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5-Hydroxymethylfurfural synthesis from fructose over deep eutectic solvents in batch reactors and continuous flow microreactors

Chencong Ruan¹ · Hero Jan Heeres¹ · Jun Yue¹

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Abstract

In this work, a deep eutectic solvent (DES) composed of choline chloride (ChCl) and ethylene glycol (EG) was prepared and applied for the conversion of fructose to 5-hydroxymethylfurfural (HMF), catalyzed by HCl in both laboratory batch reactors and continuous flow microreactors. The effects of reaction temperature, batch time, catalyst loading and molar ratio of ChCl to EG on the fructose conversion and HMF yield were first investigated in the monophasic batch system of ChCl/EG DES. To inhibit HMF-involved side reactions (e.g., its polymerization to humins), methyl isobutyl ketone (MIBK) was used as the extraction agent to form a biphasic system with DES in batch reactors. As a result, the maximum HMF yield could be enhanced at an MIBK to DES volume ratio of 3:1, e.g., increased from 48% in the monophasic DES (with a molar ratio ChCl to EG at 1:3) to 63% in the biphasic system at 80°C and 5 mol% of HCl loading. Based on the optimized results in batch reactors, biphasic experiments were conducted in capillary microreactors under slug flow operation, where a maximum HMF yield of *ca.* 61% could be obtained in 13 min, which is similar to that in batch under otherwise the same conditions. The slight mass transfer limitation in microreactors was confirmed by performing experiments with microreactors of varying length, and comparing the characteristic mass transfer time and reaction time, indicating further room for improvement.

Highlights

- The efficient fructose conversion to HMF in deep eutectic solvents was achieved in batch reactors and microreactors.
- An HMF yield over 60% could be obtained at a fructose conversion above 90% in both reactors at 80°C within 14 min.
- The HMF yield was enhanced from 48% in the monophasic ChCl/EG system to 63% in the DES-MBIK biphasic system in batch.
- A slight mass transfer limitation was found in the biphasic slug flow microreactor.

Keywords HMF · Fructose · Deep eutectic solvents · Microreactor · Biphasic system · Mass transfer

Introduction

With the continuously growing concerns over the depletion of fossil fuels and environmental problems, numerous research efforts have been paid to the use of lignocellulosic biomass as raw materials for the production of fuels, chemical products and performance materials recently [1, 2]. Lignocellulosic biomass abundantly available in nature with low cost is a green and sustainable substitute to conventional unsustainable fossil fuel resources [3–5]. The transformation

of lignocellulosic biomass and its derivatives to 5-hydroxymethylfurfural (HMF) is considered as a promising strategy in the scope of biorefinery, since HMF is a versatile platform chemical that can be converted into a variety of products with applications as biobased chemicals, polymers and bio-fuels [6–8]. For example, HMF can be selectively oxidized into 2,5-furandicarboxylic acid (FDCA) and 2,5-diformylfuran (DFF). FDCA is a promising building block to produce biobased polymers, e.g., polyethylene 2,5-furandicarboxylate (PEF) that is a good substitute to petroleum-derived polyethylene terephthalate (PET) plastic materials [9–11]. DFF is a precursor for the production of pharmaceuticals, antifungal agents and furanic biopolymers [12]. Two appealing products via the selective hydrogenation of HMF are 2,5-dihydroxymethylfuran (DHMF) and 2,5-dimethylfuran. DHMF is widely used as a building block to produce furan-based polymers with applications in foams and fibers [13, 14], and 2,5-dimethylfuran is a promising alternative biofuel

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and additive to gasoline and diesel because of its high energy density and research octane number [15, 16]. HMF can also be converted into levulinic acid, a top value-added chemical to produce its downstream products like levulinate esters, gamma-valerolactone (GVL) and acrylic acid [17].

HMF is generally produced from hexoses (e.g., fructose and glucose) via dehydration [7, 18]. Fructose always gives higher reactivity and selectivity to HMF, compared with glucose that has a more stable ring structure. In the presence of Brønsted acid catalysts such as mineral and organic acids, fructose can be dehydrated into HMF, while glucose first needs to be isomerized into fructose by Lewis acid catalysts (e.g., metal salts) prior to dehydration into HMF [19, 20]. In order to achieve an efficient HMF production, different types of solvents have been applied as reaction media for the dehydration of hexoses, such as water, organic solvents and ionic liquids (ILs). Since water holds the advantages of green solvent and low price, the conversion of fructose to HMF in aqueous solutions has been widely studied, in which HMF production suffers from low selectivity because of side reactions involving HMF, e.g., the rehydration of HMF to levulinic acid and formic acid, and the polymerization of HMF to humins [21]. Aprotic organic solvents like dimethylsulfoxide (DMSO) and dimethylformamide were also used as the solvent for HMF production, as they offer the advantage of providing non-aqueous environment, thus limiting the rehydration of HMF [22]. In addition, DMSO facilitates the conversion of fructose to HMF by promoting the formation of furanoid form of fructose that shows a higher reactivity to HMF [23]. However, the toxicity of dimethylformamide, and the formation of sulfurized products from DMSO are still issues to be solved [22]. Due to the good thermal stability, negligible vapor pressure and low flammability of ILs, they have received high attention as reaction media [2]. ILs provide a significant higher solubility to lignocellulosic biomass-derived carbohydrates (the feedstock for HMF synthesis) over organic solvents, because of the ability of ILs to form hydrogen bond with carbohydrates [24]. Deep eutectic solvents (DESs) are a sustainable and green alternative to ILs, which overcome some shortcomings of ILs (e.g., high preparation cost, poor biodegradability and toxic pollutant emission in their preparation process) [25] and share the similar properties to ILs (e.g., low volatility and non-flammability) [26, 27]. In general, DESs are prepared from hydrogen bond acceptor (HBA, e.g., quaternary ammonium salts) and donor (HBD, e.g., organic acids and amides) via hydrogen bond interaction [28, 29]. As a result, the melting point of deep eutectic mixture is lower than that of their individual components. Given the advantages of simple preparation process, low cost and being biocompatible and biodegradable, DESs have been applied as a substitute to ILs in the pretreatment and/or conversion of biomass [30], e.g., the delignification of native biomass for the subsequent enzymatic hydrolysis

[31], and its catalytic valorization to furan chemicals [24, 32, 33]. As for HMF production, DESs prepared from organic acids, alcohols or monosaccharides as HBD were usually used as reaction media, in the presence of catalysts like inorganic acids (e.g., HCl), organic acids (e.g., oxalic acid), metal salts (e.g., CrCl_3) or solid catalysts (e.g., Amberlyst 15 resin) [24, 34–36]. In DESs, the undesired rehydration of HMF is generally inhibited, as it is a non-aqueous reaction system and the limited water comes from its constituent components or the dehydration reaction is stabilized via hydrogen bonding between water and DES [37].

The aqueous-organic biphasic system as a potential and efficient solvent system has also been applied for HMF synthesis, because of the suppression of HMF-involved side reactions. In general, organic solvents used as the extraction agent, including among others methyl isobutyl ketone (MIBK) [38], tetrahydrofuran (THF) [39], 1-butanol [40] and acetonitrile [41], allow the *in-situ* extraction of HMF from the aqueous phase to organic phase. This reduces the HMF concentration in the aqueous phase, leading to lower rates of HMF-consumed side reactions, and therefore the selectivity and yield of HMF are enhanced in biphasic systems. However, limited attention has been paid to the DES-organic biphasic system for the conversion of biomass(-derived) feedstock to HMF [33, 42–44]. Although the rehydration of HMF can be decreased to a great extent, the polymerization of HMF in the DES system itself still tends to cause a low selectivity of HMF. Thus, an additional organic phase as the extraction agent is a promising process intensification approach to further increase the HMF yield.

