions (e.g., at elevated temperatures where the excess FA formation seems more favored) [49], leading to a certain deviation of the model predictions for other components such as sugars and FA. Moreover, FA (and LA) as weak acid might play a catalytic role in the sugar conversion given sufficient proton dissociation [45,53], and thus a precise prediction of FA is necessary particularly when using high sugar concentration feedstocks (where a large amount of FA formed could possibly affect the kinetics to a significant extent). To this date, kinetic studies on the dehydration of fructose-glucose mixture to HMF have been rarely reported. One exception is seen in the work of Woodley et al. [27]. In order to develop a process allowing the use of HFCS for HMF synthesis, they performed a kinetic study on the conversion of fructose-glucose mixture over the HCl catalyst in the aqueous acetone solution at 150–200 °C. Since the reaction was conducted in the monophasic acetone–water mixture with modified chemistry environment (e.g., better HMF selectivity), the proposed reaction network differs significantly from the aforementioned ones in water. For example, FA was considered to form only via fructose and glucose decomposition rather than HMF rehydration, and humins were assumed to be primarily formed from fructose and glucose. For other researches on the HFCS conversion to HMF or CMF [26,28], only experimental demonstration was reported without deep kinetic insights obtained, together with a significant and unselective conversion of glucose. Recently, Tan-Soetedjo et al. [36] conducted kinetic studies on the conversion of sucrose to LA and HMF over the H₂SO₄ catalyst in water. In their proposed reaction network, FA was simply assumed equimolar with respect to LA. As such, the developed kinetic model did not fully capture the details of FA formation. In summary, it appears still necessary for a detailed experimental and kinetic study on the conversion of fructose-glucose mixture to HMF in water using simple homogeneous Brønsted acid such as sulfuric acid (cheaper and less corrosive than other strong mineral acid like HCl). In principle, combining the accurate kinetic models of individual glucose and fructose dehydration (i.e., by further considering the extra FA formation if present) might work in this case, which has not been attempted yet. Moreover, the incorporation of HMF extraction into the kinetic model for describing the enhanced HMF yield from hexose dehydration in an aqueous-organic biphasic system has not been reported either, which should also address the (significant) phase volume change due to

partial phase miscibility depending on the reaction temperature. Such model is of high importance for the process condition optimization and the rational design of reactor units for the selective fructose dehydration from fructose-glucose mixture (or their dimer sucrose) towards obtaining the maximized HMF yield, and thus is the aim of this work. In terms of reactor development for HMF synthesis (on a large scale), microreactors turn out to be an efficient production unit, due to its superior heat/mass transfer properties and ease of productivity increase by numbering-up [58,59]. Particularly for the aqueous-organic biphasic operation in microreactors, a slug flow pattern can be easily generated to achieve a narrowed residence time distribution [60] and an enhanced HMF extraction rate (by the strong inner circulation inside droplets/slugs) [21]. Therefore, increasing research attention has been given to the use of microreactors for the synthesis of HMF or 5-chloromethylfurfural (CMF) from sugars [21,28,37,58,61,62]. However, the efficient HMF synthesis from HFCS in slug flow microreactors (i.e., via the selective dehydration of fructose) has not been reported so far.

In this work, experiments on the conversion of fructose-glucose mixture (as well as individual sugars and HMF) using sulfuric acid as the catalyst were firstly performed in a monophasic water system in laboratory batch reactors to study the kinetics under varying reaction conditions (including temperature of ca. 120 to 160 °C, catalyst concentration of 0.005 to 0.45 M and each sugar concentration of 0.1 to 0.5 M). Based on the literature findings and the results of our experiments and ESI-MS spectroscopy, a reaction network was proposed with a reasonable addition of separate reaction pathways for the extra FA formation. Kinetic parameters for the conversion of individual glucose and fructose were estimated by fitting the kinetic model with the experimental data. The developed model could well describe the current experiments, whereas distinct deviations were found in the prediction of typical literature kinetic models [36,44,46,48]. Then, experiments were conducted in batch on the conversion of fructose-glucose mixture in a biphasic system comprising water and MIBK. Reaction results in the biphasic system can be well described by the kinetic model, with the additional incorporation of HMF extraction equilibrium between phases. In the above kinetic modelling, the appreciable phase volume change (and thus the associated change in component concentrations) was further addressed as a function of the reaction temperature and/or partial miscibility between water and MIBK. The developed kinetic model was further evaluated to indicate optimized conditions for HMF synthesis that are favored in continuous reactors with minimized back mixing. Based on the above model implications, the reaction was further optimized in biphasic slug flow microreactors to address process intensification and scale-up aspects relevant to industrial HMF production, using the simulated HFCS as a commercially available and cheap feedstock. The current work may pave the way towards developing an efficient process for HMF synthesis from glucose or glucose-rich cellulosic biomass produced in the biorefinery.

2. Experimental methods

2.1. Materials

D-glucose (99 wt%), D-fructose (99 wt%), sucrose (99 wt%) and methyl isobutyl ketone (99 wt%) were purchased from Acros Organics Co., Ltd. Sulfuric acid (95 wt%), 5-hydroxymethylfurfural (99 wt%), formic acid (99 wt%) and levulinic acid (99 wt%) were all purchased from Sigma-Aldrich Co., Ltd. All chemicals were of chemical grade and used as received without further treatment. Pressure tubes (height: 10.2 cm; outer diameter: 19 mm; capacity: ca. 9 mL) made of borosilicate glass were supplied by Ace Glass Inc. and used as laboratory batch reactors. Perfluoroalkoxy alkane (PFA) tubings with an inner diameter of 1.65 mm were supplied by Swagelok Company and used as capillary microreactors.

The fructose-glucose mixture can be used as a model system that represents highly concentrated sugar mixtures obtained from the

product or waste in the industrial food production process (e.g., HFCS, or crude sugar beet thick juice (after its fast hydrolysis)), or more ideally from non-food biomass resources (e.g., recycled pulp cellulose). The commercial HFCS is composed of water, fructose, glucose and higher saccharides, according to the data sheets provided by Archer Daniels Midland Company (ADM) [28]. In this work, HFCS was simulated with water, fructose, glucose and sucrose (to substitute for higher saccharides). 100 g of HFCS-90 was prepared by mixing 23 g of water, 69.3 g of fructose, 6.545 g of glucose and 1.155 g of sucrose. 100 g of HFCS-55 was prepared by mixing 23 g of water, 42.35 g of fructose, 31.57 g of glucose and 3.08 g of sucrose. The mixture was stirred to obtain a completely homogeneous sugar solution, which was used as substrate after a proper dilution (*vide infra*).

2.2. Experimental procedures

Experiments on the conversion of fructose-glucose mixture (as well as the individual sugars and HMF) over the sulfuric acid catalyst were primarily performed in the laboratory batch reactors in both monophasic water and biphasic water-MIBK systems. Monophasic experiments were conducted firstly to study the reaction network and develop the kinetic model, under a wide range of reaction conditions corresponding to a temperature range from ca. 120 to 160 °C, sulfuric acid catalyst concentration of 0.005–0.45 M, substrate (i.e., fructose, glucose, their mixture or HMF) concentration of 0.1–0.5 M (cf. more details in Table S2). Biphasic experiments for the conversion of fructose-glucose mixture were then conducted in batch under a selection of the above conditions, at an initial organic to aqueous volume ratio (O/A) ranging from 1 to 4.

In a typical batch reactor test, 5 mL of the aqueous reactant solution (for monophasic experiments), or 1 mL of the aqueous reactant solution and a certain volume of MIBK (typically 4 mL; for biphasic experiments), with a polytetrafluoroethylene (PTFE) stirring bar was added into the pressure tube, followed by being sealed and heated in an oil bath for a certain duration under magnetic stirring at a high speed of 900 rpm (in order to eliminate mass transfer limitation, the proof of which is provided in Section 3.2.3 hereafter). The actual reaction temperature was monitored with a calibrated thermocouple inserted into the reactor. The time at which the reactor was immersed into the oil bath maintained at the set temperature was considered as the starting point (i.e., the reaction time zero) for data collection. The temperature profile of the reactant solution during the heating stage was also recorded and incorporated in the following kinetic modeling in batch reactors. At the end of the reaction, the tubes were quenched in cooled water (at ca. 20 °C). The aqueous phase and organic phase (if present) were then filtered using a PTFE syringe filter (0.45 µm, VWR) before analyses by High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC), respectively (*vide infra*).

In addition, partition coefficients of HMF between water and MIBK at various temperatures, as required in the reaction modelling in biphasic systems, were also determined from additional experiments (see Fig. S1 and the other details in Section S3.1 of the Supplementary Material).

Based on the kinetic model implications, the conversion of fructose-glucose mixture (i.e., prepared to simulate a 10 wt% HFCS-55 or HFCS-90 solution) to HMF in the water-MIBK system was further optimized in a continuous slug flow microreactor. The experimental setup and procedure are similar to those reported in our previous work [21,37]. Briefly, the aqueous phase (containing sugars and sulfuric acid catalyst) and organic phase (MIBK) were fed into a PFA capillary microreactor (length: 3.3 m; inner diameter: 1.65 mm) using a binary HPLC pump unit (Agilent 1200 Series) at an inlet organic to aqueous volumetric flow ratio of 4 to 1. A uniform slug flow consisting of discrete aqueous droplets and continuous organic slugs was generated by mixing two phases in a polyether ether ketone (PEEK) Y-connector (inner diameter: 1.65 mm). The section of the microreactor for reaction was placed in an oven at a certain temperature, and the exit then passed through a water

bath at ca. 20 °C to quench the reaction. The residence time in the microreactor was adjusted by varying the phasic flow rate. The collected aqueous and organic samples at the microreactor exit were filtered and analyzed by HPLC and GC, respectively.

Experiments under representative conditions in the batch reactor and slug flow microreactor in this work were performed at least twice. The reported results are consistent within a 5% standard deviation. This corroborates the good reproducibility of the current experiments.

2.3. Analysis and characterization

The aqueous phase was analyzed by an Agilent 1200 HPLC, equipped with an Agilent 1200 pump, a Waters 410 refractive index detector, a standard ultraviolet detector and a Bio-Rad organic acid column (Aminex HPX-87H). A diluted aqueous H₂SO₄ solution (5 mM, 0.55 mL/min) was used as the eluent and the column temperature was maintained at 60 °C. The organic phase was analyzed by a TraceGC ultra GC, equipped with a flame ionization detector (FID) and a Stabilwax-DA fused silica column (length: 30 m; inner diameter: 0.32 mm; film thickness: 1 µm). The carrier gas was helium flowing at 2.2 mL/min, and the split ratio was set at 50:1. The oven temperature was kept at 40 °C for 5 min, then increased to 240 °C (ramp: 15 °C/min) and held at 240 °C for 10 min. The concentrations of the components in the aqueous and organic samples were calculated by the calibration curves determined using the standard solutions of known compounds with known concentrations.

It should be noted that FA is not detectable on GC due to its thermal degradation to CO₂ and H₂ at the elevated GC analysis temperature [63]. Therefore, for biphasic experiments, the product samples were maintained at room temperature (ca. 20 °C) for 2 h before analysis to ensure the establishment of the partition equilibrium (for FA as well as HMF and LA) between phases. Then, the FA concentration in the organic phase was simply calculated from its concentration in the aqueous phase (measured by HPLC) and its partition coefficient at 20 °C (measured to be 0.428; see details in Fig. S2 and Section S3.2 of the Supplementary Material).

Electro-spray ionization mass spectra (ESI-MS) has been proven as a useful technique to reveal the reaction intermediates during the sugar conversion [17,21,56,64]. In this work, the measurements were performed on an Orbitrap XL mass spectrometer (Thermo Fisher Scientific) with ESI ionization in the positive mode. Aqueous samples including the recycled solutions of fructose, glucose and HMF containing H₂SO₄ (i.e., collected after the reaction) were measured in a range of *m/z* 100–600 with the following operating parameters: sample cone voltage at 40 V, capillary voltage at 3.2 kV, cone gas (N₂) flow at 20 L/h, vaporizer temperature of the source at 150 °C, injection volume of 5 µL. Data were analyzed using an Xcalibur software.

2.4. Definitions and calculations

The conversion of substrate *s* (*X_s*) and yield of product *p* (*Y_p*) in the laboratory batch reactor are defined as

$$X_s = \frac{V_{aq,0}C_{aq,s,0} - V_{aq,1}C_{aq,p,1}}{V_{aq,0}C_{aq,s,0}} \times 100\% \quad (1)$$

$$Y_p = \frac{V_{org,1}C_{org,p,1} + V_{aq,1}C_{aq,p,1}}{V_{aq,0}C_{aq,s,0}} \times 100\% \quad (2)$$

where *V_{aq}* denotes the volume of the aqueous phase and *V_{org}* the volume of the organic phase (i.e., in the case of a biphasic system). *C_{aq}* and *C_{org}* are the concentrations in the aqueous and organic phases, respectively. The subscripts 0 and 1 refer to the start (i.e., at 20 °C) and end of the reaction (i.e., after being cooled to 20 °C), respectively. Note that in the case of using the fructose-glucose mixture as the substrate, the HMF yield is calculated based on the fructose substrate, because one optimization objective is to keep a very low glucose conversion (regulated

below 10% in this work, except some additional experiments for the purpose of kinetic modelling). This yield calculation further facilitates a comparison with the results from the individual fructose or glucose conversion.

In the case of biphasic operation, due to the partial miscibility between water and MIBK, $V_{aq,1}$ and $V_{org,1}$ differ from $V_{aq,0}$ and $V_{org,0}$, respectively, and are corrected as

$$V_{aq,1} = V_{aq,0}\alpha_{aq} \quad (3)$$

$$V_{org,1} = V_{org,0}\alpha_{org} \quad (4)$$

where α_{aq} or α_{org} is the correction factor that represents the ratio of volumes after and before the reaction for either the aqueous or organic phase, respectively (cf. Table S3 for its value at given initial MIBK to water volume ratios).

The carbon balance is defined as

$$\text{C balance} = \frac{\text{C amount in the products} + \text{C amount in the remaining substrate}}{\text{C amount in the starting substrate}} \times 100\% \quad (5)$$

The carbon balance is estimated based on the known products quantified by HPLC or GC such as glucose, fructose, mannose, HMF, levulinic acid and formic acid. The non-identified soluble/insoluble byproducts (e.g., humins) are not taken into account.

When it comes to the microreactor operation, the above definitions still hold provided that the volume terms (V_{aq} and V_{org}) in Eqs. (1)–(4) are changed to the respective phasic volumetric flow rate terms (Q_{aq} and Q_{org}). α_{aq} or α_{org} remains unchanged for the same initial MIBK to water volume ratio (in batch) and volumetric flow ratio (in flow). More details are found in our previous work [21].

