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Journal Name

COMMUNICATION

Green catalytic conversion of bio-based sugars to 5-chloromethylfurfural in deep eutectic solvent catalyzed by metal chlorides

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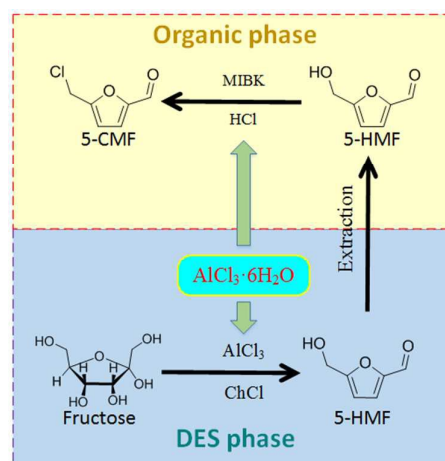
5-Chloromethylfurfural (5-CMF), a biomass derived platform chemical with great potential applications, was synthesized by a novel method from sugars using metal chlorides as catalyst in a deep eutectic solvent (DES). $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ was verified as the most effective catalyst among various metal chlorides, which provided a 5-CMF yield of 50.3% along with 8.1% 5-HMF yield at 120 °C in 5 h. By this green, mild and cost-effective approach, the dependence of 5-CMF production on the large amount and high concentration of hydrochloric acid in previous works was eliminated.

Renewable lignocellulosic biomass has been utilized for the production of fuels and chemicals in consideration of the depletion of fossil resources worldwide.^{1–3} Much efforts have been devoted to convert lignocellulose into versatile platform chemicals, such as 5-hydroxymethylfurfural (5-HMF), which can be produced by acid promoted dehydration of cellulose and has been regarded as one of the most important cellulose-derived products. However, 5-HMF is highly active and instable, especially in the presence of acid catalysts which could further promote the formation of humins and degradation of 5-HMF to levulinic acid (LA).^{4,5}

5-Chloromethylfurfural (5-CMF), which can be directly generated with a high yield up to 80% from cellulosic biomass, is also acknowledged as a novel and promising platform molecule owing to its higher stability compared with 5-HMF.^{4,6–9} Moreover, highlighted by Mascal's research, the chlorine atom in 5-CMF is rather active for substitution reactions of 5-CMF,⁴ which facilitates the conversion of 5-CMF into various chemicals such as 5-aminolevulinic acid (5-ALA)¹⁰, 2,5-dimethylfuran (DMF)¹¹ and pharmaceutical chemicals.¹² According to previous reports, 5-CMF was typically produced in a biphasic reaction system, in which concentrated HCl

solution was adopted for the generation of 5-CMF via hydrolysis, dehydration and halogenation process followed by simultaneous extraction with dichloromethane.¹³

Herein we proposed the "one-pot" conversion of carbohydrates to 5-CMF in a biphasic reaction system (Figure S1), which was composed of methyl isobutyl ketone (MIBK) and deep eutectic solvent (DES)^{14, 15}. DES is widely acknowledged as a new class of ionic liquid (IL), under mild conditions without the utilization of concentrated acid. As illustrated in Scheme 1, fructose which generated DES with choline chloride (ChCl) is firstly dehydrated to 5-HMF in DES phase with the catalysis of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$. The resulting 5-HMF is rapidly extracted by MIBK from the DES phase. The following halogenation of 5-HMF to 5-CMF in organic phase is catalyzed by HCl, which was *in-situ* generated by the hydrolysis of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$. In this work, a highest 5-CMF yield over 50% was obtained with a high feed concentration (over 15 wt%) in a DES-MIBK system in the absence of concentrated HCl. It is noted that carbohydrates used here were both reactants and part of DES.