In the concept of reactor design for HMF production, continuous flow microreactors are considered promising in view of the benefits (over conventional batch reactors) such as high mass and heat transfer rates resulted from large specific surface areas, superior mixing efficiency and precise control over reaction conditions, thus providing a compelling opportunity for the development of more efficient catalytic process including the HMF production in monophasic or biphasic systems [45]. Guo et al. conducted the HMF synthesis in capillary microreactors operated under slug flow in the aqueous-MIBK biphasic system [21, 46]. A combination of HCl and AlCl_3 catalysts gave an HMF yield of 66.2% at 160°C with a residence time of 16 min when glucose was used as the feedstock [21], and a maximum HMF yield of 81% was obtained at 155°C in 16 min from the glucose-fructose mixture over H_2SO_4 catalyst [46]. The regular slug flow operation in microreactors easily provides a well-defined residence time and a precise reaction temperature control [47]. In addition, an intensified mass transfer efficiency under slug flow operation promotes the reactant mixing in the aqueous droplet and the extraction of HMF to the organic slug, enhancing the HMF yield via inhibiting HMF-involved side reactions such as its rehydration, degradation and/or polymerization [21, 47]. Zhang and co-workers explored the possibility

of using DESs (with quaternary ammonium salts as HBA and ethylene glycol as HBD) as reaction media for the conversion of glucose to HMF in monophasic microreactors, where an optimized HMF yield of 42% was obtained at 150°C in 3.64 min over CrCl₃ catalyst [35]. However, the efficient production of HMF in the DES-organic biphasic system in slug flow microreactors has not been explored yet. Because of the high viscosity of DESs, the DES-organic biphasic solvent system tends to suffer from mass transfer limitation, which may greatly reduce the extraction efficiency of organic solvents (e.g., at a short reaction time). In this regard, the advantage of microreactors in enhancing interphase mass transfer may make it a promising candidate for the continuous and efficient production of HMF under the biphasic operation conditions. However, there is also a potential disadvantage in the high pressure drop penalty in microreactors caused by the high viscosity of DESs, which would lead to a high operation difficulty and cost. Thus, proper operational window selection and process optimization need to be well addressed.

Herein, we explored the potential of combining the microreactor operation with DES-MIBK biphasic system for the continuous production of HMF from fructose using hydrochloric acid (HCl) as the catalyst. Choline chloride (ChCl) and ethylene glycol (EG) were selected to form DES, because of its relative low viscosity and melting point that make it more favorable as a candidate in the flow chemistry for HMF synthesis, compared with other types of DESs (e.g., those prepared from ChCl with monosaccharides or organic acids). To study the reaction chemistry and screen the operational window, the dehydration of fructose to HMF in the monophasic DES system was performed in laboratory batch reactors at varying conditions (i.e., batch time, temperature, catalyst loading and molar ratio of ChCl to EG). An efficient conversion of fructose to HMF in ChCl/EG DES could be achieved at a relatively low temperature of 80°C whereas the reaction temperature higher than 120°C was commonly reported in aqueous reaction media [46, 48]. The positive effect of ChCl in the catalysis and reaction process was further confirmed in the experiments. Subsequently, the DES-MIBK biphasic system was applied in batch to obtain higher HMF yields. Finally, experiments with biphasic systems were performed in slug flow capillary microreactors to achieve the efficient HMF production in flow. Moreover, in both reactors, a mass transfer study was performed to confirm whether there was a mass transfer limitation under the biphasic operation.

Materials and methods

Materials

ChCl (98%), EG (99%), MIBK (99%), hydrochloric acid (37 wt%), HMF (99 wt%), formic acid (99 wt%), levulinic acid (99 wt%) and lactic acid (99.0 wt%) were all purchased

from Sigma-Aldrich Co., Ltd. D-fructose (99 wt%) was purchased from Acros Organics Co., Ltd. All these chemicals were of chemical grade and used as received without any further treatment. Perfluoroalkoxy alkane (PFA) tubes (inner diameter: 1.65 mm; outer diameter: 3.18 mm) were purchased from Swagelok company.

Experimental procedures

The DESs used in this work were prepared from ChCl and EG with different molar ratios (1:2, 1:3 and 1:4) in a 100 mL flask, which were labeled as [ChCl:2EG], [ChCl:3EG] and [ChCl:4EG], respectively. The ChCl and EG mixture was heated at 60°C for 1 h with magnetic stirring (400 rpm), to obtain a clear and homogenous solution. Subsequently, certain amounts of fructose and HCl were added and dissolved into the prepared DES at room temperature (*ca.* 20°C) to form the reaction mixture.

The conversion of fructose over the HCl catalyst was firstly performed in both monophasic and biphasic batch reactors. In a general procedure for monophasic operation, 1 g of reaction mixture containing the DES solvent, fructose and HCl catalyst was added into a pressure tube (Ace; height: 10.2 cm; outer diameter: 19 mm; *ca.* 9 mL in volume) with a polytetrafluoroethylene (PTFE) stirring bar. Under biphasic operation conditions, 1 g of reaction mixture and 2.15 g of MIBK were added (volume ratio of MIBK to DES at 3:1). Then, the pressure tube was sealed (to prevent the evaporation of EG and MIBK) and heated at a fixed temperature (from 60 to 100°C) in an oil bath with magnetic stirring (800 rpm). At the end of the reaction, the tubes were quenched in a cooling water bath (*ca.* 20°C) to stop the reaction. The DES phase was diluted twenty times (in mass) by deionized water and filtered by 0.45 μm PTFE syringe filters before its analysis by high performance liquid chromatography (HPLC). The organic phase was directly filtered by 0.45 μm PTFE syringe filters and analyzed by gas chromatography (GC).

The conversion of fructose to HMF in the DES-MIBK biphasic system was further optimized in PFA capillary microreactors with an inner diameter (d_c) of 1.65 mm. The scheme of the experimental setup is shown in Fig. 1a. In a typical run, MIBK was delivered into the microreactor with a length (L_c) of 4.4 m by the HPLC pump (Agilent 1200 Series). Considering the high viscosity of DES that may impose damages to the HPLC pump, the DES phase containing the substrate and catalyst was fed into the microreactor via a syringe pump (model LA30, HLL GmbH). A polyether ether ketone (PEEK) Y-junction (inner diameter: 1.65 mm) was used to mix the two phases to generate a stable and uniform slug flow (Fig. 1b). The microreactor was coiled around an aluminum block and placed in an oven at a fixed temperature of 80°C. At the end of the microreactor, a back-pressure regulator was used to maintain the outlet pressure