3. Results and discussion

3.1. Experimental studies in batch reactors

3.1.1. Monophasic experiments: conversion of sugars and HMF in water

Firstly, monophasic experiments were conducted in the laboratory batch reactor using fructose, glucose, fructose-glucose mixture or HMF as the substrate to study the kinetics and particularly, to compare the reaction behavior of fructose, glucose and their mixture. Representative experiments were performed under a reaction temperature of 135 °C, a sulfuric acid concentration of 0.05 M and a substrate concentration of 0.1 M in the aqueous feed. The substrate conversion and product yield as a function of the batch time are given in Fig. 2. HMF, LA and FA were detected as the main product from both the fructose and glucose conversions. When starting from fructose, a full conversion was reached in 150 min (Fig. 2a). HMF as the intermediate product showed a clear maximum of 42% in 50 min, accompanied by a steady increase of LA and FA yields to 42% and 65%, respectively, in 200 min. Little amounts

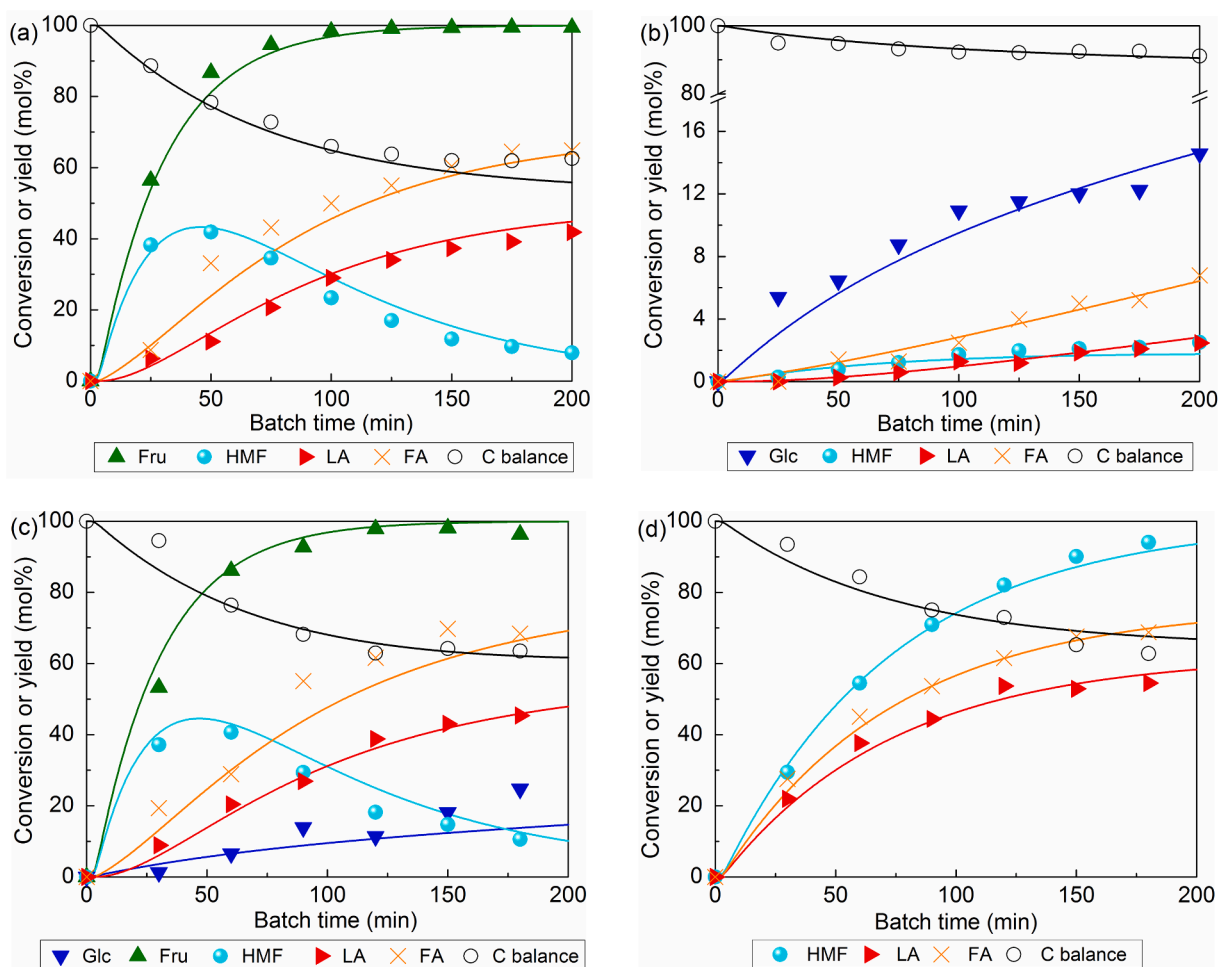


Fig. 2. Results on the conversion of (a) fructose, (b) glucose, (c) fructose-glucose mixture and (d) HMF in water in the laboratory batch reactor. Other reaction conditions: 135 °C, 0.05 M H_2SO_4 and 0.1 M substrate (glucose, fructose or HMF). In the figure legend, Glc, Fru, Man, FA and LA denote glucose, fructose, mannose, formic acid and levulinic acid, respectively. Symbols denote the experimental data and lines are for the model values (the same as shown in Figs. 3–5 and 12 hereafter).

(<1%) of glucose and mannose were also present as the respective isomerization and epimerization products from fructose (not shown for brevity). Comparatively, when starting from glucose, its conversion is much lower at such reaction conditions (Fig. 2b). A glucose conversion of 14% with 2.5% HMF yield, 2.5% LA yield and 6.8% FA yield were obtained in 200 min, together with trace amounts (<1%) of fructose and mannose (not shown). When starting from the fructose-glucose mixture (Fig. 2c), the conversion of glucose or fructose is similar to that starting from individual fructose or glucose under otherwise the same reaction conditions. Namely, fructose reacted fast while glucose was much less converted. The evolution trends of HMF, LA and FA are similar to those from the conversion of individual fructose. The possible interaction between glucose and fructose leading to humins is excluded by the fact that no distinct increase of the glucose and fructose conversions was observed compared with the cases starting from only glucose or fructose, as also experimentally proven in the work by Tan-Soetedjo et al. [36] aiming at the sucrose conversion to HMF in water. The above results indicate that fructose and glucose react independently in their mixture, and the preferential dehydration of fructose over glucose is feasible under proper conditions given large difference in their reactivity. HMF as the substrate was fast converted to LA via its rehydration (together with equimolar FA formation) (Fig. 2d). However, a stoichiometric excess of FA relative to LA was observed for all substrates (Fig. 2), indicating the presence of other reaction pathways for the FA formation and/or LA consumption (*vide infra*). For all reactions, the carbon balance decreased gradually with prolonging reaction time, indicating a more significant formation of humins from fructose, glucose and HMF.

Additionally, experiments were conducted in the batch reactor regarding the effect of reaction temperature, concentrations of sulfuric acid catalyst, sugar and HMF on the kinetic behavior in water. Generally, a higher temperature or acid concentration significantly promoted the consumption rate of fructose, glucose and HMF in water (cf. Figs. S8 and S9). An increase of temperature leads to an increase of the maximum HMF yield from sugars, though obtained at a shorter reaction time (Fig. S10), indicating an overall higher activation energy for the desirable dehydration reactions forming HMF than that for side reactions involving HMF. Comparatively, the acid catalyst concentration has a minor effect on the maximum HMF yield (Fig. S11), suggesting the similar reaction orders in acid among sub-reactions within the sugar conversion reaction network. Moreover, similar conversions of HMF and sugars (as well as the corresponding HMF yields) were observed when varying the initial substrate concentration (Fig. S12), which is indicative of an overall first-order reaction order with respect to the substrate (especially regarding the HMF formation).

3.1.2. Biphasic experiments: conversion of fructose-glucose mixture in the water-MIBK system

In addition to the preferential dehydration of fructose over glucose, the optimization of HMF yield is another goal to be achieved. Therefore, experiments on the conversion of fructose-glucose mixture were performed in the water-MIBK biphasic system in batch to improve the HMF yield. Typical results under a target reaction temperature of 135 °C with the aqueous phase containing 0.05 M H₂SO₄ and 0.1 M substrate (fed at ca. 20 °C) are displayed in Fig. 3. With the increasing initial organic to aqueous volume ratio (O/A; i.e., the ratio between water and MIBK volumes loaded in the reactor at ca. 20 °C), the maximum HMF yield was steadily increased due to more extraction into the organic phase and thus the HMF degradation in water was significantly suppressed (Fig. 3a). For example, when comparing monophasic and biphasic operations, the maximum HMF yield was increased from 41% in water (Fig. 2c) to 70% in the water-MIBK system (O/A = 4; Fig. 3b) in 60 min. The increased HMF yield is at the expense of the LA yield which was decreased from 45% (Fig. 2c) to 27% (Fig. 3b) in 180 min, as a result of the suppressed HMF rehydration. Besides, the carbon balance is significantly improved, e.g., from 65% (Fig. 2c) to 85% (Fig. 3b) in 180 min, as HMF-involved side reactions forming humins are largely prevented. Due to the partial miscibility between phases under the reaction temperature, the addition of MIBK at O/A = 4 has led to the decreased aqueous phase volume and thus the increased acid concentration. This resulted in slightly higher sugar conversions than those in monophasic experiments (by comparing Fig. 3b with Fig. 2a-c). Moreover, a proper reaction time is important to obtain the maximum HMF yield in biphasic operation. In other words, at a much longer reaction time, HMF in the organic phase tends to be further extracted back to the aqueous phase to undergo further side reactions, leading to a yield decrease (Fig. 3a). It was also observed that the promoting effect on the HMF yield gradually decreased with the increasing O/A ratio (Fig. 3a). Considering also the cost of the organic solvent and its downstream separation, an initial O/A ratio of 4 was taken for further optimization of the HMF yield hereafter (i.e., by finely tuning among others the reaction temperature and catalyst concentration). Similarly to the monophasic experiments shown above, here a stoichiometric excess of FA relative to LA was also observed (which will be discussed in details in Section 3.1.3).

As expected, the biphasic operation at higher temperatures led to a significantly enhanced conversion of both fructose and glucose (Figs. 4a and b). As a result, the highest HMF yield was reached after 30 min at 155 °C whereas it was still on the rise after 200 min at 117 °C (Fig. 4c). In addition to regulating the kinetic behavior, the temperature change affects the partition of HMF from water to MIBK (Fig. S1). Thus, the

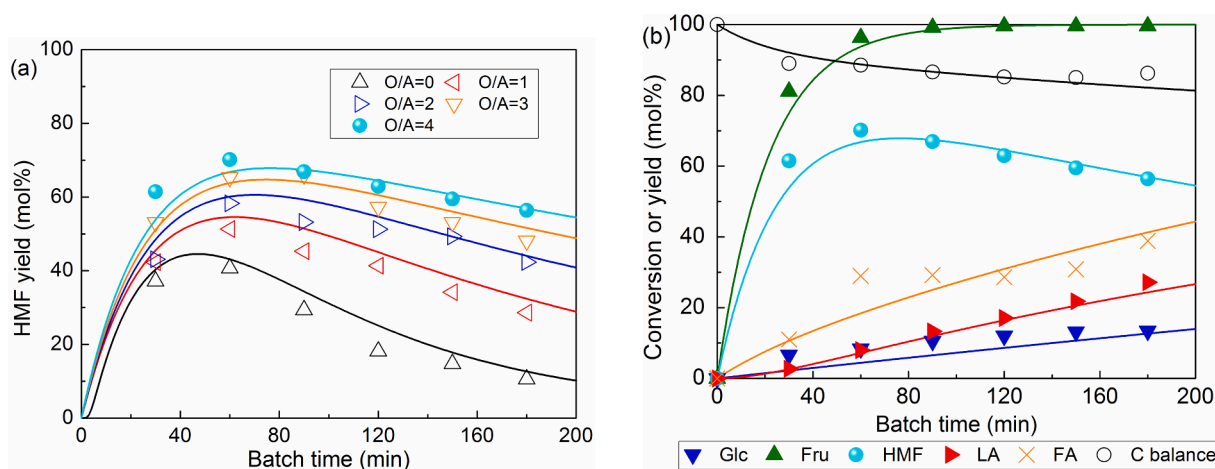


Fig. 3. Effect of initial organic to aqueous volume ratio (O/A) on the conversion of fructose-glucose mixture in the water-MIBK biphasic system in the batch reactor: (a) HMF yield as a function of O/A; (b) substrate conversion and product yield at O/A = 4. Other reaction conditions: 135 °C, 0.05 M H₂SO₄, 0.1 M glucose and 0.1 M fructose.

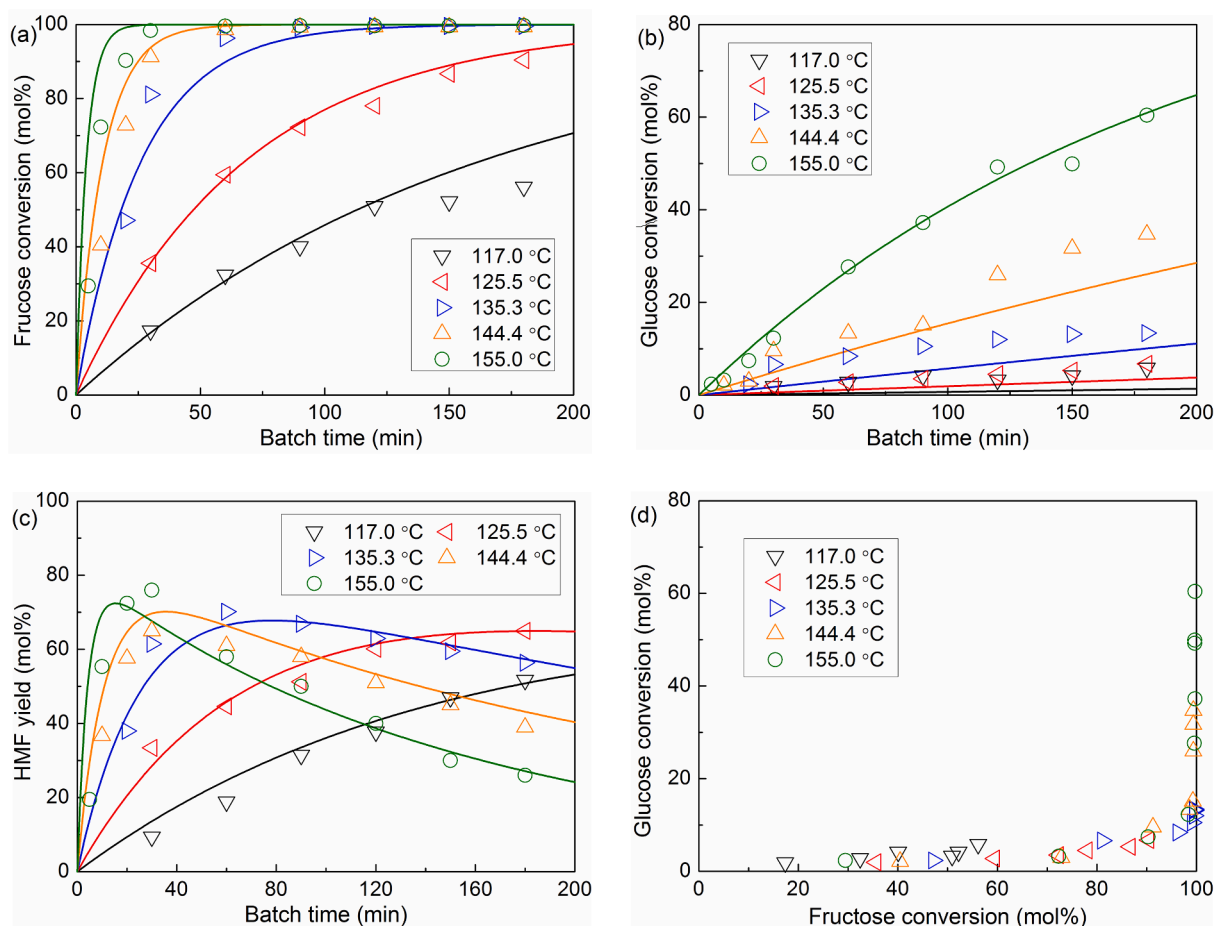


Fig. 4. Effect of reaction temperature on the conversion of fructose-glucose mixture in the water-MIBK biphasic system in the batch reactor: (a) fructose conversion, (b) glucose conversion, (c) HMF yield and (d) glucose conversion vs. fructose conversion. Other reaction conditions: 0.05 M H_2SO_4 , 0.1 M glucose, 0.1 M fructose and $\text{O/A} = 4$.

maximum HMF yield shows a strong temperature dependency, being over 75% at 155 °C in comparison to about 62% at 125.5 °C. For all the tested reaction temperatures (117–155 °C), an increase of the fructose conversion was accompanied by a by far slower increase of the glucose conversion (which remained below 10% even until the fructose conversion reached ca. 95%; Fig. 4d). A more significant glucose conversion over 10% was only observed at prolonged reaction times when fructose was completely consumed. The difference in the glucose conversion between different temperatures is minor when the fructose conversion is at a similar level. This suggests that within the temperature window here (117–155 °C), the selective fructose dehydration can be readily realized by properly tuning the reaction time to avoid overreaction of the much less reactive glucose.

