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A novel route towards high yield 5-hydroxymethylfurfural from fructose catalyzed by a mixture of Lewis and Brönsted acids†

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We have developed an effective route for obtaining 5-hydroxymethylfurfural with a yield of 92.6 mol% from the dehydration of fructose in *N*,*N*-dimethylformamide using a mixture of $AlCl_3$, H_2SO_4 and H_3PO_4 as catalyst. The NMR analysis showed the intermediate formed among fructose, $AlCl_3$ and H_3PO_4 plays an important role in the novel result.

In recent years, the hydrolysis and dehydration of carbohydrate-based biomass to 5-hydroxymethylfurfural (5-HMF) is viewed as a promising way to utilize renewable resources and therefore deserves much attention. Among the tested carbohydrates, fructose is confirmed to be the most direct precursor towards the formation of 5-HMF.[1] To achieve a high yield of 5-HMF from fructose, the selection of a suitable acid catalyst and solvent is primarily considered.

Almost all types of the acids, including inorganic/organic liquid Brönsted acids, metal salts and their oxides, zeolites, heteropoly acids and their salts, cation exchange resins, as well as the newly emerged ionic liquids have been applied and showed different reactivity in the dehydration of fructose.[2–6] In addition to the catalyst, the selection of an ideal solvent is of the same importance. At least three aspects should be considered: (1) being beneficial to the dissolution of fructose; (2) being beneficial to obtaining a high 5-HMF yield; (3) being beneficial to the post-separation of 5-HMF. So far, it is well known that some polar aprotic solvents like dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and 1,4-dioxane are the most favourite solvents for the dehydration of fructose because they have considerable solubility to fructose and can inhibit the decomposition of 5-HMF to levulinic acid as occurred in the presence of water and other protic solvents.[5,7–9] The application of imidazolium-based ionic liquids and other deep eutectic mixtures as dual acid catalyst and solvent may be the most effective strategy for the dehydration of fructose as well as other carbohydrates.[4,10–12] However, their high boiling points and excellent miscibility with 5-HMF bring a huge challenge to the post-separation of 5-HMF from the reaction bulk, which seems less feasible for industrialization even though much progress has been made in the separation of 5-HMF from ionic liquids.[4,11,13]

In the present article, we focus on developing a process for the industrial manufacture of 5-HMF from fructose at lower cost. To reach this goal, we limited the catalyst and the solvent within the conventional chemicals. The preliminary study was started by conducting the dehydration of fructose using $AlCl_3$, one of Lewis acids, as the catalyst in various aprotic polar solvents (Table 1). As expected, ionic liquid 1-methyl-3-butyl imidazolium chloride ([BMIM]Cl) exhibited the best performance, with the highest 5-HMF yield of 58.5 mol% within 30 min under the reaction conditions used in this work. 1,4-Dioxane was found to be poorly active, with a 5-HMF yield of only 30.7 mol% even though the reaction time was extended to 60 min. While conducted in DMSO and DMF solvents, the yield of 5-HMF were similar, with the value of 48.3 mol% and 44.3 mol% at 120 °C (entries 4 and 7 in Table 1), respectively.

As a typical aprotic polar solvent, DMSO was frequently applied as a reaction medium for the dehydration of fructose due to its high solubility to fructose (38.2 w% at 25 °C as shown in Table 1) and effectiveness in obtaining a high yield of 5-HMF.[6,9,15] Compared with DMSO, DMF has a boiling point lower by 36.2 °C, which means much energy may be saved if vacuum distillation is used for the subsequent concentration of 5-HMF when using DMF as the solvent. Moreover, it is generally known that even a trace amount of DMSO in the products will introduce unpleasant smell which is hard to remove. Based on the above two reasons, we finally chose DMF as the dehydration medium for fructose instead of DMSO, although a slightly lower

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Table 1 Dehydration of fructose in various aprotic polar solvents[c]

	Solvent								
Entry	Name	Volume (ml)	Boiling point (°C)	Solubility to Fructose[a] (w%)	Fructose (g)	Temperature (°C)	Time (min)	Fructose conversion (mol%)	5-HMF yield (mol%)
1	[BMIM]Cl	2 g	275	56[b]	50 mg	120	30	>99	58.5
2	1,4-Dioxane	100	101.1	0.60	1	101	30	88	26.6
3		100			1	101	60	92	30.7
4	DMSO	100	189.0	38.2	5	120	30	>99	48.3
5	DMF	50	152.8	15.5	5	120	30	>99	40.4
6		80			5	120	30	>99	42.0
7		100			5	120	30	>99	44.3
8		100			5	100	30	97	36.3
9		150			5	120	30	>99	39.1
10		200			5	120	30	>99	38.7

[a] Detected at 25 °C. [b] Adapted from ref. 14, data detected at 110 °C. [c] Note: $AlCl_3$ was applied as the catalyst, with the amount equal to 26.9 mol% of fructose.

yield of 5-HMF might be achieved. Further optimization showed that an initial concentration of fructose as 50 g l^{-1} (5 g of fructose dissolved in 100 ml of DMF, entry 7 in Table 1) was the most preferred.