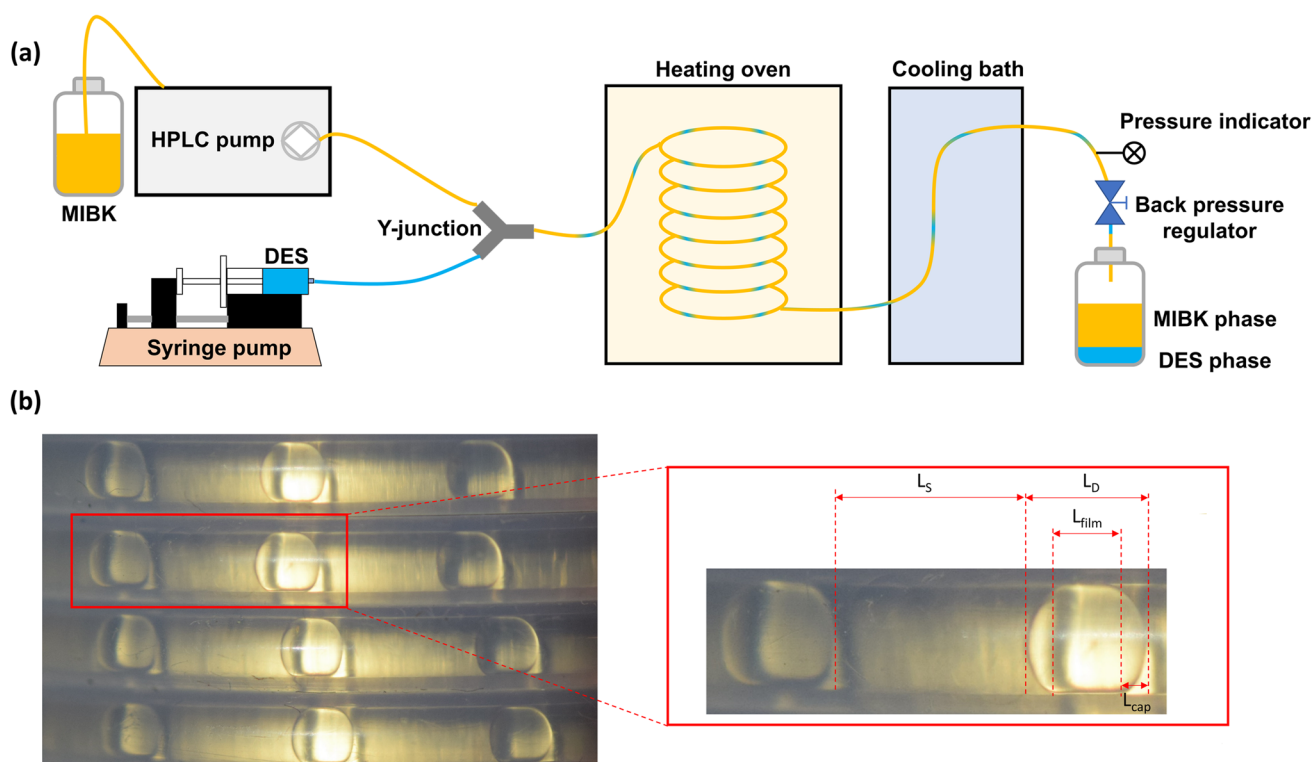


Fig. 1 **a** Schematic diagram of the conversion of fructose to HMF in the DES-MIBK biphasic slug flow microreactors. **b** Slug flow pictures in the PFA microreactor. The DES phase appeared as the droplet and the organic phase as the continuous slug

around 2 bar to keep the reaction system (especially the volatile MIBK phase) in the liquid state. The liquid mixture out of the microreactor was quenched in a water bath (*ca.* 20°C). Similar to batch experiments, the collected DES phase was treated by dilution and filtration before its analysis via HPLC, and MIBK phase was analyzed by GC after filtration.

The above experiments in batch reactors and microreactors under representative conditions were conducted at least twice, the results of which are reproducible within a standard deviation of *ca.* 2–10%.

In addition, experiments were also performed to estimate the partition coefficient of HMF between MIBK and DES phases at various temperatures and molar ratios of ChCl to EG (see more details in Section S1 of the Supporting Information). The thermal stability of the DES system was evaluated via thermogravimetric analysis (see more information in Section S2 of the Supporting information), which indicates that the DES system is stable without degradation.

Sample analysis

The DES phase was diluted by deionized water and the resulted aqueous solution was analyzed by an Agilent 1200 HPLC equipped with Agilent 1200 pump and Bio-Rad organic acid column (Aminex HPX-87H). A diluted aqueous H₂SO₄

solution (5 mM) was used as the eluent at a flow rate of 0.55 mL/min and the column temperature was kept at 60°C. A refractive index detector was equipped to detect fructose, and a standard ultraviolet detector (wavelength at 210 nm) was equipped to detect HMF, formic acid and levulinic acid. The MIBK phase was analyzed by a TraceGC ultra GC, equipped with a Stabilwax-DA fused silica column and a flame ionization detector. The GC oven temperature was firstly kept at 40°C for 5 min, subsequently increased to 240°C (ramp: 15°C/min), and finally kept at 240°C for 10 min. The carrier gas was helium flowing at 2.2 mL/min, and the split ratio was 50:1.

Definitions and calculations

The conversion of fructose (X_{Fru}) and yield of HMF (Y_{HMF}) in the laboratory batch reactor are defined as:

$$X_{Fru} = \frac{m_{DES}^{w_{Fru,DES,0}} - m_{DES}^{w_{Fru,DES,1}}}{m_{DES}^{w_{Fru,DES,0}}} \times 100\% \quad (1)$$

$$Y_{HMF} = \frac{(m_{DES}^{w_{HMF,DES,1}} + m_{MIBK}^{w_{HMF,MIBK,1}}) / M_{HMF}}{m_{DES}^{w_{Fru,DES,0}} / M_{Fru}} \times 100\% \quad (2)$$

where m_{DES} and m_{MIBK} denote the masses of the DES phase and organic phase (if present), respectively. $w_{i,DES}$ and

$w_{i,MIBK}$ are the mass fraction of substrate or product i in the DES and MIBK phases, respectively. The subscripts 0 and 1 refer to the start (i.e., at room temperature) and the end of the reaction (after cooling down to room temperature), respectively. The subscript Fru denotes fructose (the feedstock for HMF synthesis). M_{Fru} and M_{HMF} are molecular weights of fructose and HMF, respectively.

Under microreactor operation, the mass terms (m_{DES} and m_{org}) in Eqs. (1) and (2) are changed into their mass flow rates that can be calculated from the inlet volumetric flow rates ($Q_{DES,0}$ and $Q_{MIBK,0}$) and their density values (ρ_{DES} and ρ_{MIBK}) at 20°C as follows

$$X_{Fru} = \frac{Q_{DES,0}\rho_{DES,20}w_{Fru,DES,0} - Q_{DES,0}\rho_{DES,20}w_{Fru,DES,1}}{Q_{DES,0}\rho_{DES,20}w_{Fru,DES,0}} \times 100\% \quad (3)$$

$$Y_{HMF} = \frac{(Q_{DES,0}\rho_{DES,20}w_{HMF,DES,1} + Q_{MIBK,0}\rho_{MIBK,20}w_{HMF,MIBK,1})/M_{HMF}}{Q_{DES,0}\rho_{DES,20}w_{Fru,DES,0}/M_{Fru}} \times 100\% \quad (4)$$

The two-phase mixture velocity (u_M) and the residence time (τ) in the microreactor are calculated by

$$u_M = \frac{Q_{DES,0}\rho_{DES,20}/\rho_{DES,80} + Q_{MIBK,0}\rho_{MIBK,20}/\rho_{MIBK,80}}{\frac{\pi d_c^2}{4}} \quad (5)$$

$$\tau = \frac{L_c}{u_M} \quad (6)$$

Here, the actual volumetric flow rates of both the DES and MIBK phase in the microreactor are corrected for the temperature change (i.e., from *ca.* 20°C at the inlet to the reaction temperature of 80°C), based on their densities at 20 and 80°C. In Eqs. (3)–(5), Subscripts 20 and 80 refer to the temperatures of 20 and 80°C, respectively.

Results and discussion

The conversion of fructose to HMF in batch reactors

HMF synthesis in the monophasic ChCl/EG DES system

Monophasic experiments were conducted in batch reactors to explore the role of ChCl/EG DES in the transformation of fructose to HMF with HCl as the catalyst, and to obtain optimized conditions (e.g., temperature, HCl loading, substrate loading and DES composition). Firstly, the reaction systems of EG and [ChCl:4EG] with or without the presence of HCl catalyst were studied in the corresponding experiments under a reaction temperature of 80°C, a fructose loading of 10 wt% (based on the solvent; equivalent to 0.62 M at room temperature) and a catalyst loading of 10 mol% (if present; based on fructose). The reaction results are shown in Fig. 2.