The effect of acid catalyst concentration on the conversion of fructose-glucose mixture and the corresponding HMF yield in the biphasic system in batch is further illustrated in Fig. 5, at a reaction temperature of 155 °C. Clearly, the acid concentration has a profound effect on the reaction rate. For example, a full conversion of fructose was reached within 20 min with a sulfuric acid concentration over 0.05 M, while it took over 180 min with 0.005 M sulfuric acid (Fig. 5a). As for glucose, it was almost fully converted in 180 min over 0.25 M acid, while a <20% conversion was found at the same reaction time over 0.005 M acid (Fig. 5b). However, the maximum HMF yield has little dependency on the acid concentration, as all studied acid concentrations led to a similar maximum HMF yield of ca. 75% (Fig. 5c). Similar to the effect of temperature, a low glucose conversion (<10%) with high fructose conversion (>95%) can be obtained for all acid concentrations by proper tuning the reaction time to avoid overreaction of glucose (Fig. 5d).

The effect of temperature and acid concentration on the sugar mixture dehydration in the biphasic system is consistent with that in monophasic experiments (Figs. S8–S12), despite the higher HMF yield thereof due to additional physical extraction to MIBK.

3.1.3. Excess formation of formic acid

The stoichiometry of HMF rehydration indicates that FA and LA are formed equimolarly. However, in all monophasic and biphasic experiments mentioned above, a stoichiometric excess of FA relative to LA was observed (Figs. 2 and 3b). Fig. 6 summarizes the measured molar ratio of FA to LA as a function of the substrate conversion for all these experiments. The FA/LA molar ratio is around 1.1–1.3 when HMF is the substrate, but by far more FA than LA was formed when glucose or fructose is the reactant. Particularly, a general trend is that the FA/LA ratio gradually decreases with the increasing fructose or glucose conversion (cf. the inset of Fig. 6 as a clear example).

The excess FA can be attributed to either the consumption of LA or other reaction pathways that produce FA directly from HMF (besides its rehydration), fructose or glucose. One may assume that LA is possibly consumed by interacting with itself or other compounds (HMF, fructose, glucose or humins), fragmenting to FA or other byproducts. However, generally the FA/LA ratio is higher at lower substrate conversions at which less humin formation was expected (Fig. 6). This indicates a less important role of LA adsorbing on solid humins or reacting with humins (if present). This also implies that the reaction between LA and HMF, glucose or fructose (to produce FA) is absent or negligible as the amounts of HMF and subsequently LA are quite limited at the early stage of the conversion. Besides, LA was found stable under the current

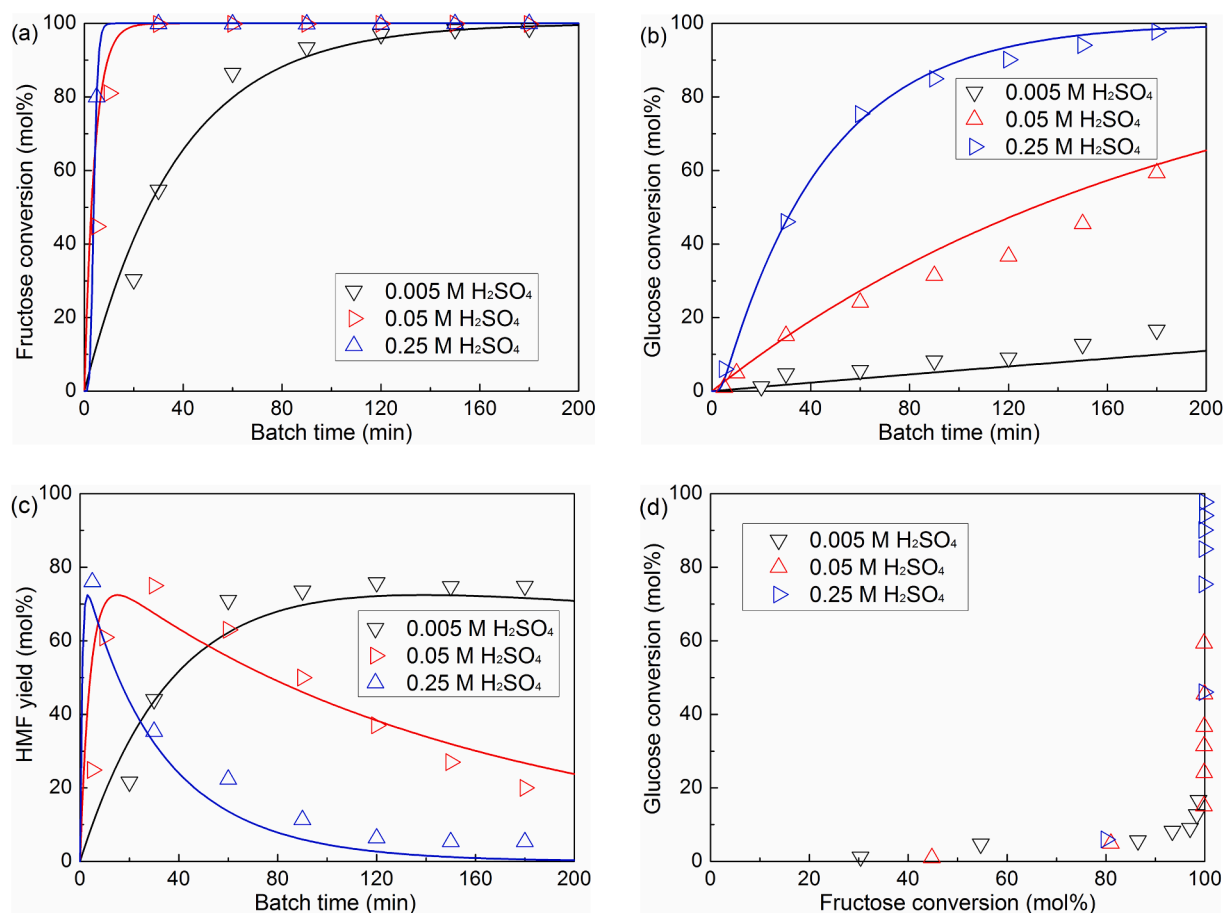


Fig. 5. Effect of sulfuric acid concentration on the conversion of fructose-glucose mixture in the water-MIBK biphasic system in the batch reactor: (a) fructose conversion; (b) glucose conversion; (c) HMF yield and (d) glucose conversion vs. fructose conversion. Other reaction conditions: 155 °C, 0.1 M glucose, 0.1 M fructose and O/A = 4.

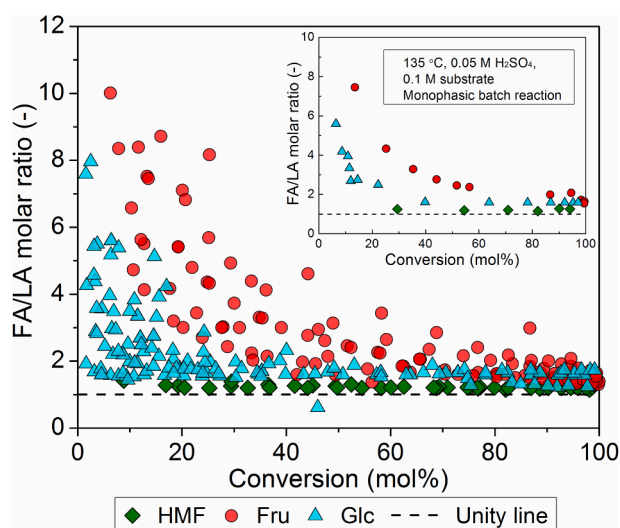


Fig. 6. Molar ratio of FA to LA as a function of the conversion of different substrates for all monophasic and biphasic experiments in batch reactors. The insert shows the data of a representative monophasic experiment under a reaction temperature of 135 °C using the aqueous feed with 0.05 M H₂SO₄ and 0.1 M substrate. The unity line (at an FA/LA molar ratio of 1) is included as a reference.

reaction conditions, ruling out the possibility of LA-LA condensation or LA fragmentation (Fig. S13), which is in line with the literature that reported a very low LA conversion (7.08%) at even harsher conditions (280 °C in 32 h) [50]. Thus, it is strongly suggested that glucose and fructose can directly produce FA (together with other byproducts). In addition, several unidentified compounds in HPLC analysis were found at the same reaction time as the excess FA was formed. These compounds degraded gradually at longer reaction times (given the respective HPLC peak intensity decrease) with the gradual decrease of carbon balance, and thus are believed to participate in the humin formation. Swift et al. [49] observed a similar phenomenon when using fructose and HMF as the starting material under the catalysis of HCl. They believed the excess FA is solely from fructose as the FA/LA molar ratio is close to 1 when starting from HMF. However, here the FA/LA ratio was found slightly above 1 rather than fluctuating around it with HMF as the substrate. Note that the evaporation of FA into the head space of the current batch reactor was estimated insignificant (details not shown for brevity) and the LA evaporation is even lower (the saturated vapor pressure of FA and LA at 155 °C are 1.65 and 0.027 bar, respectively [32]). Furthermore, the interaction of LA with HMF has never been reported. Consequently, we believe there is still a somewhat stoichiometric excess of FA (over LA) from the direct HMF decomposition.

To support the above deduction, the aqueous product of the reaction with glucose, fructose or HMF as the substrate in the monophasic water system in batch reactors (conditions: 135 °C, 0.05 M H₂SO₄ and 0.1 M substrate, 1 h reaction time) was analyzed by ESI-MS. For the sample starting from glucose (Fig. 7a), distinct peaks are present at $m/z = 71.05$

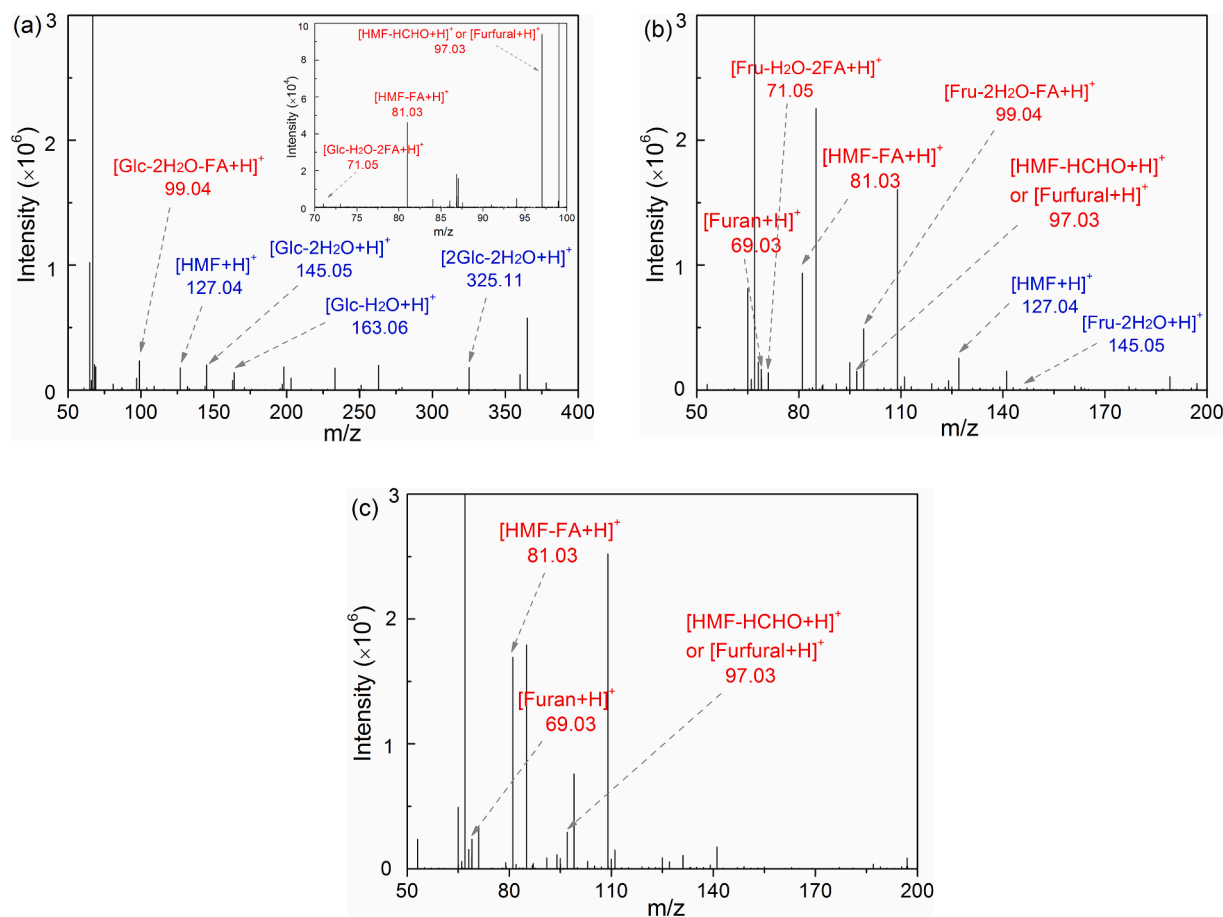


Fig. 7. ESI-MS spectra of the aqueous product sample collected after the reaction of (a) glucose, (b) fructose and (c) HMF in water in the batch reactor. Other reaction conditions: 135 °C, 0.05 M H₂SO₄, 0.1 M substrate (glucose, fructose or HMF), 1 h reaction time. The inset in (a) shows a magnified view of m/z region at 70–100.

and 99.04, which are assigned to $[\text{Glc-2H}_2\text{O-2FA} + \text{H}]^+$ and $[\text{Glc-2H}_2\text{O-FA} + \text{H}]^+$, respectively. Similarly, for the sample starting from fructose (Fig. 7b), peaks assigned to $[\text{Fru-H}_2\text{O-2FA} + \text{H}]^+$ at $m/z = 71.05$ and $[\text{Fru-2H}_2\text{O-FA} + \text{H}]^+$ at $m/z = 99.04$ are present. These peaks suggest the FA formation directly from glucose and fructose. Besides, peaks assigned to the dehydration intermediate of glucose and fructose were observed, such as $[\text{Glc-H}_2\text{O} + \text{H}]^+$ at $m/z = 163.06$ and $[\text{Glc/Fru-2H}_2\text{O} + \text{H}]^+$ at $m/z = 145.05$. For the sample starting from HMF (Fig. 7c), as well as those starting from glucose and fructose, peaks present at $m/z = 81.03$ and 97.03 were observed and are assigned to $[\text{HMF-FA} + \text{H}]^+$ and $[\text{HMF-HCHO} + \text{H}]^+$ (or $[\text{furfural} + \text{H}]^+$), respectively. These peak presence supports different reaction pathways for the FA formation from HMF in addition to its rehydration. $[\text{HMF-FA} + \text{H}]^+$ indicates the direct decomposition of HMF to FA, whereas $[\text{HMF-HCHO} + \text{H}]^+$ suggests the degradation of HMF to furfural and formaldehyde, followed by the oxidation of formaldehyde to FA by the remaining air in the solution [56]. Besides, the peak at $m/z = 69.03$ is assigned to $[\text{furan} + \text{H}]^+$ which may be formed (together with FA) via the hydrolysis of furfural [65,66]. Notably, the reaction pathway forming furfural is considered of little contribution, as a trace amount of furfural was detected in the product across all the experiments. Generally, the ESI-MS results further support the direct formation of FA from glucose, fructose and HMF.