Scheme 1. Plausible mechanism for the conversion of fructose into 5-CMF in DES-MIBK system catalyzed by $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$

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As moderate acids, metal chlorides were adopted in this study to eliminate the dependence of 5-CMF production on concentrated HCl. Various of metal chlorides were investigated for the catalytic production of 5-CMF in DES-MIBK system (Table S1). It is noted that the strength of Lewis acid greatly affected the conversion of fructose and the selectivity to 5-CMF and 5-HMF. Metal chlorides with high Lewis acid strength provided much higher 5-CMF yields than 5-HMF. A highest 5-CMF yield of 37% was obtained in the presence of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ at 110 °C in 2 h. Thus, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ was proven to be the most effective among various metal chlorides and was applied for further experiments.

When the reaction was performed in an isolated DES phase, a severe coking process was observed and the yields of 5-CMF and 5-HMF were quite low. Thus, several aprotic solvents including acetonitrile (MeCN), methyl isobutyl ketone (MIBK), γ -valerolactone (GVL), dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) were introduced for the *in-situ* extraction of products from DES reaction mixture to prevent polymerization and coking. As shown in Table 1, the addition of MeCN, DMF and DMSO effectively inhibited the coking process and 44.9%-46.8% 5-HMF yield was achieved. However, almost no 5-CMF was detected in the above mentioned cases. As for GVL, a 5-CMF yield of 18.9% was obtained. Interestingly, MIBK strongly facilitated the generation of 5-CMF and provided a yield up to 37.1% at 110 °C in 2 h.

Table 1. Effects of extractants on the yields of 5-CMF and 5-HMF

| Extractant | $Y_{5\text{-CMF}}^a$ (%) | $Y_{5\text{-HMF}}^b$ (%) |
|--------------------|--------------------------|--------------------------|
| Blank ^c | 0 | 0 |
| MeCN | 3.7 | 44.9 |
| MIBK | 37.1 | 16.7 |
| GVL | 18.9 | 32.0 |
| DMF | 0 | 44.8 |
| DMSO | 0 | 46.8 |

Reaction conditions: 5 mmol fructose, 5 mmol $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, 25 mmol ChCl , 30 ml extractant, 110 °C, 2 h. a: the yield of 5-CMF; b: the yield of 5-HMF; c: extracted by 30 ml MIBK after the reaction mixture cold down to room temperature.

The effects of temperature and reaction time on 5-CMF and 5-HMF production in the biphasic system were also studied. According to Figure 1(a), higher temperatures promoted the generation of 5-CMF and a highest yield up to 50.3% was achieved at 120 °C in 5 h. The yield was then decreased to 44.8% with a further increase of reaction time to 8 h, which probably attributed to further conversion of 5-CMF into humins and other by-products. Oppositely, the yield of 5-HMF decreased as the reaction proceeded (Figure 1(b)), from which we can deduce that fructose was firstly dehydrated into 5-HMF and then halogenated into 5-CMF in the biphasic system. The cascade generation of 5-HMF and 5-CMF was proved by GC-MS detected product distribution, as shown in Figure S2.