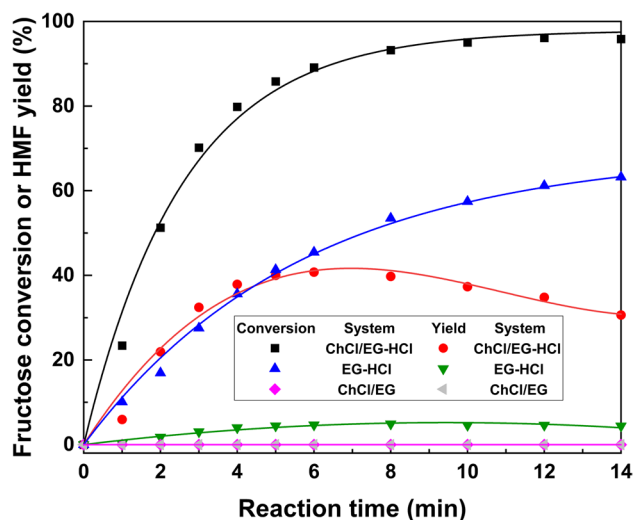


Fig. 2 The conversion of fructose and the corresponding yield of HMF in different reaction systems ([ChCl:4EG], EG-HCl and [ChCl:4EG]-HCl). Reaction conditions: 80°C, 10 wt% of fructose loading and 10 mol% of HCl loading (if present). Lines are for visual guidance, and the same as in Figs. 3, 5, 7, 8 and 9

There was no HMF detected and no conversion of fructose in [ChCl:4EG] with the absence of HCl, indicating that both EG and ChCl cannot directly catalyze the dehydration of fructose. The presence of HCl gave a fructose conversion of over 90% and HMF yield of *ca.* 40% at a batch time of 6 min in [ChCl:4EG]. It was reported that the first step for the conversion of fructose to HMF is the protonation of fructose by H^+ to form a fructofuranosyl oxocarbenium ion [49], according to which HCl played the role of providing H^+ to activate the reaction in our work. In EG and the presence of HCl (i.e., the system EG-HCl), a lower fructose conversion was obtained (*ca.* 63% in 14 min) and the HMF yield is lower than 10% compared with those in the [ChCl:4EG]-HCl system. It is obvious that the yield and selectivity of HMF were significantly promoted via the presence of ChCl (e.g., a maximum yield of *ca.* 40% with [ChCl:4EG]-HCl and *ca.* 5% with EG-HCl, and the selectivity up to 47% in the former case and 11% in the latter). This indicates a positive effect of ChCl on not only accelerating the dehydration of fructose, but also intensifying the production of HMF, as will be discussed in detail hereafter.

There is a clear maximum in the yield of HMF in the DES system ([ChCl:4EG]-HCl), indicating that HMF is an intermediate product and prone to further chemistry. It should be mentioned that no levulinic acid (LA) and formic acid (FA) were detected by HPLC in the studied reaction systems under the tested reaction conditions (temperature from 60 to 100°C, HCl loading from 5 to 15 mol%, molar ratio of ChCl to EG from 1:2 to 1:5), both of which are the expected side products in aqueous reaction media [21]. LA and FA

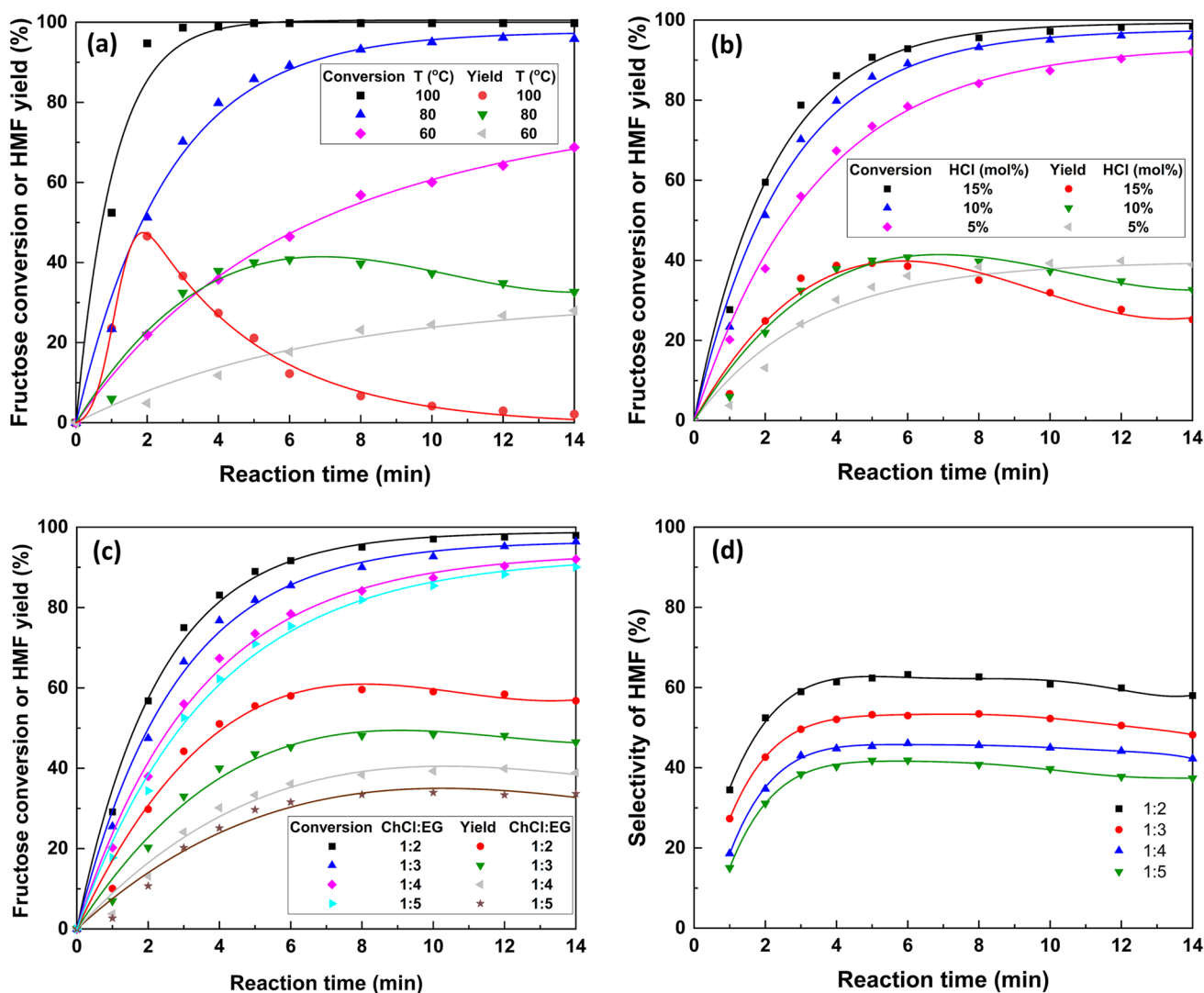


Fig. 3 The effects of temperature (a), HCl loading (b) and molar ratio of ChCl to EG (c) on the fructose conversion and HMF yield. (d) HMF selectivity at various molar ratios of ChCl to EG. Reaction con-

ditions: 80 °C, 10 wt% of fructose loading in ChCl/EG (molar ratio at 1:4), unless otherwise mentioned. The HCl loadings are 10 mol% in (a), and 5 mol% in (c) and (d)

are typically produced from HMF via its rehydration in the presence of water. In the DES system, there are only trace amounts of water formed from the dehydration of fructose, leading to a very low reaction activity for the rehydration of HMF. This also suggests that the main side product here is humin (water-soluble oligomer and insoluble polymer), which can be inferred from the color change (from colorless to brown, see Fig. S3 in the Supporting Information) of the reaction mixture in the DES over the increased reaction time. Another possible side reaction is the etherification of HMF with EG, as it is reported that HMF can be etherified with methanol and ethanol over acid catalysts [50, 51]. This seems to be supported by the presence of an unknown peak (close to HMF) in the HPLC chromatograms, which is likely the etherification product between HMF and EG (see more

details in Section S4 of the Supporting Information). However, this product could not be quantified due to the lack of pure samples, and will be studied in future work.