To summarize, the excess FA (together with humins) is considered to be produced mainly by the degradation of sugars as well as HMF (though to a lesser extent). As such, the incorporation of these routes into the reaction network is necessary to develop a more accurate kinetic model for the conversion of fructose-glucose mixture. Notably, these reaction pathways for the excess FA formation have been neglected in most literatures (Table S1), except the work of Swift et al. [49] in which the

excess formic acid formation from only fructose was assumed without further spectroscopic proof.

3.2. Kinetic modelling studies

3.2.1. Development of reaction network for the conversion of fructose-glucose mixture

Based on the current experimental results and literature work on the individual conversion of glucose and fructose to HMF [44,46,48,57], a reaction network with several tandem and parallel reactions was proposed for the conversion of fructose-glucose mixture in monophasic (water) and biphasic (water-MIBK) systems (Fig. 8).

Typically, under the catalysis of Brønsted acid such as sulfuric acid in water, it has been well proven that glucose and fructose are dehydrated individually to HMF which is subsequently rehydrated to equimolar LA and FA [11]. Simultaneously, all glucose, fructose and HMF individually react to form soluble and insoluble humins. Besides, cross condensations between HMF and sugars to humins have also been reported [67]. In the proposed reaction network and the following kinetic modelling, such cross condensation is neglected to simplify our analysis, which does not affect the prediction of the overall humin formation from sugars and HMF. The possibility of cross condensations between glucose and fructose has been investigated in the work of Tan-Soetedjo et al. [36], by comparing the concentration–time profile of the individual sugar and that of a mixture of both sugars in a 1 to 1 M ratio during dehydration. The highly similar reaction profiles between these cases indicate no or at least limited cross condensations between the two sugars. In addition, the direct decomposition of glucose, fructose and HMF to form the extra FA together with humins (neglected in most literatures; cf. Table S1) is

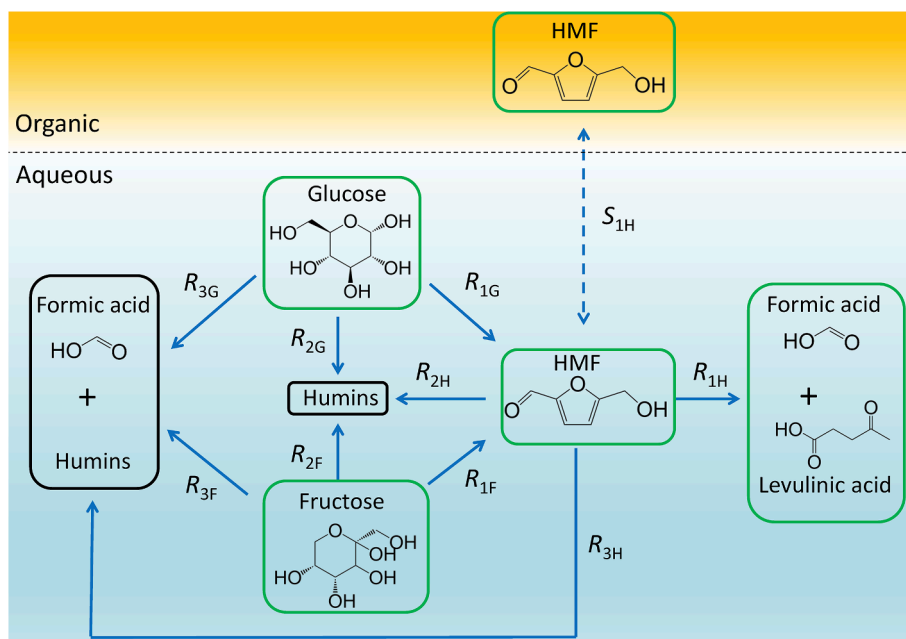


Fig. 8. Proposed reaction network for the conversion of fructose-glucose mixture catalyzed by sulfuric acid in monophasic (water) and biphasic (water-MIBK) systems. An additional extraction of HMF (as well as that of FA and LA; not shown for brevity) to the organic phase is present in the biphasic system. Symbol meanings are explained in the text.

included in this network. This inclusion is important for a more accurate prediction of the FA yield, and subsequently of the sugar conversion, HMF yield and carbon balance.

The isomerization and epimerization between glucose, fructose and mannose are believed of little contribution to the overall reaction rate and thus not included in the network. It has been experimentally proven that these reactions are only catalyzed by Lewis acids, bases and enzymes [16-21,68], while Brønsted acids such as sulfuric acid used in this work have no effect on promoting these reactions. Consequently, in this work these reactions only occurred spontaneously to a negligible extent.

In Brønsted acidic media, glucose may dehydrate inter- and intramolecularly to form glucose oligomers (mainly glucose dimer, e.g., neotrehalose) and anhydroglucoses (mainly levoglucosan), respectively. Literature studies revealed that glucose was converted to reversion products such as dimers at high sugar loadings (200 g/L), while levoglucosan was only formed in significant amounts at low glucose concentrations (<10 g/L) [69]. Under the glucose loading in this work (ca. 18–90 g/L), no glucose dimer and levoglucosan have been detected, and consequently these reversion reactions are not included in the network.

In summary, all possible side reactions of little contribution were excluded to simplify the network, otherwise the kinetic model would contain a large number of parameters rendering difficulties of the parameter estimation and thus limiting the predictive accuracy.

3.2.2. Development of the kinetic model from batch experiments in the monophasic water system

The kinetic model was developed based on the results of monophasic batch experiments with the individual HMF, glucose, fructose and fructose-glucose mixture as the starting substrate in which the reactant conversion and (quantifiable) product yields were largely demonstrated as a function of the reaction temperature, reaction time, substrate and acid catalyst concentrations (cf. Table S2 and Fig. 2, S8-S12).

Due to the heating-up of the solvent in the batch reactor, the reaction temperature (T) was raised from the initial room temperature (T_0 ; ca. 20 °C) to reach the final steady temperature (T_1) at the starting stage. To address this temperature lag, the temperature profile of the reaction solution during the heating-up process was measured (Fig. S14) and then modelled using a heat balance for the content in the batch reactor, as

shown in Eq. (6) (see Section S7 of the Supplementary Material for details).

$$T = T_1 - (T_1 - T_0)e^{-\eta t} \quad (6)$$

where t is the batch reaction time. Values of the fitting parameter η were determined by regressing the measured temperature profile using Eq. (6) (cf. Table S7 and Fig. S14).

During the heating-up, the water density varied with the increasing temperature. Thus, the volume of the aqueous solution at T (V_{aq}) differs from its initial volume at 20 °C ($V_{\text{aq},0}$), and is corrected as

$$V_{\text{aq}} = V_{\text{aq},0}\phi \quad (7)$$

where ϕ is the ratio of the water density at 20 °C and T , and can be modelled as a function of T using

$$\phi = m + ne^{zT} \quad (8)$$

where $m = 0.968$, $n = 0.0263$, $z = 0.00994$ and T is in °C (see Case 3 of Section S4 of the Supplementary Material for details). The value of ϕ falls in a range of 1.05 to 1.1 for the studied reaction temperature from ca. 120 to 160 °C (Fig. S5). Such volume change has been usually ignored in the literature. However, it leads to the changes in the actual concentrations of reactants and acid catalysts under the reaction temperature, and thus was addressed in the current kinetic modelling. It should be noted that the additional volume change caused by water evaporation to the head space in the current batch reactor was not considered, given the negligible percentage of water evaporated (estimated below ca. 0.23% relevant to our experimental conditions; calculations not shown for brevity).

Considering the above-mentioned volume change during heating-up, the mole balance of the component c ($c = \text{Fru}$, Glc , HMF , LA or FA) in water in the current batch reactor is expressed as

$$\frac{dn_c}{dt} = \frac{d(V_{\text{aq}}C_{\text{aq},c})}{dt} = R_c V_{\text{aq}} \quad (9)$$

where n_c , $C_{\text{aq},c}$ and R_c are the mole number, concentration and reaction rate of c in the aqueous phase, respectively.

Based on the reaction network in Fig. 8, Eq. (9) is further rearranged for each component as

$$\frac{dC_{\text{aq, Fru}}}{dt} = -R_{1F} - R_{2F} - R_{3F} - \frac{C_{\text{aq, Fru}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \frac{dT}{dt} \quad (10)$$

$$\frac{dC_{\text{aq, Glc}}}{dt} = -R_{1G} - R_{2G} - R_{3G} - \frac{C_{\text{aq, Glc}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \frac{dT}{dt} \quad (11)$$

$$\frac{dC_{\text{aq, HMF}}}{dt} = R_{1G} + R_{1F} - R_{1H} - R_{2H} - R_{3H} - \frac{C_{\text{aq, HMF}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \frac{dT}{dt} \quad (12)$$

$$\frac{dC_{\text{aq, LA}}}{dt} = R_{1H} - \frac{C_{\text{aq, LA}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \frac{dT}{dt} \quad (13)$$

$$\frac{dC_{\text{aq, FA}}}{dt} = R_{1H} + R_{3H} + R_{3F} + R_{3G} - \frac{C_{\text{aq, FA}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \frac{dT}{dt} \quad (14)$$

where R_{1F} and R_{1G} are reaction rates for fructose and glucose dehydration to HMF, respectively. R_{1H} is the reaction rate for HMF rehydration to equimolar FA and LA. R_{2F} , R_{2G} and R_{2H} are reaction rates for the respective repolymerization of fructose, glucose and HMF to humins. R_{3F} , R_{3G} and R_{3H} denote reaction rates for the direct formation of excess FA (together with humins) from fructose, glucose and HMF, respectively.

In our previous group work [11,44,46], kinetic studies on the individual dehydration of glucose and fructose as well as the HMF rehydration over the sulfuric acid catalyst were modelled using a power law approach. Reaction orders in HMF, fructose, glucose and H^+ (representing the acid catalyst) were then found to lie between 0.88 and 1.38 for all reactions starting from HMF, fructose or glucose. In the present work, experiments on reactions of glucose, fructose and HMF at different substrate and acid catalyst concentrations have been performed (Figs. S9 and S12). Fig. S12 shows that the sugar conversion (as well as the corresponding HMF yield) and the HMF conversion are independent of substrate concentrations, indicating that at least the overall consumption of sugars or HMF can be assumed first-order in each substrate. To avoid adding more parameters and causing more difficulty in the parameter estimation, a first-order reaction dependence on the reactant is assumed in the present work for all sub-reactions.

Then, the reaction rate for each individual sub-reaction step in Fig. 8 (R_{ij} ; $i = 1, 2$ or 3 ; $j = F, G$ or H) is defined as

$$R_{iF} = k_{\text{app, iF}} C_{\text{aq, Fru}} \quad (15)$$

$$R_{iG} = k_{\text{app, iG}} C_{\text{aq, Glc}} \quad (16)$$

$$R_{iH} = k_{\text{app, iH}} C_{\text{aq, HMF}} \quad (17)$$

where $k_{\text{app, ij}}$ is the apparent reaction rate constant for the individual sub-reaction.

By further considering the phase volume change, the proton concentration (C_{H^+}) at the reaction temperature can be found as [70]

$$C_{H^+} = C_{H_2SO_4} + \frac{1}{2} \left(-K_{a, HSO_4^-} - C_{H_2SO_4} + \sqrt{\left(K_{a, HSO_4^-} + C_{H_2SO_4} \right)^2 + 4C_{H_2SO_4} K_{a, HSO_4^-}} \right) \quad (18)$$

In this case, for a given concentration of sulfuric acid solution at 20 °C ($C_{H_2SO_4,0}$), $C_{H_2SO_4} = C_{H_2SO_4,0} / \phi$. K_{a, HSO_4^-} is the dissociation constant of HSO_4^- and its dependency on the reaction temperature is represented by Eq. (19) (T in K) [70]:

$$pK_{a, HSO_4^-} = 0.0152T - 2.636 \quad (19)$$

Noteworthy, the by-product FA and LA as weak acid could catalyze the sugar conversion [45,53]. In this study with the presence of the

strong acid H_2SO_4 , the dissociation of FA and LA was largely inhibited and thus produced little proton. Therefore, their catalytic roles were not considered in the kinetic modelling studies here (cf. Fig. S15 and other calculation details in Section S8 of the Supplementary Material). However, in some situations (e.g., when using highly diluted acid solutions or other weak organic acid catalysts, or in the case of forming a significant amount of FA and LA), the dissociation of FA and LA should be well considered in order to obtain the accurate proton concentration responsible for catalysis.

In the case of a first order dependency on the acid catalyst, $k_{\text{app, ij}}$ should be linearly dependent on the proton concentration (C_{H^+}). This has been correctly reflected in the current experiments, using the similar model fitting approach as shown below (cf. more details in Section S9 of the Supplementary Material). Consequently, it is reasonable to describe $k_{\text{app, ij}}$ as

$$k_{\text{app, ij}} = k_{ij} C_{H^+} \quad (20)$$

Here k_{ij} represents the intrinsic rate constant for each sub-reaction and its temperature dependency is described according to the Arrhenius equation as

$$k_{ij} = k_{ij, \text{Ref}} \exp \left[\frac{Ea_{ij}}{R} \left(\frac{T - T_{\text{Ref}}}{TT_{\text{Ref}}} \right) \right] \quad (21)$$

where T_{Ref} is the reference temperature (taken as 135 °C). $k_{ij, \text{Ref}}$ is the kinetic constant at the reference temperature and Ea_{ij} is the activation energy.

In summary, the developed kinetic model for the conversion of fructose-glucose mixture in the monophasic water system in the laboratory batch reactor comprises a set of coupled nonlinear ordinary differential equations (Eqs. (10)–(14)), together with additional algebraic equations to describe the reaction temperature lag and volume change during the heating-up (Eqs. (6)–(8)) as well as the reaction rate (Eqs. (15)–(21)). The model was analyzed with Matlab R2010a (MathWorks). k_{ij} for each sub-reaction in the proposed network was determined by processing the experimental data simultaneously in Matlab using the *lsqnonlin* nonlinear least-squares fitting function, based on a Trust-region-reflective algorithm to perform a local minimization of the errors between the model values and experimental data (i.e., in terms of the reactant conversion and product yields).