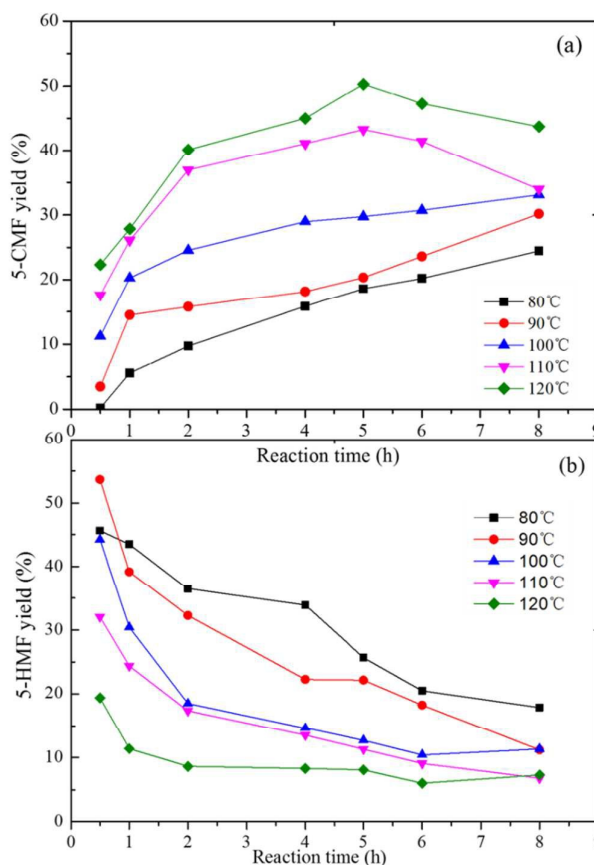


Figure 1. Effects of reaction time and temperature on the conversion of fructose into 5-CMF (a) and 5-HMF (b); Reaction conditions: 5 mmol fructose, 5 mmol $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, 25 mmol ChCl , 30 ml MIBK

The effect of the catalyst dosage was studied, as shown in Figure 2. In a blank experiment, 20.9% of 5-HMF yield was obtained and no 5-CMF was detected. 5-CMF yield of 23.6% and 5-HMF yield of 13.4% were obtained when the mole ratio of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ to fructose was 0.5. As the mole ratio of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ to fructose increased to 1.0, a sharp increase of 5-CMF yield from 0 to 50.3% was observed while 5-HMF yield decreased from 20.9% to 8.1%. However, 5-CMF yield was reduced to 40% as the mole ratio of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ to fructose was further increased to 4.0, probably due to the overmuch acid sites which would promoted the formation of undesired by-products such as humins.

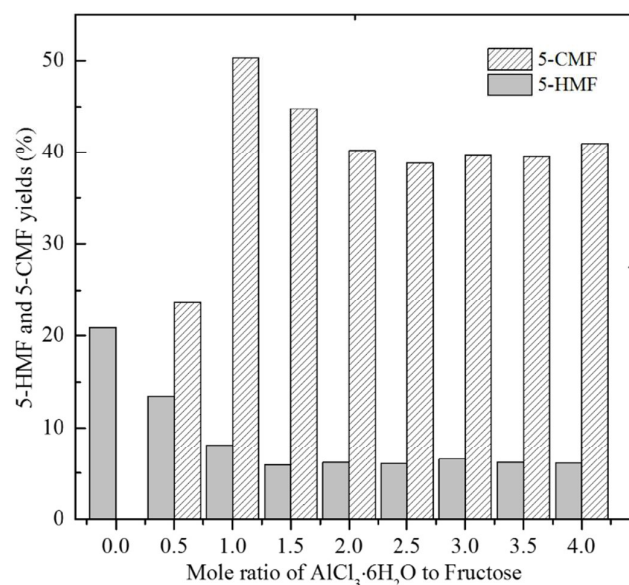


Figure 2. Effect of catalyst loading on the conversion of fructose into 5-CMF & 5-HMF; Reaction conditions: 5mmol fructose, different amounts of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, 25 mmol ChCl, 120 °C, 5 h. Catalyst loading is relative to fructose.

As Table 2 showed, low concentration of ChCl helps to reduce the costs of 5-CMF production which is desirable for the practical production. Hence, the effect of the initial ChCl concentration on 5-CMF and 5-HMF yields was studied at a reaction temperature of 120 °C in 5 h with 5 mmol fructose and 5 mmol catalyst. As demonstrated in Table 2, the equal quality of fructose to ChCl content resulted in the predomination of 5-HMF in the products. However, 5-CMF yield gradually increased from 17.4% to 50.3% when the weight ratio of ChCl to fructose increased from 1 to 4, and the 5-HMF yield sharply descended from 30.8% to 7.4%. This was ascribed to that a suitable content of ChCl promoted the conversion process from fructose to 5-CMF. It was also noted that high content of ChCl have a promoting function on the total yield of 5-HMF and 5-CMF.