In the next step, we tested the catalytic reactivity of the acids $AlCl_3$, HCl, H_2SO_4 and H_3PO_4 for the dehydration of fructose to 5-HMF in DMF solvent, and found that either a Lewis acid or Brönsted acid alone failed to obtain a 5-HMF yield higher than 60 mol% (Fig. 1). We therefore further tried the mixture of Brönsted and Lewis acids as a catalyst system, which has been reported to have positive synergistic effect on many catalytic reactions.[16,17] As expected, a mixture of $AlCl_3$ with either H_2SO_4 or H_3PO_4 was more effective for the dehydration of fructose to 5-HMF, with an increase in the yield of 5-HMF by 10 mol% to 15 mol% compared with using $AlCl_3$ alone.

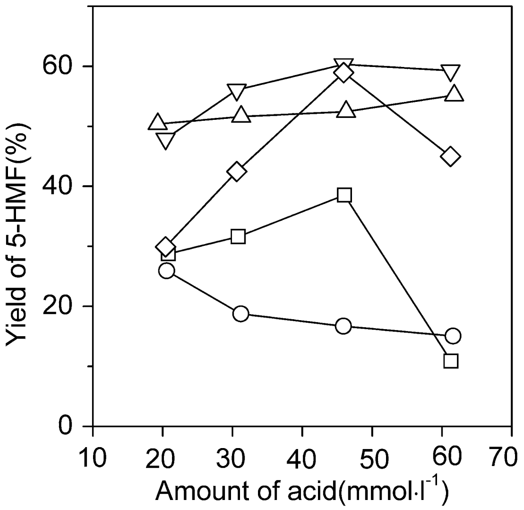


Fig. 1 Effects of the type and amount of the acids on the yield of 5-HMF from fructose. Reaction conditions: DMF 100 ml, fructose 5 g, 120 °C, 20 min. △ Hydrochloric acid; ☐ Sulfuric acid; ○ phosphoric acid; ∇ Sulfuric acid + $AlCl_3$ (7.49 mmol); ◇ phosphoric acid + $AlCl_3$ (7.49 mmol).

Inspired by Harmer's work[17] in which a mixture of phosphoric-sulfuric acid showed surprising performance in the transformation of biomass to sugars, we further investigated the synergistic effect of $AlCl_3$, H_2SO_4 and H_3PO_4 on the dehydration of fructose to 5-HMF in DMF. As shown in Fig. 2, the yield of 5-HMF was even higher when fructose was catalyzed by a combination of $AlCl_3$, H_2SO_4 and H_3PO_4. We investigated the mixtures with a range of S/P ratio (S/P denotes the molar ratio of H_2SO_4/H_3PO_4) from 0.5 to 2.0 as well as L/B ratio (L/B denotes the molar ratio of $AlCl_3/(H_2SO_4 + H_3PO_4)$) from 0 to 0.33. Over this range, a 5-HMF yield as high as 92.6 mol% was achieved at $S/P = 2/3$ and $L/B = 0.15$ (*i.e.*, $AlCl_3 : H_2SO_4 : H_3PO_4$ was $1 : 2.7 : 4$). The yield could be repeated well while the reaction was scaled up to 5–25 times in 1–5 l stirred reactors. To our best knowledge, this is a very high yield of 5-HMF from fructose by using conventional solvents and catalysts.