Note that to account for the phase volume change, the conversion and yields in the model are calculated as

$$X_s = \frac{C_{\text{aq, s, 0}} - \phi C_{\text{aq, s}}}{C_{\text{aq, s, 0}}} \times 100\% \quad (22)$$

$$Y_p = \frac{\phi C_{\text{aq, p}}}{C_{\text{aq, s, 0}}} \times 100\% \quad (23)$$

Ea_{ij} for each sub-reaction was then estimated by plotting $\ln k_{ij}$ versus $1/T$ and fitting according to the Arrhenius expression. The best estimations of intrinsic kinetic parameters and their standard deviations are given in Table 1 for the reference temperature of 135 °C as a typical example. The kinetic constant for glucose conversion to HMF (k_{1G}) are

Table 1
Kinetic parameter values at 135 °C for the proposed reaction network.

ij (-)	k_{ij} (L·mol ⁻¹ ·min ⁻¹)	Ea_{ij} (kJ·mol ⁻¹)
1G	0.0085 ± 0.0017	156 ± 8
2G	0.0014 ± 0.0006	181 ± 2
3G	0.0019 ± 0.0005	177 ± 11
1F	0.6072 ± 0.0754	133 ± 5
2F	0.0852 ± 0.0061	142 ± 13
3F	0.0637 ± 0.0031	147 ± 20
1H	0.1925 ± 0.0105	97 ± 3
2H	0.0760 ± 0.0189	108 ± 11
3H	0.0433 ± 0.0110	104 ± 4

two orders of magnitude lower than that for fructose conversion to HMF (k_{1F}), while the activation energy for the former ($Ea_{1G} = 156$ kJ/mol) is higher than for the latter ($Ea_{1F} = 133$ kJ/mol). Thus, fructose appears to be far more reactive than glucose to form HMF, in line with the experimental findings (Fig. 2) and literature [44,46]. The less reactive nature of glucose than fructose (towards FA and humins) is further supported by the much smaller k_{1G} values than k_{1F} values ($i = 2, 3$). Besides, the comparable value between k_{2G} and k_{3G} as well as that between k_{2F} and k_{3F} or between k_{2H} and k_{3H} , suggests the more or less equally important contribution of the two reaction routes from sugars/HMF to humins (of which one also forms FA; Fig. 8). Generally, the rate constant of sugar conversion to HMF (k_{1G} or k_{1F}) is far higher than those of the respective side reactions leading to humins (k_{2G} and k_{3G} ; or k_{2F} and k_{3F}), indicating that the formation of HMF is preferred in the sugar conversion. Thus, high HMF yields are feasible via a proper process optimization. The activation energy for the desired sugar dehydration reaction to form HMF (Ea_{1G} or Ea_{1F}) are higher than those for the HMF rehydration and the polymerization of HMF to form humins (Ea_{1H} , Ea_{2H} and Ea_{3H}). Moreover, activation energies for the reaction of glucose or fructose to humins (and excess FA) are even higher (Ea_{2G} and Ea_{3G} , or Ea_{2F} and Ea_{3F}). This implies that both the HMF formation and side reactions of sugars to form humins (and excess FA) tend to be more enhanced at higher reaction temperatures, corroborating the importance of temperature selection in the process optimization (*vide infra*).

It is worth mentioning that without the consideration of water volume change during the heating-up (Eqs. (7) and (8)), the estimated activation energies are rather different (e.g., being ca. 10–20% lower than the values in Table 1 for Ea_{2G} , Ea_{2F} and Ea_{3H}), and thus might lead to inaccurate predictions. This substantiates the necessity of considering phase volume change in the current kinetic modelling.

3.2.3. Kinetic modelling of batch experiments in the biphasic system

In the biphasic system, due to the partial miscibility between water and MIBK as well as the liquid density change with temperature, the volume of both phases changed after mixing and heating from ca. 20 °C to the reaction temperature in batch. Therefore, the actual volumes of two phases during the reaction are corrected as

$$V_{\text{aq}} = V_{\text{aq},0}\gamma_{\text{aq}} \quad (24)$$

$$V_{\text{org}} = V_{\text{org},0}\gamma_{\text{org}} \quad (25)$$

$$\frac{dC_{\text{aq,HMF}}}{dt} = \frac{R_{1G} + R_{1F} - R_{1H} - R_{2H} - R_{3H} - \left(\frac{C_{\text{aq,HMF}} V_{\text{org}}}{V_{\text{aq}}} \frac{dm_{\text{HMF}}}{dT} + \frac{C_{\text{org,HMF}}}{V_{\text{aq}}} \frac{dV_{\text{org}}}{dT} + \frac{C_{\text{aq,HMF}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \right) \frac{dT}{dt}}{1 + \frac{m_{\text{HMF}} V_{\text{org}}}{V_{\text{aq}}}} \quad (32)$$

where γ_{aq} or γ_{org} is the correction factor that denotes the ratio of the volume after mixing at the reaction temperature (T) to the initial volume at 20 °C for either the aqueous or organic phase. For a given initial MIBK to water volume ratio (O/A) at 20 °C, γ is a function of T and approximated as

$$\gamma = u + v e^{wT} \quad (26)$$

where values of the fitting parameters (u , v and w) are provided in Table S5 for the aqueous and organic phases separately (see Case 4 of Section S4 of the Supplementary Material for details). It appears that the phase volume change in biphasic systems is more significant. For example, at an initial O/A ratio of 4 (fed at 20 °C), γ_{aq} and γ_{org} are estimated to be, respectively, 0.899 and 1.289 at 155 °C, and the actual O/A ratio is increased to 5.60 (entry 4, Table S6). For higher initial O/A

ratios, γ_{aq} and γ_{org} deviate farther from 1, and the actual O/A ratio becomes much larger than the initial one (Table S6). The consideration of such volume change is thus equally important in the modelling of biphasic systems as this not only changes the actual concentration of reactants and acid catalysts, but also the actual O/A ratio, thus affecting the kinetics and HMF extraction behavior.

During the reaction, a certain amount of HMF product in water was extracted to MIBK. MIBK is known non-reactive and only serves as an extraction media [71]. Then, the concentrations of HMF in both phases (i.e., $C_{\text{aq,HMF}}$ and $C_{\text{org,HMF}}$) are described by the following mole balances

$$\frac{dC_{\text{aq,HMF}}}{dt} = R_{1G} + R_{1F} - R_{1H} - R_{2H} - R_{3H} - S_{1H} - \frac{C_{\text{aq,HMF}}}{V_{\text{aq}}} \frac{dV_{\text{aq}}}{dT} \frac{dT}{dt} \quad (27)$$

$$\frac{d(V_{\text{org}} C_{\text{org,HMF}})}{dt} = V_{\text{aq}} S_{1H} \quad (28)$$

where S_{1H} is the extraction rate of HMF from the aqueous phase to the organic phase (Fig. 8). Eq. (28) is further reduced to

$$\frac{dC_{\text{org,HMF}}}{dt} = \frac{V_{\text{aq}}}{V_{\text{org}}} S_{1H} - \frac{C_{\text{org,HMF}}}{V_{\text{org}}} \frac{dV_{\text{org}}}{dT} \frac{dT}{dt} \quad (29)$$

The experimental study on the conversion of fructose-glucose mixture under different stirring speeds in the batch reactor reveals no appreciable difference in the measured reactant conversion and HMF yield when the stirring speed was above 400 rpm (cf. Fig. S17 and Section S10 of the Supplementary Material). Since all the current (monophasic and biphasic) experiments in batch were performed at 900 rpm, mass transfer limitations are not present and the results were obtained in the kinetic regime. This allows to assume the HMF concentrations in both phases to be at equilibrium instantaneously. That is,

$$\frac{C_{\text{org,HMF}}}{C_{\text{aq,HMF}}} = m_{\text{HMF}} \quad (30)$$

Here m_{HMF} is the partition coefficient of HMF between the two phases at the involved reaction temperature. In this work, m_{HMF} values at different reaction temperatures were measured and are approximated as (see details in Section S3.1 of the Supplementary Material)

$$m_{\text{HMF}} = aT + b \quad (31)$$

where $a = -0.00323$, $b = 1.278$ and T is in °C. By combining with Eqs. (29)–(31), Eq. (27) is further simplified to

A certain amount of the byproduct LA and FA was also extracted to MIBK (partition coefficient 0.428 for FA at 20 °C (Fig. S2); 0.289–0.697 for LA of various concentrations at 25 °C [72]). However, since LA and FA are the end product of the reaction, their overall yields are not affected by their extraction. Therefore, mole balance equations for FA and LA in the biphasic system in batch can be simply represented by Eqs. (13) and (14), respectively, assuming the absence of their extraction. For sugars, mole balance equations herein are represented by Eqs. (10) and (11).

With the kinetic parameter values estimated from batch experiments in the monophasic system (cf. Section 3.2.2), the biphasic system modelling was conducted by solving the differential equations (i.e., Eqs. (10), (11), (13), (14) and (32)) in Matlab, subject to additional

conditions including Eqs. (24)–(26) (for phase volume change), 30 and 31 (for HMF extraction equilibrium). Note that in this case, the acid concentration needed for C_{H^+} estimation with Eq. (18) is corrected as

$$C_{\text{H}_2\text{SO}_4} = \frac{C_{\text{H}_2\text{SO}_4,0}}{\gamma_{\text{aq}}} \quad (33)$$

With the modelled component concentration during the reaction, the substrate conversion and product yield in the biphasic system in batch are then predicted by

$$X_s = \frac{C_{\text{aq},s,0} - \gamma_{\text{aq}} C_{\text{aq},s}}{C_{\text{aq},s,0}} \times 100\% \quad (34)$$

$$Y_p = \frac{V_{\text{org}} C_{\text{org},p} + V_{\text{aq}} C_{\text{aq},p}}{V_{\text{aq},0} C_{\text{aq},s,0}} \times 100\% \quad (35)$$

3.2.4. Evaluation of the developed kinetic model and comparison with the literature models

The accuracy of the model is evaluated by comparing the model predictions with experimental data through parity plots (Fig. 9). The goodness of fit was assessed by the coefficient of determination (R^2) calculated by [73]

$$R^2 = 1 - \frac{\sum_{i=1}^n (x_i - \hat{x}_i)^2}{\sum_{i=1}^n (x_i - \bar{x}_i)^2} \quad (36)$$

where x_i is the experimental conversion or yield (of glucose, fructose, HMF, FA or LA), \hat{x}_i is the kinetic model prediction, \bar{x}_i and n represents the average and number of the experimental data, respectively.

For monophasic experiments, the modelled kinetic profiles precisely predict the evolution trend of each component (sugars, HMF, LA and FA) during the reaction, and a good agreement is obtained between the model predictions and experimental data for all these components (Fig. 2, S8–S12, S18a–d). This is also supported by R^2 values being close to 1 (Fig. 9a). For biphasic systems, where the experimental data thereof were not used for kinetic parameter estimation, still a good prediction of the evolution trend for the above components is obtained (Figs. 3–5 and S18e–f), together with an overall good fitting performance of the model, except that a somewhat significant deviation was found for the prediction of HMF yield (R^2 being 0.747; Fig. 9b). More specifically, the HMF yield seems to be often underestimated by the model (e.g., see Fig. S18f). One possible reason is the underestimation of HMF partition from the aqueous phase to MIBK phase under reaction conditions, so that actually more HMF might have been extracted and prevented from side reactions forming LA, FA and humins. The HMF partition coefficient used for

modelling in this work was measured under an ideal condition that only HMF existed in two phases at low concentrations (cf. Fig. S1 and Section S3.1 in the Supplementary Material). However, the HMF partition coefficient was reported to be positively affected by the existence of glucose and fructose, as well as HMF, particularly in high concentrations, which is similar to the effect of adding salts [74,75]. Thus, an even more accurate prediction of the current model is expected, if a full information regarding the HMF partition coefficient as a function of temperature, sugar/HMF concentrations and organic solvent type becomes available in further studies.

The representative experimental results of glucose or fructose conversions in the monophasic water system in the batch reactor of this work are also compared with the predictions from some typical literature models [36,44,46,48]. Distinct deviations in the sugar conversion or product yields were found in these model predictions (Figs. S19 and S20). Specifically, for the case with glucose as the substrate, the models of Tan-Soetedjo et al. [36], Girisuta et al. [44] and Weingarten et al. [48] underestimate significantly the glucose conversion, despite a satisfactory prediction of the HMF yield (Figs. S19a and b). Moreover, all the three models underestimate either the FA or LA yield (Figs. S19c and d). For the case with fructose as the substrate (Fig. S20a–d), the model of Fachri et al. [46] tends to (significantly) overestimate the fructose conversion, HMF and LA yields, though well describing the FA yield. A poor agreement also exists between the prediction of the model of Tan-Soetedjo et al. [36] and these experimental data, except the FA yield. In comparison, the kinetic model developed in this work provides generally a better prediction (Figs. S19 and S20). The observed deviations with these literature models may be primarily ascribed to different reaction networks proposed (e.g., the excess FA formation from the direct sugar/HMF decomposition is not considered), in addition to the influence of other factors such as different experimental/modelling procedures (e.g., FA might not be precisely measured or phase volume change was not considered in the model) or the anion effect (i.e., using different homogeneous Brønsted acids) on the kinetic behavior. More discussions are found in Sections S12 of the Supplementary Material.

To further evaluate the rationality of the developed kinetic model, a comparison of activation energies estimated for main reactions between this study and literatures using various homogeneous acid catalysts was made (cf. Table S1 and Fig. S21). Generally, activation energies for glucose/fructose dehydration and HMF rehydration in this work are in a similar value range to the literature ones using sulfuric acid as catalyst [11,36,44,46], despite the more comprehensive reaction network proposed in this study including additional reactions of the direct decomposition of sugars and HMF to extra FA and humins (Fig. 8). This similarity is an additional proof of the validity of the current kinetic model. Some difference in activation energies for glucose/fructose

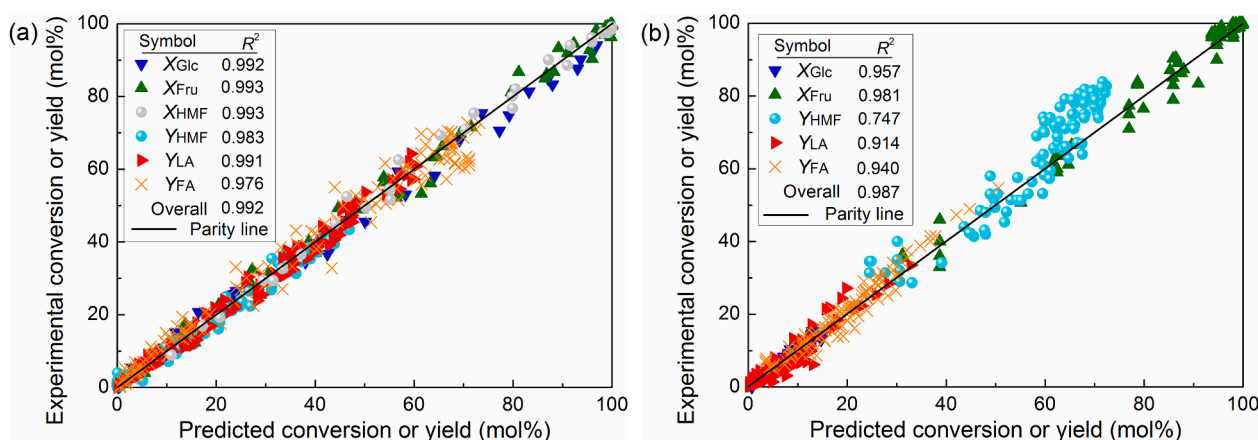


Fig. 9. Parity plot for the model predictions and experimental results for the conversion and yield of all components in (a) monophasic water and (b) biphasic water-MIBK systems in the batch reactor.

dehydration was found between different acid catalysts (see Table S1), which could be due to the anion effect (Fig. S21; cf. further discussions in Section S13 of the Supplementary Material).