Table 2. Effect of fructose concentration to the conversion of fructose into 5-CMF & 5-HMF

| Fructose : ChCl weight ratio | $Y_{5\text{-CMF}}$ (%) | $Y_{5\text{-HMF}}$ (%) | Total (%) | C_{fructose} (%) |
|------------------------------|------------------------|------------------------|-----------|---------------------------|
| 1:1 | 17.4 | 30.8 | 48.2 | 87.3 |
| 1:2 | 25.8 | 21.9 | 47.7 | 95.5 |
| 1:3 | 32.6 | 18.6 | 51.2 | 100 |
| 1:4 | 50.3 | 8.1 | 58.4 | 100 |
| 1:5 | 50.2 | 7.4 | 57.9 | 100 |

Reaction conditions: 5 mmol (0.9g) fructose, 5 mmol $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, 30 ml MIBK, 120 °C, 5 h

Other kinds of ionic liquids, such as [BMIM]Cl and [BMIM]BF₄, were applied to the comparison with ChCl-based DES in the

function of 5-CMF production, as shown in Table S2. 5-CMF was obtained with a best yield of 50% in the presence of ChCl while the yield was only 6% and 0% in the cases of [BMIM]Cl and [BMIM]BF₄ respectively. It indicated that the composition of DES reaction system was crucial for the production of 5-CMF from fructose.

As our previous works shown, the fructose firstly converted into 5-HMF rapidly, and then transformed into 5-CMF. In order to investigate the forming process from 5-HMF to 5-CMF, a series of experiments were conducted with 5-HMF as raw material. As demonstrated in Table S3, low yield of 5-CMF and 5-HMF conversion were obtained with the addition of independent $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ or ChCl (entry 1, 4). However, around 100% 5-HMF conversion and 86% 5-CMF yield were obtained in the presence of both $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ and ChCl. Moreover, HCl was detected from the MIBK extraction solvent, which formed in the DES with the existence of both $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ and ChCl. It was inferred that 5-CMF could be produced from 5-HMF catalyzed by HCl. Unfortunately, the source of chloride anions in 5-CMF could not be exactly determined.

The continuous solvent extraction method which was highlighted by Mascall has achieved an effective improvement in the conversion of carbohydrates into 5-CMF.⁶ When MIBK was used as the extractant and formed a biphasic system with DES, as shown in Figure S3, 5-CMF yield decreased significantly with an enhanced 5-HMF yield, whereas the total yield of furfuran products was maintained at about 60%, corresponded with our aforementioned work. This could be explained by that the transfer of extraction solvent would lead to the loss of HCl in the organic phase, which might affect the further halogenation reaction of 5-HMF in MIBK. Moreover, those experiment results indicated that the organic extraction solvent was also participated in the process of 5-CMF production.

To study the recycle performance of the catalyst, the catalyst and ChCl were reused with water-washing and distillation after separated from the reaction mixture (the HPLC analysis result shown in Figure S4). A slight descending of 5-CMF yield was observed in the successive 2 cycles. A 5-CMF yield of 41.3% and a 5-HMF yield of 11.7% were still achieved after 5 h in the 3rd run.

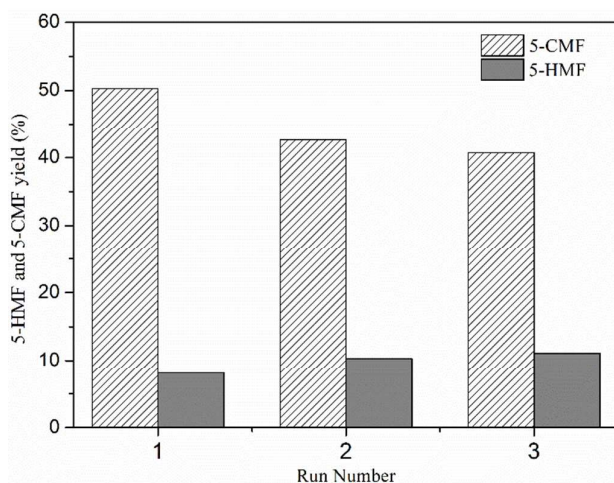


Figure 3. Performance of recycled catalyst mixture. Reaction conditions: 5mmol (0.9g) fructose, 4.8g catalyst mixture (ChCl and $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$), 30ml MIBK, 120 °C, 5 h. The used catalysts mixture were washed by deionized water and dried in a rotary evaporator before reutilization

In addition to fructose, other biomass derived carbohydrates were also tested to produce 5-CMF in this MIBK/DES biphasic system. As shown in Figure 3, 5-CMF yields of 16.93%, 22.66% and 17.86% were obtained with glucose, inulin and sucrose as substrates, respectively. Compared with the high yield of 5-CMF achieved from fructose, these carbohydrates showed low reaction activity in the production of 5-CMF. It was probably due to that those carbohydrates could not convert into 5-HMF easily in the DES-biphasic system, in which the isomerization into fructose was not favored and the formation of 5-CMF was further impeded. Thus, our further study would focus on the conversion of different types of carbohydrates into 5-CMF with high yields in a green DES-biphasic system.