To obtain the optimized reaction condition for HMF production, the effects of temperature, HCl loading and DES composition were investigated. As shown in Fig. 3a, the conversion of fructose (with an initial loading of 10 wt%) was boosted by increasing the reaction temperature from 60 to 100 °C, over a HCl loading of 10 mol% in [ChCl:4EG]. For instance, a conversion of over 90% was obtained in 2 min at 100 °C while it is still lower than 70% at 60 °C in 14 min. At 100 °C, the HMF yield reached a maximum of 46% within 2 min, and subsequently it suffered from a fast drop because of HMF-involved side reactions. Compared with the reaction at 100 °C, a bit lower maximum HMF yield of 40% was

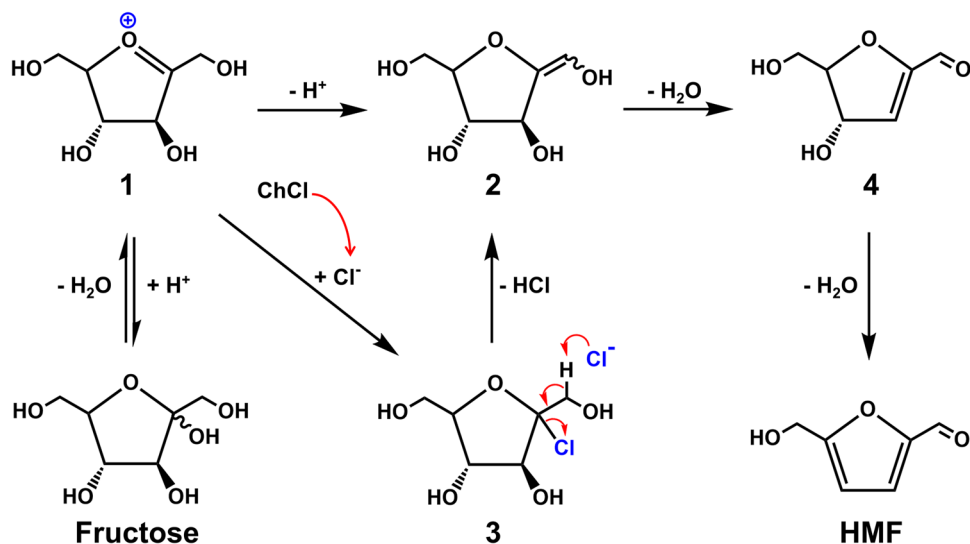
obtained within 6 min at 80°C, followed by a gradual yield decrease at longer reaction times. As for 60°C, the HMF yield was steadily increased with the reaction time (being 31% in 14 min). These results indicate that the higher temperature not only promoted the conversion rate of fructose and the production of HMF (in terms of its maximum yield), but also accelerated the consumption of HMF to generate side products. Thus, based on the observed effect of temperature on the reaction performance as well as from the energy-saving point of view, the following study was conducted under 80°C. In addition, it is noticeable that a substantial conversion of fructose to HMF was achieved at a relatively mild reaction conditions (i.e., temperature at 80 or even 60°C) in the present DES, while a much higher temperature (e.g., 150°C) is usually required in aqueous reaction media [46, 52].

To gain insights into the effect of catalyst loading, experiments were performed under reaction conditions of 80°C and 10 wt% of fructose loading in [ChCl:4EG], with the HCl loading varying from 5 mol% to 15 mol%. As shown in Fig. 3b, the rate of fructose conversion and that of HMF production (at least in the initial period) were boosted at higher catalyst loadings. For example, a 90% fructose conversion was obtained within 5 min with a HCl loading of 15%, while it took 14 min with 5% of HCl loading. However, the maximum HMF yield had little dependency on the catalyst loading, which is similar to our previous work on the effect of acid concentration on the conversion of fructose-glucose mixture in the aqueous system [46], indicating similar reaction orders in the HCl-catalyzed sub-reactions in the network of fructose conversion in the current DES system.

We noticed the promoted fructose conversion and HMF yield resulted from the presence of ChCl in the DES (Fig. 2). Thus, the effect of DES composition (molar ratio of ChCl to

EG) was studied to provide insights into the role of ChCl in the catalysis and reaction process. As illustrated in Fig. 3c, increasing the ChCl content in the DES clearly boosted the rates of the fructose conversion and HMF production, as well as the maximum HMF yield. As an example, a maximum yield of 59% was obtained in [ChCl:2EG], while it turned out to be 34% in [ChCl:5EG] under 80°C and 5 mol% HCl loading. This is also in line with the results obtained in pure EG and [ChCl:4EG] (Fig. 2), where the HMF yield was significantly enhanced from *ca.* 5% in the former to 40% via the introduction of ChCl into the reaction under 80°C and 10 mol% HCl loading. Considering the possible catalytic mechanism and reaction process for the conversion of fructose to HMF, the positive effect caused by the presence of ChCl can be ascribed to the synergistically catalytic effect of Cl⁻ and the stabilizing effect of ChCl on HMF. Based on the literature results [49, 53] and this work, a mechanism of fructose dehydration to HMF was proposed to explain the role of ChCl during the catalysis process (Fig. 4). Fructose is firstly protonated by the H⁺ proton provided by HCl catalyst to form intermediate 1 (furanosyl oxocarbenium ion) with one water molecule removal, which is subsequently followed by the tandem deprotonation (forming an enolic furan intermediate 2) and water removal step (finally forming HMF). Among them, the enolization reaction of furanosyl oxocarbenium ion to an enolic furan intermediate 2 is the rate-limiting step for HMF synthesis from fructose, which can be promoted by Cl⁻ ions with strong electronegativity to act as a nucleophile to assist this enolization reaction via intermediate 3 [53]. The improved selectivity of HMF in [ChCl:2EG] (Fig. 3d) can be attributed to not only the promoted fructose dehydration caused by the synergistic catalysis of Cl⁻ ions, but also the stabilizing effect of ChCl on HMF via the hydrogen bond

Fig. 4 Proposed mechanism of fructose dehydration to HMF in the DES composed of ChCl and EG over the HCl catalyst, adapted with permission from reference [53]. Copyright 2020 American Chemical Society



between the Cl^- ion and the aldehyde/hydroxyl groups of HMF [54]. The latter leads to an inhibition effect on the further transformation of HMF to side products.

HMF synthesis in the biphasic ChCl/EG DES-MIBK system

To suppress HMF-involved side reactions in the presence of acid catalysts and thus enhance the HMF yield, the dehydration of fructose was performed in the ChCl/EG DES-MIBK biphasic system in batch reactors to enable the *in-situ* extraction of the formed HMF from the DES phase. The reaction results in the biphasic system under 80°C with 5 mol% of HCl loading are illustrated in Fig. 5. It is noteworthy that no drop of HMF yield was observed within the tested reaction time up to 14 min in the biphasic system (Fig. 5a), while the HMF yield already started to decrease from *ca.* 8–10 min in DESs with various ChCl contents in the monophasic system (Fig. 3c). In addition, the application of biphasic system enhanced the yield of HMF obviously. For example, a maximum HMF yield of *ca.* 63% was obtained in the [ChCl:3EG]-MIBK biphasic system, in contrast to *ca.* 48% for the monophasic [ChCl:3EG] system (Fig. 3c). This corroborates the promotional effect of adding MIBK as the extraction agent for HMF that inhibits side reactions involving HMF effectively. However, the introduction of biphasic system led to a small drop of fructose conversion especially in the start of the reaction process, e.g., being 57% for biphasic system (Fig. 5b) and 66% for monophasic system (Fig. 3c) with [ChCl:3EG] at a batch time of 3 min. This conversion reduction can be explained by the decreased heating rate of biphasic system, as illustrated in the heating profile of batch reactors (see more details in Section S5 of the Supporting Information).