3.3. Model implications for the conversion of fructose-glucose mixture in the biphasic system

3.3.1. Relative conversion rate of sugars and HMF yield in an ideal batch reactor

The developed kinetic model and parameters allow to estimate the effect of key operating factors (e.g., the reaction temperature, acid concentration and O/A ratio) on the sugar conversion and product yields in the water-MIBK biphasic system in an ideal batch reactor (i.e., without considering the heating-up stage; cf. Section S14 in the Supplementary Material for modelling procedures). Such model implications are of more generic uses since it is preferred to operate the batch reactor in the absence of heat/mass transfer limitations. These are also directly useful for reaction performance optimization in continuous reactors with a more or less plug flow profile (*vide infra*).

The above modelling was thus conducted to study the operating parameter influence, based on the reference conditions under a reaction temperature of 155 °C, 0.05 M H₂SO₄, 0.5 M fructose and 0.5 M glucose in the aqueous phase (loaded at 20 °C), and an initial O/A ratio of 4. The model implications for sugar conversion and HMF yield are presented in Fig. 10 (cf. more results in Section S14 of the Supplementary Material).

The model suggests that higher temperatures lead to both higher glucose conversions and HMF yields at the same fructose conversion. In a relatively mild temperature range (120–155 °C), a selective fructose dehydration is present since the glucose conversions corresponding to the maximum HMF yields are all kept at a low level below 10% (Fig. 10a), which is also consistent with the current experimental results (Fig. 4). After extrapolation of the present kinetic model to higher temperatures (e.g., 170 and 180 °C), only a limited further increase (<5%) in the maximum HMF yield is observed, whereas the corresponding glucose conversion increases to an unacceptable level (over 10%). Therefore, to ensure a preferential dehydration of fructose over glucose and higher HMF (space time) yield, 155 °C is identified as the optimal reaction temperature. The modelled HMF yield as a function of fructose conversion with varying initial O/A ratios at 155 °C is summarized in Fig. 10b. The maximum HMF yield increases with increasing the O/A ratio, because more MIBK phase present extracts more HMF during the reaction. In line with the experimental observation (Fig. 3a), a limited further increase in the maximum HMF yield is present when raising the O/A ratio above 4. Thus, an initial O/A ratio of 4 is chosen for further reaction optimization in the present water-MIBK system. This

ratio value was also widely used in literatures for HMF synthesis in biphasic systems [21,37,62].

Since all the sub-reactions are first order in the acid catalyst, the acid concentration has no effect on the relative conversions of sugars and maximum HMF yields (Fig. S23). Given that highly concentrated sulfuric acid may cause equipment corrosion and pollution issues, a low acid concentration of 0.05 M is considered environmentally more desirable and suggested for further reaction optimization, which allows a full conversion of fructose within 20 min with glucose conversion below 5% at 155 °C (Fig. S23).

3.3.2. Insights into continuous flow reactor design

The HMF synthesis in continuous flow reactors other than batch reactors is more favored from the industrial application point of view (e.g., in terms of large production capacity and product quality consistency). Herein, the conversion of substrates as well as the HMF yield are a function of not only process parameters (e.g., the reaction temperature, substrate and acid catalyst concentrations, organic to aqueous flow ratio and residence time), but also the extent of back mixing in the reactor. On the basis of the kinetic model in this work (assuming the absence of heat and mass transfer limitations), the HMF synthesis from fructose-glucose mixture in the water-MIBK biphasic system in two extreme cases regarding back mixing, *viz* a plug flow reactor (PFR) and a continuously ideally stirred tank reactor (CSTR), were modelled. The CSTR modelling is realized by analytically solving mole balance equations based on the reaction network and kinetic parameters derived in this work, and the PFR modelling is the same as that for an ideal batch reactor shown above provided that the batch time (t) is replaced with the residence time (τ). More details are found in the Supplementary Material (Section S15). Fig. 11 shows the modelling results for the favorable reaction conditions under a reaction temperature of 155 °C, 0.05 M H₂SO₄, 0.5 M fructose and 0.5 M glucose, and an initial organic to aqueous flow ratio of 4 (cf. Section 3.3.1).

Fig. 11a shows that the conversions of both sugars are higher in the PFR, due to higher average substrate concentrations therein leading to higher overall reaction rates. The HMF yield in the PFR is significantly higher than that in the CSTR, particularly at high fructose conversions (>60%) (Fig. 11b). The predicted highest HMF yield in the PFR is over 70% at a fructose conversion over 95%, while in the CSTR it is less than 60% at a fructose conversion of ca. 70%. Moreover, the glucose conversion in the PFR is significantly lower than that in CSTR at the same fructose conversion (>30% at a fructose conversion of 95% in the CSTR compared with only ca. 6% glucose conversion in the PFR). Consequently, to minimize the back mixing level (e.g., in the PFR as an ideal case) is more favorable for obtaining a higher HMF yield from a more

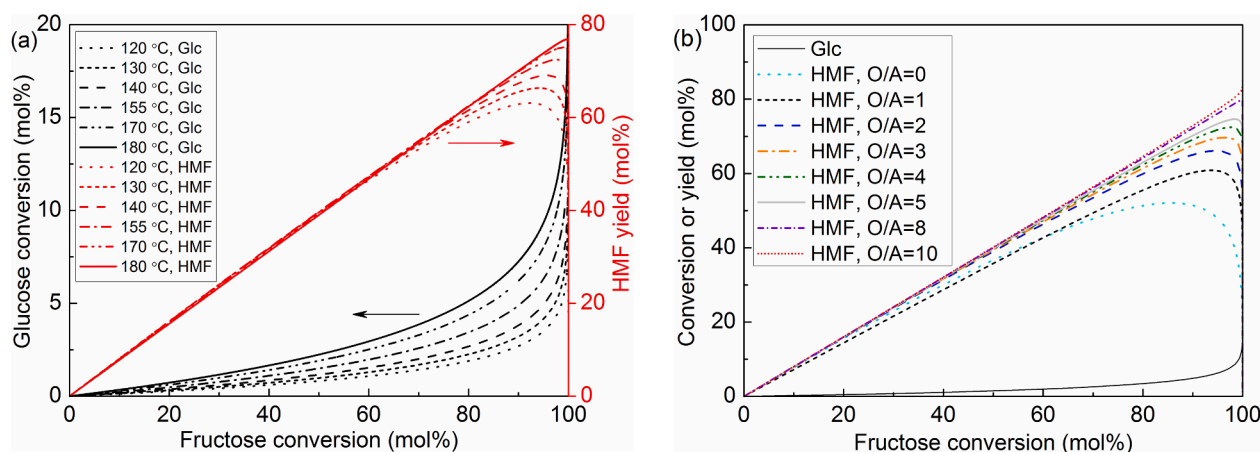


Fig. 10. Modelled glucose conversion and HMF yield in an ideal batch reactor as a function of the fructose conversion in the water-MIBK system by varying (a) the reaction temperature and (b) initial O/A ratio. Other reaction conditions (unless otherwise stated): reaction temperature of 155 °C, 0.05 M H₂SO₄, 0.5 M fructose and 0.5 M glucose, O/A = 4 (fed at 20 °C).

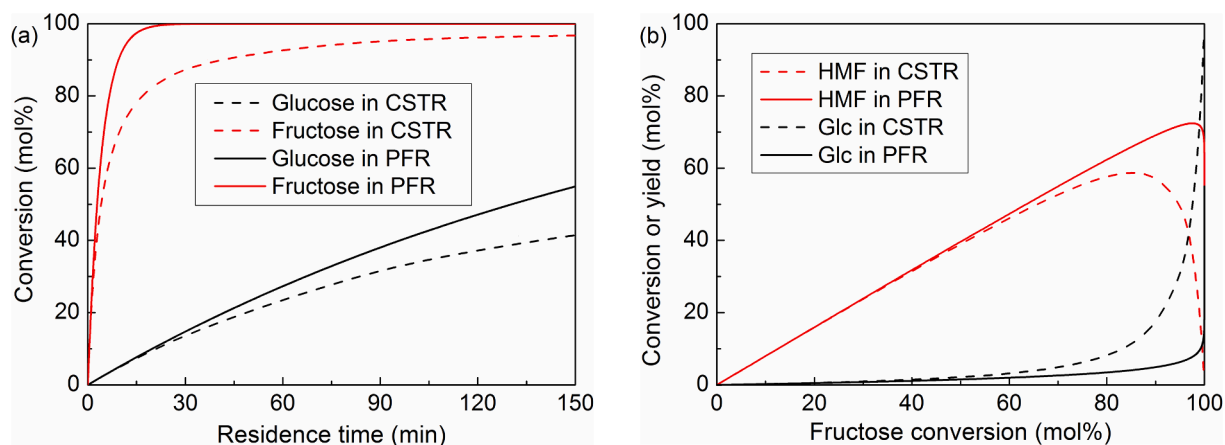


Fig. 11. (a) Modelled conversions of fructose and glucose in the water-MIBK biphasic system in different continuous flow reactor configurations and (b) the corresponding HMF yield as a function of fructose conversion. Other conditions: reaction temperature of 155 °C, 0.05 M H₂SO₄, 0.5 M fructose and 0.5 M glucose, initial organic to aqueous volumetric flow ratio of 4 (fed at 20 °C).

selective fructose dehydration over glucose. Besides, the by far higher reaction rate in the PFR renders a higher space time yield of HMF, which is more desirable for scaled-up industrial production.

3.4. Optimized HMF synthesis in a slug flow microreactor

The modelled favorable reaction results in the PFR (Fig. 11) is based on the absence of both the back mixing and heat/mass transfer limitations in the reaction system. These requirements have led to the use of microreactors for the optimized HMF synthesis in this work. By operating under slug flow in a PFA capillary microreactor (i.e., the reactive aqueous phase as the droplet and MIBK as the continuous slug phase), a narrowed residence time distribution (minimized back mixing) and superior heat/mass transfer properties could be obtained, which is close to an ideal PFR behavior [21,58,60]. It has been revealed in our previous work that the heating-up process relevant to HMF synthesis could be finished within seconds in microreactors and the strong inner circulation inside droplets/slugs largely eliminates the mass transfer resistance, rendering the reaction under kinetic control [21]. Moreover, the production capacity increase in microreactors is relatively easy and straightforward by numbering-up of microchannels in parallel [59]. In

comparison, conventional batch reactors tend to suffer from the slowed heat/mass transfer rates during scale-up, adversely affecting the HMF (space time) yield. Therefore, the identified favorable conditions (155 °C, 0.05 M H₂SO₄ and an initial organic to aqueous volumetric flow ratio of 4 to 1) were further tested in the slug flow microreactor using 10 wt% HFCS-55 and HFCS-90 as a promising commercial feedstock (cf. Sections 2.1 and 2.2). The HFCS was diluted to 10 wt% so that the sugar concentration fell in the initial substrate concentration window (0.1–0.5 M) in this work, which corresponds to 0.26 M fructose and 0.20 M glucose for 10 wt% HFCS-55, and 0.42 M fructose and 0.05 M glucose for 10 wt% HFCS-90 (the sugar content was measured by HPLC; with a minor contribution from the simultaneous hydrolysis of sucrose present). A selective dehydration of fructose (>95% conversion) over glucose (<5% conversion) was realized with reproducible high HMF yields of ca. 80–81% at a short residence time of 16 min in both feedstock cases (Fig. 12). This maximum yield is higher than that reported in the literature exploiting HFCS for HMF synthesis in a tubular flow reactor [27]. The experimental results in microreactors are generally well in line with the kinetic modelling (i.e., for the PFR). The somewhat higher HMF yield in the measurements than the model prediction is understood as a result of the slight underestimation of HMF partition

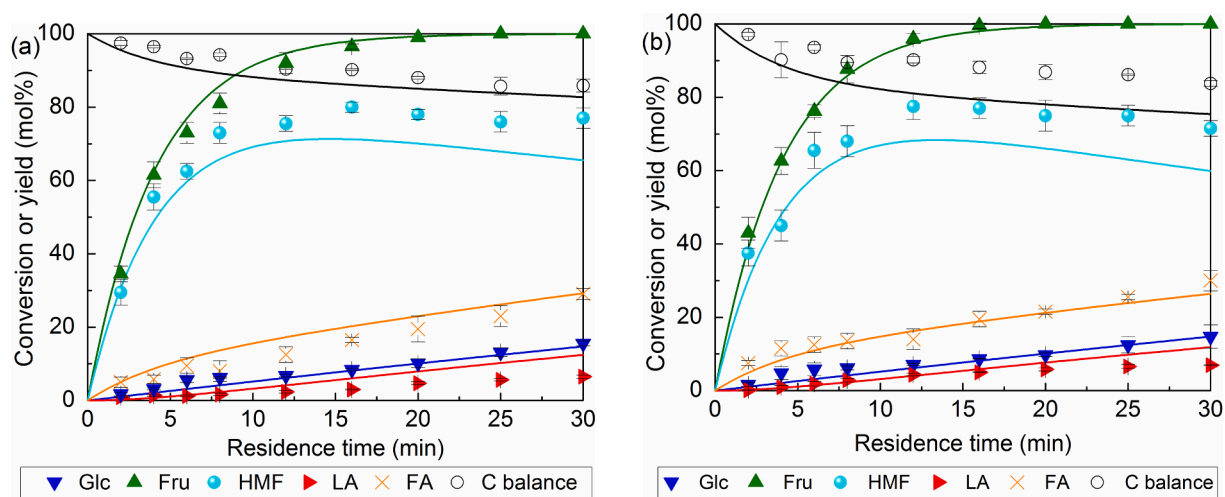


Fig. 12. Conversion of (a) 10 wt% HFCS-55 (0.26 M fructose and 0.20 M glucose) and (b) 10 wt% HFCS-90 (0.42 M fructose and 0.05 M glucose) in slug flow microreactors. Other reaction conditions: reaction temperature of 155 °C, 0.05 M H₂SO₄ and an initial organic to aqueous volumetric flow ratio of 4 (fed at ca. 20 °C). Error bars represent the standard deviation based on experiments in at least duplicate.

coefficient, given possibly the positive influence of higher sugar concentrations involved (cf. Section 3.2.4 for more discussions). This deduction is also supported by the (slightly) lower LA yield than the modelled one at prolonged residence times (Figs. 12a and b). For comparison, reactions were also performed in the laboratory batch reactor under otherwise the same conditions. A similar maximum HMF yield was also obtained with a selective fructose conversion, but at a longer reaction time of ca. 20 min due to the temperature lag in the heating-up process (Fig. S25; see more details in Section S16 of the Supplementary Material). This further highlights the potential of microreactors for the efficient HMF synthesis in high space time yields.