Owing to the application of the relatively lower boiling DMF as the solvent, we are able to remove the solvent and obtain pure

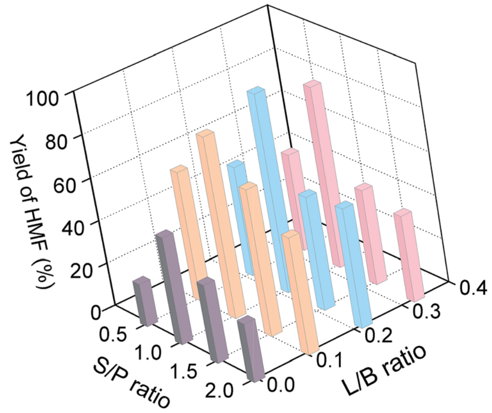


Fig. 2 Synergistic effect of $AlCl_3$, sulfuric acid and phosphoric acid on the yield of 5-HMF from fructose. Reaction conditions: DMF 100 ml, fructose 5 g, 120 °C, 20 min. S/P denotes the molar ratio of H_2SO_4/H_3PO_4; L/B denotes the molar ratio of $AlCl_3/(H_2SO_4 + H_3PO_4)$.

5-HMF more easily by simple distillation. After reaction, a given amount of Na_2CO_3 was added to neutralize the reaction solution, and then DMF was completely removed by reduced pressure distillation at 120 °C to achieve brown viscous slurry. Further vacuum distilling the slurry at 10–100 Pa at raised temperature of 150–180 °C, a light yellow crystal of 5-HMF with the purity higher than 95% was obtained. Nevertheless, the recovery of 5-HMF only reached 20–30%, which is due to the strong interaction between 5-HMF and the byproduct of humic acid, sulfuric acid or phosphoric acid that prevents 5-HMF from evaporation from the reaction solution. However, by treating the slurry with our previous developed EIVRD process,[13] in which nitrogen gas was introduced to intensify the vacuum evaporation of 5-HMF, a much higher recovery of 85–90% of 5-HMF with the purity around 95% was obtained. For comparison, the slurry was also extracted with various solvent combinations for optimization and 1 : 1 molar ratio of ethyl acetate to hexane achieved the best 5-HMF recovery of 98.7% with the purity less than 70% after evaporation of the solvents. Considering that it is very difficult for 5-HMF to crystallize from conventional solvents due to its low melting point (*ca.* 33.6 °C) and excellent miscibility with most organic solvents, obtaining final 5-HMF with high purity by solvent extraction method is challenging.

Although we lack a clear picture of why a mixture of $AlCl_3$, H_2SO_4 and H_3PO_4 is a distinctively effective catalyst for the dehydration of fructose to 5-HMF in DMF solvent, we are able to offer some insights into the mechanism. As we know, D-fructose exists as a mixture of five tautomeric forms in an aprotic solvent, *i.e.* (a) open-chain; (b) α-D-fructofuranose ($F_{5\text{-}\alpha}$); (c) β-D-fructofuranose ($F_{5\text{-}\beta}$); (d) α-D-fructopyranose ($F_{6\text{-}\alpha}$); (e) β-D-fructopyranose ($F_{6\text{-}\beta}$). Recent work from NMR and FT-IR techniques as well as molecular dynamics calculations has confirmed that only fructofuranoses ($F_{5\text{-}\alpha}$ and $F_{5\text{-}\beta}$) can lead to the formation of 5-HMF, while pyranose isomers may lead to the formation of humins.[3,6,8,18]

In our research, we first investigated the distribution of cyclic tautomers of fructose in DMF-d_7 solvent with or without different combinations of acids by ^{13}C-NMR (Fig. 3). The results showed that the composition of the four tautomers in pure DMF-d_7 was about 10% ($F_{5\text{-}\alpha}$): 27% ($F_{5\text{-}\beta}$): 61% ($F_{6\text{-}\beta}$): 3% ($F_{6\text{-}\alpha}$) (Table S2†). The addition of H_3PO_4 or $AlCl_3$ shifted the equilibrium from $F_{6\text{-}\beta}$ to $F_{5\text{-}\beta}$ and $F_{5\text{-}\alpha}$ isomers, whereas sulfuric acid tended to transfer $F_{5\text{-}\alpha}$ to $F_{5\text{-}\beta}$ isomer but little transformation of $F_{6\text{-}\beta}$ to $F_{5\text{-}\beta}$ isomer occurred, indicating that too strong Brönsted acidity is not preferred to the formation of fructofuranose. The result is also consistent with the reports that Lewis acids possess better catalytic ability than Brönsted acids in the reaction.[4,11] Although H_2SO_4 and H_3PO_4 are typical Brönsted acids, they caused different effects on the transformation of isomers, which suggests that not only protons from phosphoric acid participate in the isomerization and dehydration of fructose.

By further comparing the chemical shifts of carbon atoms in fructose, we found that the chemical shifts of all the carbon atoms from $F_{5\text{-}\beta}$ isomer moved to higher fields by 0.6–1.4 ppm in the presence of both H_3PO_4 and $AlCl_3$, whereas single addition of H_2SO_4, H_3PO_4 or $AlCl_3$ changed them far less (Table S3†).