Besides, the promotional effect of biphasic system was influenced by the molar ratio of ChCl to EG in the DES. When the biphasic system was applied, there is an increase of 17% in the maximum HMF yield (i.e., raised from 39% in the monophasic system to 56% in the biphasic system with [ChCl:4EG]), and such yield increase is 15% (from 48 to 63%) with [ChCl:3EG] and 7% (from 60 to 67%) with [ChCl:2EG]. On the one hand, this difference in the maximum HMF yield increase at varying ChCl contents in the DES can be ascribed to a lower partition coefficient of HMF in the DES with a higher ChCl content. In detail, the partition coefficient is 0.2581 at 80°C for the [ChCl:2EG]-MIBK system, whereas the values are 0.3240 and 0.3465 in the cases of using [ChCl:3EG] and [ChCl:4EG] respectively, as illustrated in Fig. 6. A similar phenomenon was reported in the aqueous-MIBK biphasic system (with ChCl as an additive to the aqueous phase) [55], viz., the partition coefficient was significantly reduced when continuously increasing the ChCl content because of the stronger hydrogen bonding interaction between HMF and ChCl at higher ChCl concentrations. On the other hand, this is also probably caused by a lower mass transfer rate in the [ChCl:2EG]-MIBK biphasic system resulting from a higher DES viscosity, as it increases with the increased ChCl content [56].

Herein, an intensified HMF production was achieved via the biphasic system operation in batch reactors. An enhanced HMF yield of 63% or 67% was obtained in 14 min, when [ChCl:3EG] or [ChCl:2EG] was used as the reaction phase. Considering the higher viscosity of [ChCl:2EG], [ChCl:3EG] represents a better candidate for further study of HMF production in slug flow microreactors, in order to reduce the operation difficulties and costs.

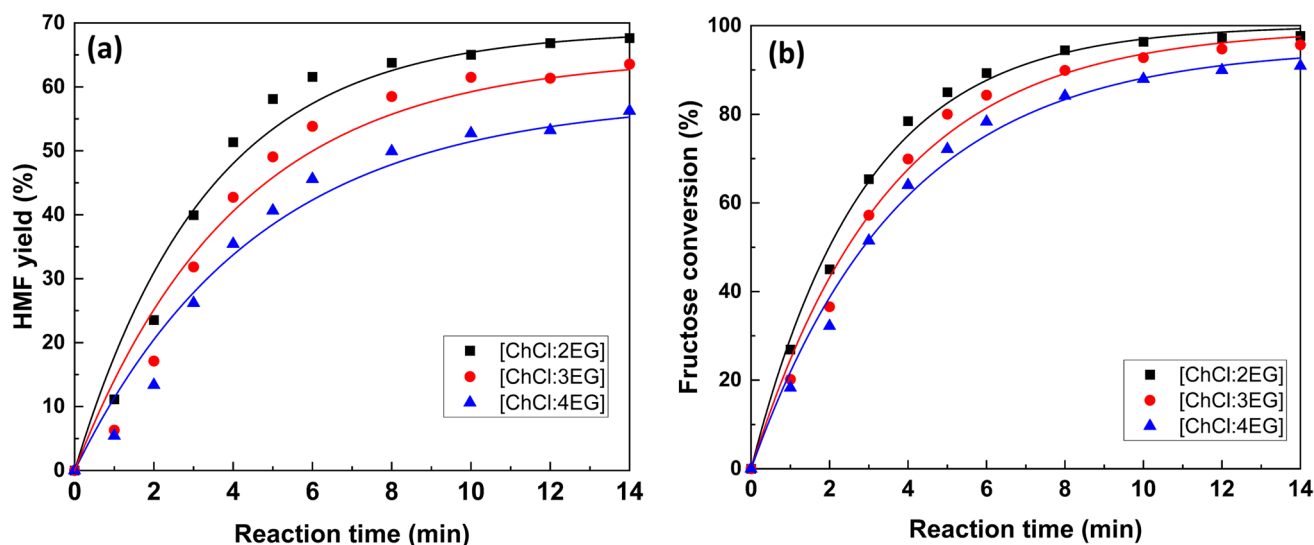


Fig. 5 The conversion of fructose to HMF in the biphasic system in batch reactors. **a** HMF yield, **b** fructose conversion. Reaction conditions: 80°C , 10 wt% of fructose loading, 5 mol% of HCl loading and 3:1 volume ratio of MIBK to DES

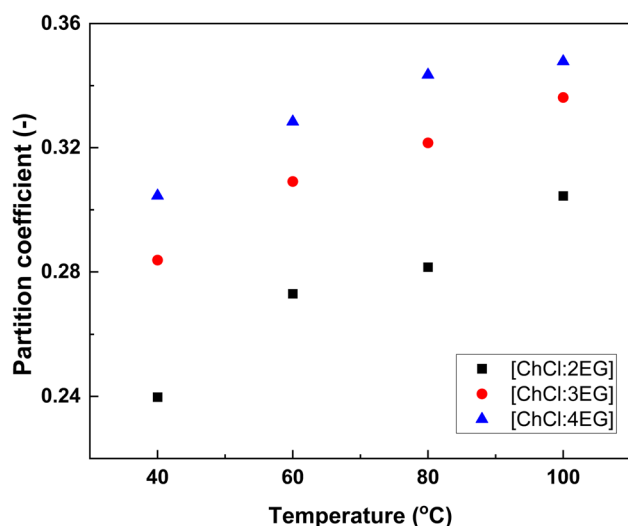


Fig. 6 Partition coefficient of HMF between the MIBK and DES phases ([ChCl:2EG], [ChCl:3EG] and [ChCl:4EG]) in a temperature range of 40 to 100°C

In addition, the lower partition coefficient in [ChCl:2EG] may pose some difficulties in the separation of HMF from DES phase for downstream product purification.

The conversion of fructose to HMF in slug flow microreactors

Reaction performance in the biphasic ChCl/EG DES-MIBK system in microreactors

Continuous flow reactors are more favorable than batch reactors for the industrial production of HMF, because of

their larger production capacity and more consistent product quality. In this aspect, microreactors represent a promising tool to enable efficient flow chemistry by significantly improving transport limitations that are likely present in biphasic systems for HMF synthesis, especially when conducted in scaled-up batch reactors. Herein, the conversion of fructose (10 wt% loading) to HMF was performed in the ChCl/EG DES-MIBK biphasic system under slug flow in capillary microreactors (Fig. 1a), under 80°C in the presence of 5 mol% of HCl catalyst. As revealed in Fig. 7a, the conversion of fructose was raised very slightly when increasing the inlet volumetric flow ratio of MIBK to [ChCl:3EG] from 1:1 to 3:1, while almost the same fructose conversion was obtained upon further raising this ratio to 5:1. The barely enhanced fructose conversion herein can be ascribed to the superior heat transfer performance of slug flow microreactors, despite the slightly faster heating rate of MIBK phase than that of DES phase. This ensured an almost constant temperature inside the microreactor at such different volumetric flow ratios of MIBK to [ChCl:3EG], except at the very beginning of the reaction (< 30 s) (see more details in Section S5 of the Supporting Information). The faster heating rate in microreactors also rendered a higher conversion rate of fructose than that in batch, e.g., a fructose conversion of *ca.* 58% was achieved with 2 min in microreactors (Fig. 7a) compared with 36% in batch reactors (Fig. 5b). That is, it took a much shorter time in microreactors to reach the target reaction temperature, ensuring faster kinetic rates attainable during the course of the reaction (see more details in Section S5 of the Supporting Information). Different from the conversion of fructose, the HMF yield was promoted significantly with increasing the flow ratio of MIBK to