A general good agreement between the microreactor results and the kinetic model predictions (Fig. 12) is indicative of the reaction under kinetic control in our experiments. This also confirms no mass transfer limitations in the current slug flow operation (i.e., regarding the reactant mixing/transport in the aqueous droplet and the extraction of HMF produced thereof to the continuous organic slug). In the microreactor, a constant inlet organic to aqueous volumetric flow ratio of 4 to 1 was used and the residence time was adjusted by changing the phasic flow rate (cf. Section 2.2). Herein, a uniform slug flow could be observed with the droplet and slug lengths being around 1.24 and 3.24 times of the microreactor inner diameter, respectively. Thus, such microflow conditions has provided sufficiently high mass transfer coefficients and interfacial areas for the reaction to run in the kinetic regime [21,76]. However, it should be noted that the droplet/slug size is dependent on among others the microreactor diameter, inlet mixing geometry and the flow ratios of two phases [77]. To ensure a fast mass transfer, the droplet and slug sizes (and with that the microreactor diameter) need to be relatively small [78], thus requiring a fine tuning of the microreactor geometry and flow conditions. This also implies that when performing HMF synthesis from sugars using other microreactor setups, whether the kinetic behavior is present or not needs to be carefully analyzed, e.g., by comparing the obtained experimental results with the kinetic model predictions, or alternatively by comparing the physical mass transfer rates (estimated based on parameters such as the droplet/slug size and flow rates) with the intrinsic reaction rate [79].

To further increase the HMF yield, one option is to improve the extraction capacity of organic phase via adding NaCl (salting-out effect; cf. Fig. S26 for an example where a 90% HMF yield was demonstrated in microreactors). In addition, to increase the economic feasibility of the microreactor process in the industry, more concentrated HFCS feedstocks can be used to achieve an even higher space time yield of HMF [15,80,81]. In the latter case, the viscosity increase should be well handled (e.g., by using more capable pump units, or using relatively large diameter microreactors without a significant loss of heat/mass transfer efficiency). Significant humin formation at much increased sugar concentrations might be another issue to be well addressed. In this work, the tested sugar concentration is in a moderate range of about 0.1–0.5 M and humins formed were confined within the aqueous slugs without contacting the hydrophobic microreactor wall (made of PFA) [21]. Thus, humins could be transported out of the microreactor system continuously. However, it is envisaged that in the presence of a significant amount of humin formation (in the aqueous droplet), humins might come out of the droplet and be more easily accumulated onto the microreactor wall (e.g., at the outlet junctions of the microreactor system where the flow disturbance likely occurs), increasing the risk of reactor clogging or malfunction (to be addressed in our future work).

4. Conclusions

In order to develop a process that allows the integration with and upgrading of the industrial processes producing fructose-glucose mixtures (such as HFCS and sugar beet thick juice) in the current biorefinery, experimental and kinetic modeling studies on the conversion of fructose-glucose mixture were performed in this work using sulfuric acid as the catalyst in both monophasic water and biphasic water-MIBK

systems, over a broad range of reaction conditions (e.g., a mild temperature window of 117–155 °C, initial sugar concentrations of 0.1–0.5 M, and acid concentrations of 0.005–0.45 M). Based on the experimental findings in the laboratory batch reactor and ESI-MS spectroscopy characterization, the stoichiometric excess FA with respect to LA was observed and confirmed to be derived from the direct decomposition of mainly sugars (and HMF to a lesser extent), particularly in the early stage of the reaction. Therefore, a more comprehensive reaction network than the literature ones was proposed, with the addition of these reaction pathways for the excess FA formation together with humins. The kinetic model and parameters thereof were estimated based on experiments starting from individual HMF, fructose, glucose and fructose-glucose mixture in water in batch. The developed kinetic model well describes these monophasic experimental data, whereas distinct deviations were found in the prediction of typical literature models (e.g., those of Tan-Soetedjo et al. [36], Girisuta et al. [44], Fachri et al. [46] and Weingarten et al. [48]). Furthermore, the HMF equilibrium extraction between water and MIBK was incorporated into the kinetic model which can well predict reaction results in the biphasic system in batch. In the modelling of both monophasic and biphasic systems in batch, the phase volume change as a function of the reaction temperature and partial miscibility between phases (if present) was considered, as this could lead to large variations in the acid/reactant concentrations in the aqueous phase and in the HMF extraction capacity of the organic phase, affecting the reaction behavior.

The kinetic model developed in this work enables the process optimization towards a preferential dehydration of fructose over glucose and the enhanced HMF yield from fructose-glucose mixture in the biphasic system in both (ideal) batch and flow reactors. The HMF yield can be promoted with the increased organic to aqueous volume or flow ratios and higher reaction temperatures. By maintaining the reaction temperature at 155 °C or below, an inappreciable glucose conversion (<5%) can be controlled at a close to full fructose conversion (>95%) via a fine tuning of the acid catalyst concentration and reaction time to avoid the overreaction of glucose and obtain the maximum HMF yield. Lower extent of back mixing in the flow reactor (e.g., close to PFR behaviour) is more favorable for higher HMF yields and more selective dehydration of fructose over glucose. Based on the model implications and to better address process intensification and scale-up aspects for HMF production, reactions were optimized in continuous slug flow microreactors (made of PFA with an inner diameter 1.65 mm) using 10 wt% HFCS-55 or HFCS-90 as a promising commercial feedstock. Under 155 °C, 0.05 M sulfuric acid and an inlet MIBK to water volumetric flow ratio of 4, an HMF yield of 81% was achieved at a short residence time of 16 min, with 96% fructose conversion and over 95% of glucose remaining unconverted. This work provides useful insights into the proper design of reactor configurations and processes for the selective fructose dehydration to HMF from fructose-glucose mixture feedstocks, which contributes towards developing an efficient HMF synthesis from glucose or glucose-rich cellulosic biomass in the biorefinery.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Financial support from the University of Groningen (start-up package in the area of green chemistry and technology for Jun Yue) is gratefully acknowledged. W. Guo is grateful for financial support from the China Scholarship Council (grant number 201606740069). Besides, W. Guo gratefully acknowledged the technical staff of the Department of Chemical Engineering at the University of Groningen for the experimental and analytical supports.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cej.2020.128182>.

References

- [1] A. Corma, S. Iborra, A. Velty, Chemical routes for the transformation of biomass into chemicals, *Chem. Rev.* 107 (6) (2007) 2411–2502, <https://doi.org/10.1021/cr050989d>.
- [2] I. Delidovich, K. Leonhard, R. Palkovits, Cellulose and hemicellulose valorisation: an integrated challenge of catalysis and reaction engineering, *Energy Environ. Sci.* 7 (2014) 2803–2830.
- [3] L.T. Mika, E. Cséfalvay, Á. Németh, Catalytic conversion of carbohydrates to initial platform chemicals: chemistry and sustainability, *Chem. Rev.* 118 (2) (2018) 505–613, <https://doi.org/10.1021/acs.chemrev.7b00395>.
- [4] R.-J. van Putten, J.C. van der Waal, E.d. de Jong, C.B. Rasrendra, H.J. Heeres, J. G. de Vries, Hydroxymethylfurfural, a versatile platform chemical made from renewable resources, *Chem. Rev.* 113 (3) (2013) 1499–1597, <https://doi.org/10.1021/cr300182k>.
- [5] A.A. Rosatella, S.P. Simeonov, R.F.M. Frade, C.A.M. Afonso, 5-Hydroxymethylfurfural (HMF) as a building block platform: Biological properties, synthesis and synthetic applications, *Green Chem.* 13 (2011) 754–793.
- [6] O. Casanova, S. Iborra, A. Corma, Biomass into chemicals: aerobic oxidation of 5-hydroxymethyl-2-furfural into 2,5-furandicarboxylic acid with gold nanoparticle catalysts, *ChemSusChem* 2 (2009) 1138–1144.
- [7] M. Sajid, X. Zhao, D. Liu, Production of 2,5-furandicarboxylic acid (FDCA) from 5-hydroxymethylfurfural (HMF): recent progress focusing on the chemical-catalytic routes, *Green Chem.* 20 (2018) 5427–5453.
- [8] L. Hu, T. Li, J. Xu, A. He, X. Tang, X. Chu, J. Xu, Catalytic transfer hydrogenation of biomass-derived 5-hydroxymethylfurfural into 2,5-dihydroxymethylfuran over magnetic zirconium-based coordination polymer, *Chem. Eng. J.* 352 (2018) 110–119, <https://doi.org/10.1016/j.cej.2018.07.007>.
- [9] N. Chen, Z. Zhu, T. Su, W. Liao, C. Deng, W. Ren, Y. Zhao, H. Lü, Catalytic hydrogenolysis of hydroxymethylfurfural to highly selective 2,5-dimethylfuran over FeCoNi/h-BN catalyst, *Chem. Eng. J.* 381 (2020), 122755.
- [10] Y. Román-Leshkov, C.J. Barrett, Z.Y. Liu, J.A. Dumesic, Production of dimethylfuran for liquid fuels from biomass-derived carbohydrates, *Nature* 447 (2007) 982.
- [11] B. Girisuta, L.P.B.M. Janssen, H.J. Heeres, A kinetic study on the decomposition of 5-hydroxymethylfurfural into levulinic acid, *Green Chem.* 8 (8) (2006) 701, <https://doi.org/10.1039/b518176c>.
- [12] S. Dutta, I.K.M. Yu, D.C.W. Tsang, Y.H. Ng, Y.S. Ok, J. Sherwood, J.H. Clark, Green synthesis of gamma-valerolactone (GVL) through hydrogenation of biomass-derived levulinic acid using non-noble metal catalysts: a critical review, *Chem. Eng. J.* 372 (2019) 992–1006.
- [13] J. Molletti, M.S. Tiwari, G.D. Yadav, Novel synthesis of Ru/OMS catalyst by solvent-free method: Selective hydrogenation of levulinic acid to γ -valerolactone in aqueous medium and kinetic modelling, *Chem. Eng. J.* 334 (2018) 2488–2499.
- [14] T. Wang, M.W. Nolte, B.H. Shanks, Catalytic dehydration of C 6 carbohydrates for the production of hydroxymethylfurfural (HMF) as a versatile platform chemical, *Green Chem.* 16 (2) (2014) 548–572, <https://doi.org/10.1039/C3GC41365A>.
- [15] A.H. Motagamwala, K. Huang, C.T. Maravelias, J.A. Dumesic, Solvent system for effective near-term production of hydroxymethylfurfural (HMF) with potential for long-term process improvement, *Energy Environ. Sci.* 12 (7) (2019) 2212–2222, <https://doi.org/10.1039/C9EE00447E>.
- [16] H. Li, S. Yang, S. Saravanamurugan, A. Riisager, Glucose isomerization by enzymes and chemo-catalysts: status and current advances, *ACS Catal.* 7 (4) (2017) 3010–3029, <https://doi.org/10.1021/acscatal.6b03625>.
- [17] J. Tang, X. Guo, L. Zhu, C. Hu, Mechanistic study of glucose-to-fructose isomerization in water catalyzed by [Al(OH) 2 (aq)] +, *ACS Catal.* 5 (9) (2015) 5097–5103, <https://doi.org/10.1021/acscatal.5b01237>.
- [18] M. Moliner, Y. Roman-Leshkov, M.E. Davis, Tin-containing zeolites are highly active catalysts for the isomerization of glucose in water, *Proc. Natl. Acad. Sci.* 107 (14) (2010) 6164–6168, <https://doi.org/10.1073/pnas.1002358107>.
- [19] C. Liu, J.M. Carraher, J.L. Swedberg, C.R. Herndon, C.N. Fleitman, J.-P. Tessonnier, Selective base-catalyzed isomerization of glucose to fructose, *ACS Catal.* 4 (12) (2014) 4295–4298, <https://doi.org/10.1021/cs501197w>.
- [20] J.M. Carraher, C.N. Fleitman, J.-P. Tessonnier, Kinetic and mechanistic study of glucose isomerization using homogeneous organic Brønsted base catalysts in water, *ACS Catal.* 5 (6) (2015) 3162–3173, <https://doi.org/10.1021/acscatal.5b00316>.
- [21] W. Guo, H.J. Heeres, J. Yue, Continuous synthesis of 5-hydroxymethylfurfural from glucose using a combination of AlCl3 and HCl as catalyst in a biphasic slug flow capillary microreactor, *Chem. Eng. J.* 381 (2020), 122754.
- [22] Y.B. Tewari, Thermodynamics of industrially-important, enzyme-catalyzed reactions, *Appl. Biochem. Biotechnol.* 23 (3) (1990) 187–203, <https://doi.org/10.1007/BF02942054>.
- [23] J.S. White, Straight talk about high-fructose corn syrup: what it is and what it ain't, *Am. J. Clin. Nutrition* 88 (2008) 1716S–1721S.
- [24] L. Hobbs, Chapter 21 - Sweeteners from starch: production, properties and uses, in: J. BeMiller, R. Whistler (Eds.) *Starch* (Third Edition), Academic Press, San Diego, 2009, pp. 797–832.
- [25] J.S. White, Sucrose, HFCS, and Fructose: History, manufacture, composition, applications, and production, in: J.M. Rippe (Ed.) *Fructose, High Fructose Corn Syrup, Sucrose and Health*, Springer New York, New York, NY, 2014, pp. 13–33.
- [26] H.H. Szmant, D.D. Chundury, The preparation of 5-hydroxymethylfurfuraldehyde from high fructose corn syrup and other carbohydrates: Preparation of 5-hydroxymethylfurfuraldehyde, *J. Chem. Technol. Biotechnol.* 31 (1) (1981) 135–145, <https://doi.org/10.1002/jctb.280310119>.
- [27] A. Toftgaard Pedersen, R. Ringborg, T. Grotkjær, S. Pedersen, J.M. Woodley, Synthesis of 5-hydroxymethylfurfural (HMF) by acid catalyzed dehydration of glucose–fructose mixtures, *Chem. Eng. J.* 273 (2015) 455–464, <https://doi.org/10.1016/j.cej.2015.03.094>.
- [28] T.M. Kohl, B. Bizet, P. Kevan, C. Sellwood, J. Tsanakis, C.H. Hornung, Efficient synthesis of 5-(chloromethyl)furfural (CMF) from high fructose corn syrup (HFCS) using continuous flow processing, *React. Chem. Eng.* 2 (4) (2017) 541–549, <https://doi.org/10.1039/C7RE00039A>.
- [29] L. Dessbesell, S. Souza, K.T. Venkateswara Rao, A.A. Carrillo, D. Bekker, K. A. Hall, K.M. Lawrence, C.L.J. Tait, C.C. Xu, Production of 2,5-furandicarboxylic acid (FDCA) from starch, glucose, or high-fructose corn syrup: techno-economic analysis, *Biofuels, Bioprod. Bioref.* 13 (5) (2019) 1234–1245, <https://doi.org/10.1002/bbb.2014>.
- [30] B. Saha, M.M. Abu-Omar, Advances in 5-hydroxymethylfurfural production from biomass in biphasic solvents, *Green Chem.* 16 (1) (2014) 24–38, <https://doi.org/10.1039/C3GC41324A>.
- [31] Y. Román-Leshkov, J.N. Chheda, J.A. Dumesic, Phase modifiers promote efficient production of hydroxymethylfurfural from fructose, *Science* 312 (2006) 1933–1937.
- [32] NIST Chemistry Webbook. <https://webbook.nist.gov/chemistry/fluid/>.
- [33] J.N. Chheda, Y. Román-Leshkov, J.A. Dumesic, Production of 5-hydroxymethylfurfural and furfural by dehydration of biomass-derived mono- and polysaccharides, *Green Chem.* 9 (4) (2007) 342–350, <https://doi.org/10.1039/B611568C>.
- [34] L. Hu, Y. Jiang, Z. Wu, X. Wang, A. He, J. Xu, J. Xu, State-of-the-art advances and perspectives in the separation of biomass-derived 5-hydroxymethylfurfural, *J. Cleaner Prod.* 276 (2020), 124219.
- [35] H. Wu, T. Huang, F. Cao, Q. Zou, P. Wei, P. Ouyang, Co-production of HMF and gluconic acid from sucrose by chemo-enzymatic method, *Chem. Eng. J.* 327 (2017) 228–234, <https://doi.org/10.1016/j.cej.2017.06.107>.
- [36] J.N.M. Tan-Soetedjo, H.H. van de Bovenkamp, R.M. Abdilla, C.B. Rasrendra, J. van Ginkel, H.J. Heeres, Experimental and Kinetic Modeling Studies on the Conversion of Sucrose to Levulinic Acid and 5-Hydroxymethylfurfural Using Sulfuric Acid in Water, *Ind. Eng. Chem. Res.* 56 (45) (2017) 13228–13239, <https://doi.org/10.1021/acs.iecr.7b01611.s001>.
- [37] R.M. Abdilla-Santes, W. Guo, P.C.A. Bruijninx, J. Yue, P.J. Deuss, H.J. Heeres, High-yield 5-hydroxymethylfurfural synthesis from crude sugar beet juice in a biphasic microreactor, *ChemSusChem* 12 (18) (2019) 4304–4312, <https://doi.org/10.1002/cssc.201901115>.
- [38] J.S. Kruger, V. Nikolakis, D.G. Vlachos, Carbohydrate dehydration using porous catalysts, *Curr. Opin. Chem. Eng.* 1 (3) (2012) 312–320, <https://doi.org/10.1016/j.coche.2012.06.003>.
- [39] J. Stas, H. Alsaaf, Liquid–liquid extraction of hydrochloric acid from aqueous solutions by Tri-n-dodecylamine and Tri-n-octylamine/diluents, *Period. Polytech. Chem. Eng.* 60 (2016) 130–135.
- [40] E.-S. Manaa, T.A. Lasheen, Liquid–Liquid Extraction of Sulfuric Acid from Aqueous Sulfate Solution using Alamine 336/Kerosene/TBP Solvent, *J. Dispersion Sci. Technol.* 37 (2) (2016) 137–143, <https://doi.org/10.1080/01932691.2015.1034362>.
- [41] H.M. IJmker, M. Gramblička, S.R.A. Kersten, A.G.J. van der Ham, B. Schuur, Acetic acid extraction from aqueous solutions using fatty acids, *Sep. Purif. Technol.* 125 (2014) 256–263, <https://doi.org/10.1016/j.seppur.2014.01.050>.
- [42] A.V. Forster, L.E. Martz, D.E. Leng, Process for separating and recovering concentrated hydrochloric acid from the crude product obtained from the acid hydrolysis of cellulose, *US Patent* 4237110A, 1980.
- [43] H. Hohenschütz, J.E. Schmidt, H. Kiefer, Isolation of formic acid from its aqueous solutions, *US Patent* 4217460A, 1980.
- [44] B. Girisuta, L. Janssen, H. Heeres, Green chemicals: A kinetic study on the conversion of glucose to levulinic acid, *Chem. Eng. Res. Des.* 84 (2006) 339–349.
- [45] L. Kupiainen, J. Ahola, J. Tanskanen, Kinetics of glucose decomposition in formic acid, *Chem. Eng. Res. Des.* 89 (12) (2011) 2706–2713, <https://doi.org/10.1016/j.cherd.2011.06.005>.
- [46] B.A. Fachri, R.M. Abdilla, H.H.V.D. Bovenkamp, C.B. Rasrendra, H.J. Heeres, Experimental and kinetic modeling studies on the sulfuric acid catalyzed conversion of d-Fructose to 5-hydroxymethylfurfural and levulinic acid in water, *ACS Sustainable Chem. Eng.* 3 (2015) 3024–3034.
- [47] F.S. Asghari, H. Yoshida, Kinetics of the decomposition of fructose catalyzed by hydrochloric acid in subcritical water: formation of 5-hydroxymethylfurfural, levulinic, and formic acids, *Ind. Eng. Chem. Res.* 46 (2007) 7703–7710.
- [48] R. Weingarten, J. Cho, R. Xing, W.C. Conner Jr., G.W. Huber, Kinetics and Reaction Engineering of Levulinic Acid Production from Aqueous Glucose Solutions, *ChemSusChem* 5 (7) (2012) 1280–1290, <https://doi.org/10.1002/cssc.201100717>.
- [49] T.D. Swift, C. Bagia, V. Choudhary, G. Peklaris, V. Nikolakis, D.G. Vlachos, Kinetics of Homogeneous Brønsted Acid Catalyzed Fructose Dehydration and 5-Hydroxymethyl Furfural Rehydration: A Combined Experimental and Computational Study, *ACS Catal.* 4 (1) (2014) 259–267, <https://doi.org/10.1021/cs4009495>.