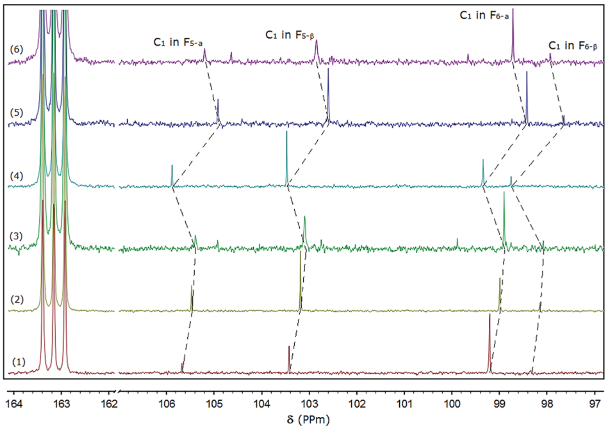
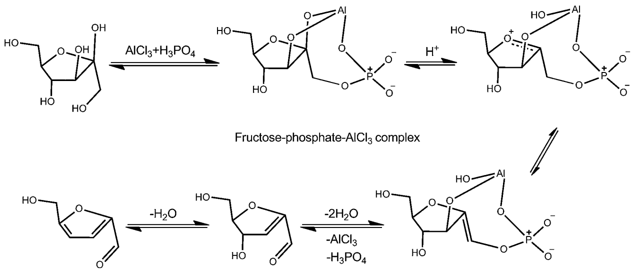


Fig. 3 C-1 chemical shifts of fructose isomers in DMF-d_7 in the presence of different combinations of acids. (1) fructose; (2) fructose + H_3PO_4; (3) fructose + H_2SO_4; (4) fructose + $AlCl_3$; (5) fructose + H_3PO_4 + $AlCl_3$ and (6) fructose + H_3PO_4 +H_2SO_4 + $AlCl_3$.



Scheme 1 Speculated pathway from fructose–phosphate–$AlCl_3$ complex to 5-HMF.

The same phenomenon was also found on the chemical shifts of hydrogen atoms in $F_{5\text{-}\beta}$ isomer by ^{1}H-NMR analysis (Table S4†). We therefore deduce that some stronger interactions should have formed among fructose, H_3PO_4 and $AlCl_3$. According to the research on the glycose–phosphate–metal interactions,[19] we propose a possible intermediate during the dehydration of fructose, as presented in Scheme 1. Owing to the formation of the fructose-phosphate-$AlCl_3$ complex, the fructofuranose can stably exist in the reaction system, which shifts the balance to the formation of fructofuranose from fructopyranose. The formed complex further dehydrates along the pathway to 5-HMF in the presence of high proton concentration provided by H_2SO_4 to obtain a high yield of 5-HMF.

It should be pointed out that the discussion on the mechanism is rather preliminary due to the complexity of the reaction system and the limitation of the analysis techniques. To further reveal the mechanism of the synergistic effect of sulfuric acid, phosphoric acid and $AlCl_3$ on the dehydration of fructose, more advanced experimental *in situ* ^{13}C, ^{1}H, ^{31}P, ^{27}Al-NMR, and *in situ* FTIR may be needed.

Conclusions

We have developed a simple and effective method to convert fructose to 5-HMF using DMF as the solvent and a mixture of

$AlCl_3$, H_2SO_4 and H_3PO_4 (optimized mole ratio of 1 : 2.7 : 4) as the catalyst, by which a 92.6 mol% yield of 5-HMF with a nearly 100% conversion of fructose could be achieved at 120 °C in 20 min. By vacuum distillation, a final light yellow crystal of 5-HMF with purity around 95% was obtained. ^{13}C-NMR and ^{1}H-NMR analysis showed that the existence of H_3PO_4 or $AlCl_3$ promotes the transformation of $F_{6\text{-}\beta}$ isomer of fructose to $F_{5\text{-}\beta}$ and $F_{5\text{-}\alpha}$ isomers, while H_2SO_4 is favourable to the transformation of $F_{5\text{-}\alpha}$ to $F_{5\text{-}\beta}$ isomer. The novel catalytic reactivity may be explained that the complex formed by $AlCl_3$, H_3PO_4 and fructose accelerates the dehydration of fructose along the pathway to 5-HMF in the presence of high proton concentration provided by H_2SO_4.

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