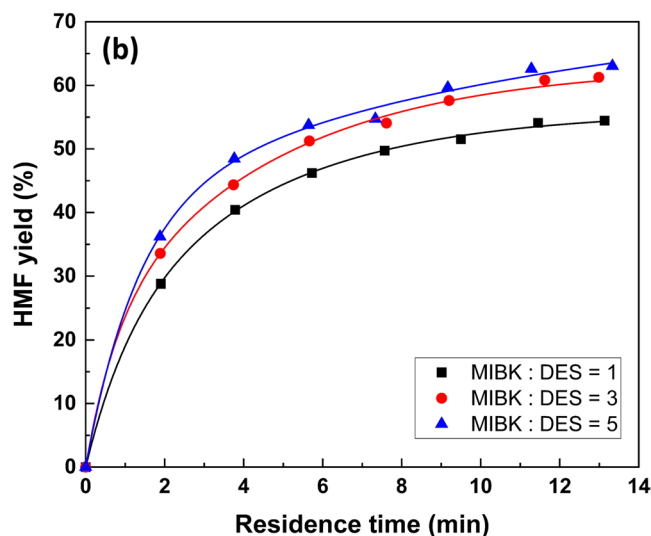
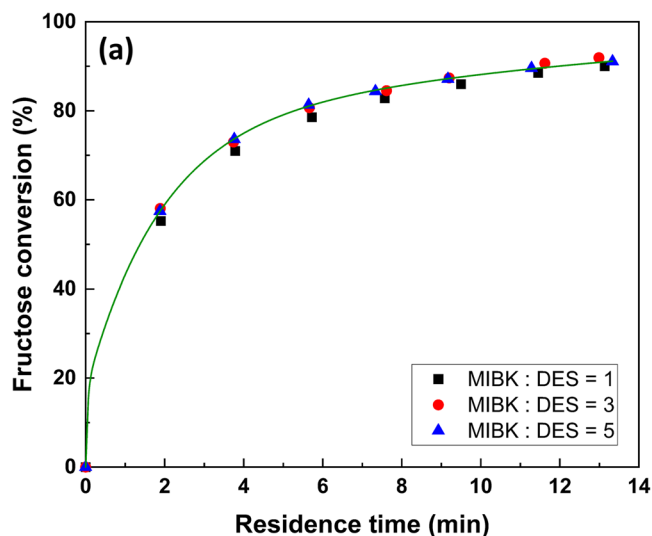


Fig. 7 HMF synthesis from fructose in the [ChCl:3EG]-MIBK biphasic system in microreactors. **a** fructose conversion; **b** HMF yield. Reaction conditions: inlet volumetric flow ratios of MIBK to DES at

1:1, 3:1 and 5:1, 80°C, 10 wt% of fructose loading, 5 mol% of HCl loading, $L_c = 4.4$ m

[ChCl:3EG]. For example, the HMF yield was boosted from 54% to 61% at 80°C within a residence time of 13 min upon raising the volumetric flow ratio of MIBK to [ChCl:3EG] from 1:1 to 3:1, and further to 63% at a higher ratio of 5:1 (Fig. 7b). This is because more produced HMF could be extracted into the MIBK phase since a higher HMF extraction capacity was present at such a higher ratio.

In addition, the maximum HMF yield (61%) in biphasic systems in microreactors is a bit lower than that (63%) in batch reactors under the same reaction conditions (80°C, 5% mol of HCl loading, 10 wt% of fructose loading and MIBK to [ChCl:3EG] volume or volumetric flow ratio at 3:1). In the biphasic batch reactors, the mass transfer limitation was eliminated via increasing the magnetic stirring rate (cf. Section S6 of the Supporting Information). Therefore, such a small yield difference indicates the likely presence of a slight mass transfer limitation under biphasic operations in microreactors. This is further supported by a detailed mass transfer analysis for microreactors as given in the following section.

Mass transfer analysis in microreactors

To further determine whether there was a mass transfer limitation in microreactors, additional experiments on fructose dehydration to HMF in the [ChCl:3EG]-MIBK biphasic system was conducted in microreactors with varying lengths (i.e., $L_c = 2.4$ m and 8.4 m in addition to the normally used length of 4.4 m; inner diameter of 1.65 mm) and the outlet pressure being kept at *ca.* 2 bar. As illustrated in Fig. 8a, there is a rather limited increase in the fructose conversion when extending the microchannel length from 2.4 m to

4.4 m, and the conversion remained essentially unchanged with a further length increase to 8.4 m. In contrast, the corresponding HMF yield experienced a slightly more significant increase at prolonged microchannel lengths, especially from 2.4 m to 4.4 m (Fig. 8b). As higher mass transfer rates are expected in longer microchannels for a given residence time (resulted from enhanced internal circulation in droplets/slugs at higher mixture flow rates) [57, 58], the above results imply that under typical reaction conditions in this work (i.e., $L_c = 4.4$ m; see Fig. 7), the DES-MIBK biphasic system still suffered a bit from mass transfer limitation in microreactors, especially regarding the HMF yield. In other words, the reaction rate seems to be slightly limited by the interfacial transfer of HMF from the DES droplet to the continuous MIBK slug (Fig. 1b).

Moreover, the values of the overall liquid–liquid volumetric mass transfer coefficient ($K_L a$) were roughly estimated under typical reaction conditions in microreactors. Under slug flow operation (Fig. 1b), the produced HMF was extracted *in-situ* from the DES phase (as droplets) to the continuous MIBK phase via (i) the caps of the droplet and (ii) the MIBK film between the droplet and microreactor wall. Based on the model of Van Baten et al. [58], a simplified mass transfer analysis for liquid–liquid slug flow was conducted similarly to our previous work [59], in which the pathway (i) was estimated to be dominant in mass transfer and the pathway (ii) was considered to be of minor or negligible contribution (see the calculation details in Section S7 of the Supporting Information). As such, the overall mass transfer coefficient (K_L) was assumed to be that in the cap region and can be approximated as

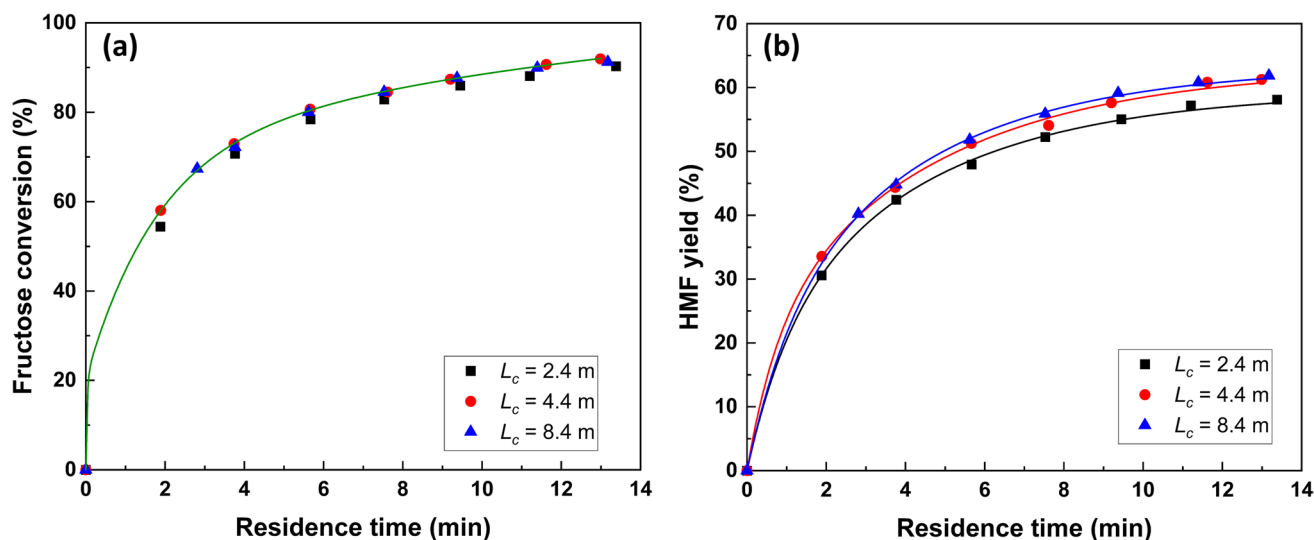


Fig. 8 Fructose conversion to HMF in the [ChCl:3EG]-MIBK biphasic system in microreactors with varying microchannel lengths ($L_c = 2.4$ m, 4.4 m and 8.4 m) and an inlet volumetric flow ratio of