- [50] Q. Jing, X. Lü, Kinetics of Non-catalyzed Decomposition of Glucose in High-temperature Liquid Water, *Chin. J. Chem. Eng.* 16 (6) (2008) 890–894, [https://doi.org/10.1016/S1004-9541\(09\)60012-4](https://doi.org/10.1016/S1004-9541(09)60012-4).
- [51] C. Chang, X. Ma, P. Cen, Kinetics of Levulinic Acid Formation from Glucose Decomposition at High Temperature, *Chin. J. Chem. Eng.* 14 (5) (2006) 708–712, [https://doi.org/10.1016/S1004-9541\(06\)60139-0](https://doi.org/10.1016/S1004-9541(06)60139-0).
- [52] R.-J. vanPutten, J.N.M. Soetedjo, E.A. Pidko, J.C. van der Waal, E.M. Hensen, E. deJong, H.J. Heeres, Dehydration of Different Ketoses and Aldoses to 5-Hydroxymethylfurfural, *ChemSusChem* 6 (9) (2013) 1681–1687, <https://doi.org/10.1002/cssc.201300345>.
- [53] Y. Li, X. Lu, L. Yuan, X. Liu, Fructose decomposition kinetics in organic acids-enriched high temperature liquid water, *Biomass Bioenergy* 33 (9) (2009) 1182–1187, <https://doi.org/10.1016/j.biombioe.2009.05.003>.
- [54] T.D. Swift, H. Nguyen, A. Anderko, V. Nikolakis, D.G. Vlachos, Tandem Lewis/Brønsted homogeneous acid catalysis: conversion of glucose to 5-hydroxymethylfurfural in an aqueous chromium (III) chloride and hydrochloric acid solution, *Green Chem.* 17 (2015) 4725–4735.
- [55] Y. Jiang, L. Yang, C.M. Bohn, G. Li, D. Han, N.S. Mosier, J.T. Miller, H. I. Kenttämaa, M.M. Abu-Omar, Speciation and kinetic study of iron promoted sugar conversion to 5-hydroxymethylfurfural (HMF) and levulinic acid (LA), *Org. Chem. Front.* 2 (10) (2015) 1388–1396, <https://doi.org/10.1039/C5QO00194C>.
- [56] J. Tang, L. Zhu, X. Fu, J. Dai, X. Guo, C. Hu, Insights into the Kinetics and Reaction Network of Aluminum Chloride-Catalyzed Conversion of Glucose in NaCl–H₂O/THF Biphasic System, *ACS Catal.* 7 (1) (2017) 256–266, <https://doi.org/10.1021/acscatal.6b02515.s001>.
- [57] K.D. Baugh, P.L. McCarty, Thermochemical pretreatment of lignocellulose to enhance methane fermentation: I. Monosaccharide and furfurals hydrothermal decomposition and product formation rates, *Biotechnol. Bioeng.* 31 (1988) 50–61.
- [58] A. Hommes, H.J. Heeres, J. Yue, Catalytic Transformation of Biomass Derivatives to Value-Added Chemicals and Fuels in Continuous Flow Microreactors, *ChemCatChem* 11 (19) (2019) 4671–4708, <https://doi.org/10.1002/cctc.201900807>.
- [59] J. Yue, R. Boichot, L. Luo, Y. Gonthier, G. Chen, Q. Yuan, Flow distribution and mass transfer in a parallel microchannel contactor integrated with construal distributors, *AIChE J.* 56 (2010) 298–317.
- [60] F. Trachsel, A. Günther, S. Khan, K.F. Jensen, Measurement of residence time distribution in microfluidic systems, *Chem. Eng. Sci.* 60 (21) (2005) 5729–5737, <https://doi.org/10.1016/j.ces.2005.04.039>.
- [61] M. Brasholz, K. von Känel, C.H. Hornung, S. Saubern, J. Tsanaktsidis, Highly efficient dehydration of carbohydrates to 5-(chloromethyl)furfural (CMF), 5-(hydroxymethyl)furfural (HMF) and levulinic acid by biphasic continuous flow processing, *Green Chem.* 13 (5) (2011) 1114, <https://doi.org/10.1039/c1gc15107j>.
- [62] Y. Muranaka, H. Nakagawa, R. Masaki, T. Maki, K. Mae, Continuous 5-Hydroxymethylfurfural Production from Monosaccharides in a Microreactor, *Ind. Eng. Chem. Res.* 56 (39) (2017) 10998–11005, <https://doi.org/10.1021/acs.iecr.7b02017>.
- [63] W.L. Nelson, C.J. Engelder, The Thermal Decomposition of Formic Acid, *J. Phys. Chem.* 30 (4) (1926) 470–475, <https://doi.org/10.1021/j150262a003>.
- [64] Z. Li, Y. Luo, Z. Jiang, Q. Fang, C. Hu, The Promotion Effect of NaCl on the Conversion of Xylose to Furfural, *Chin. J. Chem.* 38 (2) (2020) 178–184, <https://doi.org/10.1002/cjoc.201900433>.
- [65] A.P. Dunlop, Furfural Formation and Behavior, *Ind. Eng. Chem.* 40 (2) (1948) 204–209, <https://doi.org/10.1021/ie50458a006>.
- [66] D.L. Williams, A.P. Dunlop, Kinetics of Furfural Destruction in Acidic Aqueous Media, *Ind. Eng. Chem.* 40 (2) (1948) 239–241, <https://doi.org/10.1021/ie50458a012>.
- [67] X. Hu, C. Lievens, A. Larcher, C.-Z. Li, Reaction pathways of glucose during esterification: Effects of reaction parameters on the formation of humin type polymers, *Bioresour. Technol.* 102 (2011) 10104–10113.
- [68] Y. Román-Leshkov, M. Moliner, J.A. Labinger, M.E. Davis, Mechanism of Glucose Isomerization Using a Solid Lewis Acid Catalyst in Water, *Angew. Chem. Int. Ed.* 49 (47) (2010) 8954–8957, <https://doi.org/10.1002/anie.201004689>.
- [69] H.M. Pilath, M.R. Nimlos, A. Mittal, M.E. Himmel, D.K. Johnson, Glucose Reversion Reaction Kinetics, *J. Agric. Food Chem.* 58 (10) (2010) 6131–6140, <https://doi.org/10.1021/jf903598w>.
- [70] A.G. Dickson, D.J. Wesolowski, D.A. Palmer, R.E. Mesmer, Dissociation constant of bisulfate ion in aqueous sodium chloride solutions to 250.degree.C, *J. Phys. Chem.* 94 (20) (1990) 7978–7985, <https://doi.org/10.1021/j100383a042>.
- [71] T. Shimanouchi, Y. Kataoka, T. Tanifuji, Y. Kimura, S. Fujioka, K. Terasaka, Chemical conversion and liquid-liquid extraction of 5-hydroxymethylfurfural from fructose by slug flow microreactor, *AIChE J.* 62 (6) (2016) 2135–2143, <https://doi.org/10.1002/aic.15201>.
- [72] D. Datta, M.E. Marti, D. Pal, S. Kumar, Equilibrium study on the extraction of levulinic acid from aqueous solution with Aliquat 336 Dissolved in different diluents: Solvent's polarity effect and column design, *J. Chem. Eng. Data* 62 (2017) 3–10.
- [73] A.G. Asuero, A. Sayago, A.G. González, The Correlation Coefficient: An Overview, *Crit. Rev. Anal. Chem.* 36 (1) (2006) 41–59, <https://doi.org/10.1080/10408340500526766>.
- [74] S.G. Wettstein, D.M. Alonso, Y. Chong, J.A. Dumesic, Production of levulinic acid and gamma-valerolactone (GVL) from cellulose using GVL as a solvent in biphasic systems, *Energy Environ. Sci.* 5 (8) (2012) 8199, <https://doi.org/10.1039/c2ee22111j>.
- [75] L.C. Blumenthal, C.M. Jens, J. Ulbrich, F. Schwing, V. Langrehr, T. Turek, U. Kunz, K. Leonhard, R. Palkovits, Systematic Identification of Solvents Optimal for the Extraction of 5-Hydroxymethylfurfural from Aqueous Reactive Solutions, *ACS Sustainable Chem. Eng.* 4 (1) (2016) 228–235, <https://doi.org/10.1021/acssuschemeng.5b01036>.
- [76] A. Hommes, T. de Wit, G.J.W. Euverink, J. Yue, Enzymatic Biodiesel Synthesis by the Biphasic Esterification of Oleic Acid and 1-Butanol in Microreactors, *Ind. Eng. Chem. Res.* 58 (34) (2019) 15432–15444, <https://doi.org/10.1021/acs.iecr.9b02693.s001>.
- [77] P. Garstecki, M.J. Fuerstman, H.A. Stone, G.M. Whitesides, Formation of droplets and bubbles in a microfluidic T-junction—scaling and mechanism of break-up, *Lab Chip* 6 (3) (2006) 437, <https://doi.org/10.1039/b510841a>.
- [78] D. Tsaoulidis, P. Angeli, Effect of channel size on mass transfer during liquid–liquid plug flow in small scale extractors, *Chem. Eng. J.* 262 (2015) 785–793, <https://doi.org/10.1016/j.ces.2014.10.012>.
- [79] A. Hommes, B. Dasselhorst, H.M.M. Janssens, R.J.A. Stevelink, H.J. Heeres, J. Yue, Mass transfer and reaction characteristics of homogeneously catalyzed aerobic oxidation of 5-hydroxymethylfurfural in slug flow microreactors, *Chem. Eng. J.* (2020) 127552, <https://doi.org/10.1016/j.ces.2020.127552>.
- [80] H. Chang, I. Bajaj, G.W. Huber, C.T. Maravelias, J.A. Dumesic, Catalytic strategy for conversion of fructose to organic dyes, polymers, and liquid fuels, *Green Chem.* 22 (16) (2020) 5285–5295, <https://doi.org/10.1039/D0GC01576H>.
- [81] E.G.L. de Carvalho, F. de A. Rodrigues, R.S. Monteiro, R.M. Ribas, M.J. da Silva, Experimental design and economic analysis of 5-hydroxymethylfurfural synthesis from fructose in acetone–water system using niobium phosphate as catalyst, *Biomass Conv. Biorefr.* 8 (3) (2018) 635–646, <https://doi.org/10.1007/s13399-018-0319-5>.