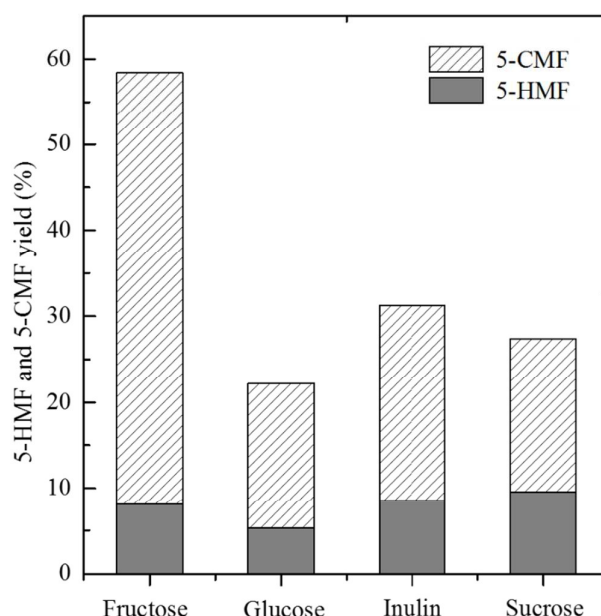


Figure 4. Conversion of various carbohydrates into 5-CMF & 5-HMF in the presence of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ and ChCl. Reaction conditions: 0.9 g different carbohydrate, 5 mmol $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, 25 mmol ChCl, 30 ml MIBK 120 °C, 5 h

Conclusions

In this work, 5-CMF was effectively produced in a DES/MIBK biphasic reaction system. Although the 5-CMF yield obtained in this work was lower than the yield reported by other literatures, the major advantages of the present work was that a combination of metal chlorides and ChCl was suitable for the conversion of fructose into 5-CMF, without the large amount of hydrochloric acid. This method provided a moderate and green condition for the production of 5-CMF with a high yield. In conclusion, this study presents a new green method to efficiently produce important platform chemicals 5-CMF from biomass derived carbohydrates under a one pot/two-step mild biphasic reaction system.

Acknowledgements

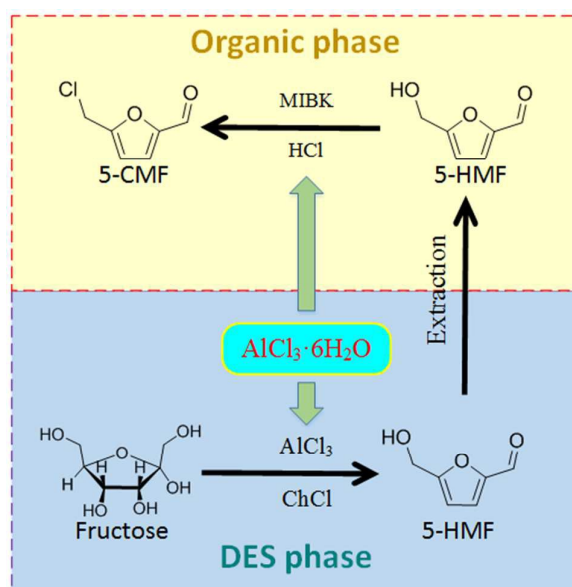
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Graphical Abstract



5-Chloromethylfurfural (5-CMF) was effectively prepared from fructose and other carbohydrates, in a biphasic reaction system, which was composed of methyl isobutyl ketone (MIBK) and deep eutectic solvent (DES) with catalyst of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$.