MIBK to DES at 3:1. **a** fructose conversion; **b** HMF yield. Other reaction conditions are the same as in Fig. 7

$$K_L = \frac{1}{\frac{1}{\frac{2\sqrt{2}}{\pi} \sqrt{\frac{D_{HMF,DES} U_{slug}}{d_c}}} + \frac{1}{m \frac{2\sqrt{2}}{\pi} \sqrt{\frac{D_{HMF,MIBK} U_{slug}}{d_c}}}} \quad (7)$$

where $D_{HMF,DES}$ and $D_{HMF,MIBK}$ are the diffusion coefficients of HMF in the DES ([ChCl:3EG]) and the organic (MIBK) phase, respectively. U_{slug} is the slug velocity (i.e., equal to the two-phase mixture velocity), and m is the partition coefficient of HMF between the MIBK and DES phases (see Fig. 6). The end cap of droplets was assumed to have a shape of oblate spheroid, the specific interfacial area (a) of which could be calculated based on the lengths of droplet, slug and cap (i.e., L_D , L_S and L_{cap} , respectively) that were measured from the images of slug flow (Fig. 1b) [57]. Thus, there is

$$a = \frac{\frac{\pi}{2} d_c^2 + \pi \frac{L_{cap}^2}{e} \ln\left(\frac{1+e}{1-e}\right)}{\frac{\pi}{4} d_c^2 (L_D + L_S)} \quad (8)$$

where e is the ellipticity of the oblate spheroid and defined as

$$e = \sqrt{\frac{\frac{d_c^2}{4} - L_{cap}^2}{\frac{d_c^2}{4}}} \quad (9)$$

The calculated values of $K_L a$ (based on Eqs. (7) and (8)) for the [ChCl:3EG]-MIBK biphasic system in the microreactor are depicted in Fig. 9 as a function of the total volumetric flow rate of the mixture at the inlet under 80°C and an inlet MIBK-to-[ChCl:3EG] volume flow ratio of 3:1. It

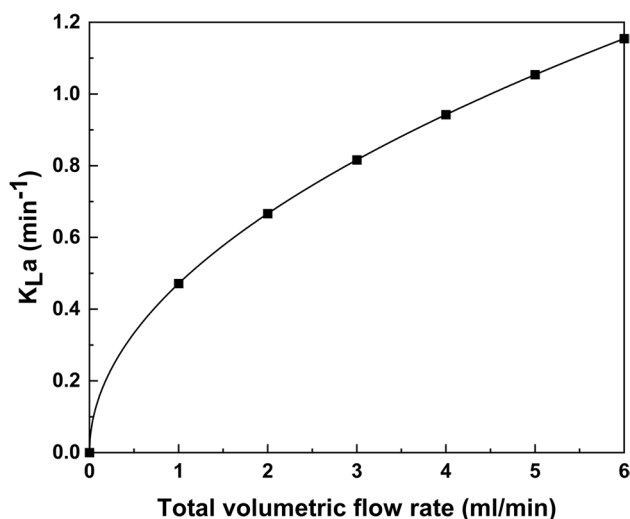


Fig. 9 Estimated overall liquid–liquid volumetric mass transfer coefficient as a function of the total volumetric flow rate of the mixture at the inlet in slug flow microreactors ($L_c=4.4$ m) under 80°C and an inlet [ChCl:3EG] to MIBK volumetric ratio of 3:1

is apparent that higher flow rates (i.e., higher droplet/slug velocities) lead to higher mass transfer coefficients, due to the enhanced inner circulation in both droplets and slugs [60]. The estimated values of $K_L a$ under the reaction condition of this work are in the range of 0.40–1.05 min^{-1} for $L_c=4.4$ m (corresponding to the total volumetric flow rate at the inlet from 0.72 to 4.98 mL/min). Thus, the characteristic mass transfer time (i.e., the reciprocal of $K_L a$) varied from 0.95 to 2.49 min, which can be roughly considered less than the reaction time (2–14 min), but still they are almost on the same order of magnitude. This indicates that the produced HMF in the DES phase could not be instantly transferred into the MIBK phase before its further conversion [61]. As such, both experimental results and mass transfer calculation herein infer the presence of interfacial mass transfer resistance of HMF to some (limited) extent during fructose conversion in the present DES-MIBK biphasic system in slug flow microreactors. Consequently, the reaction was not fully under the kinetic control regime, implying some additional room for process intensification (e.g., by working in longer microchannels with increased flow rates).

Conclusion

The dehydration of fructose to HMF was performed with the DES (composed of ChCl and EG) as the reaction solvent and HCl as the catalyst in both laboratory batch reactors and capillary microreactors. In the batch reactors, a maximum HMF yield of ca. 39%, 48% or 59% was obtained from fructose (10 wt% loading) at 80°C over 5 mol% HCl catalyst in the monophasic DES system of [ChCl:4EG] (in 12 min), [ChCl:3EG] (in 10 min) or [ChCl:2EG] (in 8 min), respectively. In addition, the fructose conversion rate was significantly promoted via increasing the content of ChCl in the DES. The enhancement on both the HMF yield and fructose conversion can be ascribed to the synergistic catalysis effect of Cl^- anions in the reaction pathway and the stabilizing effect of ChCl on HMF via their hydrogen bonding interactions. In the DES-MIBK biphasic system, the enhanced HMF production could be achieved via the *in-situ* extraction of the formed HMF from the DES to MIBK phase. As a result, the maximum HMF yield could be increased to 56%, 63% and 67% in the cases of using [ChCl:4EG], [ChCl:3EG] and [ChCl:2EG] as the DES, respectively, at an initial MIBK-to-DES volumetric ratio of 3:1 and a reaction time of 14 min. Among them, [ChCl:2EG] gave the lowest increase in the HMF yield when biphasic system was applied because of the lowest partition coefficient of HMF. In capillary microreactors under slug flow operation, an HMF yield of ca. 61% was obtained at an inlet volumetric flow ratio of 3:1 (MIBK to [ChCl:3EG]) and a microreactor length of 4.4 m, which is slightly lower than that (63%) in biphasic

batch reactors under otherwise identical conditions. However, the fructose conversion rate in microreactors is higher than that in batch because of the faster heat transfer rate in microreactors. Additional reaction experiments in microreactors with varying lengths and a simplified mass transfer analysis further confirmed the presence of mass transfer limitation to some (limited) extent in the DES-MIBK biphasic system in slug flow microreactors. Thus, additional mass transfer improvement in microreactors is needed towards obtaining the maximized kinetic rate. Nevertheless, the present study clearly shows that the ChCl/EG DES-MIBK biphasic system, combined with microreactor operation under slug flow, holds great potential for the selective and efficient HMF production from fructose in flow under relatively mild reaction conditions.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s41981-023-00262-4>.

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Data availability The data that support the results of this work are available on request from the corresponding author upon reasonable request.

Declarations

Conflict of Interest The authors declare no conflict of interest.

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