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Microwave-Assisted Production of 5-Hydroxymethylfurfural from Glucose

Jameson Brett Mason and Yujie Sun*[a]

Among many biomass-derived intermediate compounds, 5-hydroxymethylfurfural (HMF) has been regarded as a platform chemical because it can be used to produce numerous valuable products. However, the difficulty of HMF isolation from reaction media coupled with its poor stability have significantly inhibited its large-scale production and application. In this work, we report a single-step process for the direct production of HMF from glucose using green chemical methods. Optimized glucose isomerization and dehydration under microwave irradiation achieved a respectable HMF yield (70%) using a biphasic solvent mixture (water/THF), high glucose concentration (30% w/v), catalytic amounts of $AlCl_3$ (5 mol%) and HCl (15 mol%). The reaction can be completed within minutes at 165 °C. Overall, our microwave-assisted strategy enables the direct conversion of commercially available glucose to the highly valuable platform chemical HMF without the use of expensive solvents or catalysts, suggesting an economically attractive approach for upgrading carbohydrates.

Introduction

Fossil-based materials have been the predominant carbon source to produce fuels, solvents, polymers, and many other commodity chemicals for the past century or more. With rising concern over global warming, overall health of the environment, and availability of energy, it has become necessary to find sustainable and carbon-neutral sources to replace fossil-based chemicals. One such source is biomass, whose presence in nature is abundant, renewable, and carbon neutral. Hence, biomass has been widely accepted as a promising carbon source to produce value-added chemicals.[1–3] Due to the complex nature of raw biomass, many biomass-derived intermediate compounds require further upgrading to make commodity chemicals. Among many biomass-derived intermediates, 5-hydroxymethylfurfural (HMF) has drawn a great deal of attention because it can be upgraded to a variety of valuable products, including biodegradable plastic monomers,[4,5] adhesives,[6] and fuels, as well as alcohols and acids that are useful intermediates for wetting agents, solvents, and pharmaceuticals.[7]

HMF is commonly derived from monosaccharides such as fructose and glucose.[8] There are many benefits of using fructose as the feedstock for HMF production because only dehydration is required. However, fructose is a costly feedstock whose main source (fruit) is already in high demand in other markets. Conversely, glucose is a common component in plant waste that is mostly discarded, and its price tends to be lower than that of fructose. The decomposition of cellulose to glucose must be considered a separate reaction, however. Consequently, it appears very appealing to explore the production of HMF directly from glucose.

Different from the direct dehydration of fructose to produce HMF, an additional isomerization step is required for glucose to transform to fructose prior to the final dehydration step. The glucose isomerization step could be catalysed by Lewis acids or Bronsted bases while the subsequent dehydration step is usually catalysed by Bronsted acids. In recent years, many efforts have been made to produce HMF from glucose (Table 1). For instance, Tagaki *et al.* (entry 1) reported the use of hydrotalcite (HT) and Amberlyst-15 catalysts in DMF to achieve 73% conversion of glucose and 42% yield of HMF from 73% glucose within nine hours.[9] Intermediate products such as anhydroglucose and fructose were also produced. Unfortunately, the co-utilization of a Bronsted acid and a Bronsted base made the reproduction of their results difficult. When tin-vanadium phosphate (Sn-VPO, entry 2) was employed as a Lewis acid (LA) and Bronsted Acid (BA) catalyst, a 74% yield of HMF could be obtained from glucose in DMSO.[10] Significantly, TiO_2 nanoparticles coupled with microwave irradiation (entry 3) in DMSO produced 37% HMF within 5 minutes, highlighting the benefit of using a microwave reactor to drastically reduce reaction times.[11] A high yield of 80% HMF from a relatively high [glucose] in dimethylacetamide (DMA) was obtained at a low temperature using a simple metal chloride ($CrCl_3$, entry 4).[12] However, chromium is extremely toxic, and the boiling point of DMA is too high to allow for easy isolation of HMF from the reaction mixture.

High boiling point solvents are not ideal for HMF production despite high yields in DMSO and DMA. This due to difficulty of HMF isolation. However, pure water is also not ideal. Polycondensation produces insoluble humins and rehydration generates levulinic acid and formic acid. In pure aqueous media these reactions are favoured. A favourable

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[a] *J. B. Mason, Dr. Y. Sun*
Department of Chemistry,
University of Cincinnati,
Cincinnati, OH, USA, 45220
E-mail: yujie.sun@uc.edu

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Table 1. Summary of the representative conditions and yields for the conversion of glucose to HMF.

entry	catalyst (LA/BA)	solvent	T (°C)	t (min)	% w/v	Conversion (%)	Yield (%)	Ref.
1	HT/Amberlyst-15	N,N-DMF	80	540	3	73	42	[9]
2	Sn-VPO	DMSO	110	360	–	100	74	[10]
3	TiO2 NP[b]	DMSO	120	5	5	–	37	[11]
4	$CrBr_3+LiBr$[a]	DMA	100	360	10	–	80	[12]
5	Sn-beta/HCl	$NaCl_{(aq)}$/THF	180	70	10	79	57	[14]
6	LiCl/PS-PEG-OSO_3H	water/DMSO	120	90	–	–	84	[15]
7	K10 clay-Cr	[BMIM]Cl/DMSO	120	120	3.6	99	56	[16]
8	$AlCl_3$/HCl [a]	$NaCl_{(aq)}$/SBP	170	40	5	91	68	[17]
9	Zr-MCM-41	H_2O/MIBK	175	150	3	73	19	[18]
10	Sn-W oxide	water/THF	120	1080	3.6	–	48	[19]

[a] homogeneous reaction [b] performed under microwave irradiation.

solution is the use of a biphasic system. Recently, Qu *et al.* used a biphasic system coupled with sulphate and ZrO_2 catalysts to produce HMF in a 61% yield.[13] A biphasic system of sat. aqueous NaCl and THF with a solid Sn-based LA and homogeneous BA catalysts (entry 5) produced a yield of 57% and 79% glucose conversion.[14] This biphasic solvent mixture favours the extraction of HMF from the aqueous phase into the organic phase, thus limiting the formation of by-products. The low boiling point of THF also increases the ability to isolate HMF from the solution at later stages.

However, a biphasic system is not the only way to improve HMF yield. A polymer-based BA catalyst (entry 6) and DMSO $_{(aq)}$ can be used to produce a high yield of HMF (84%). This is due to the strong hydrogen-bonding character of DMSO, which serves to stabilize HMF and reduce its interaction with water molecules.[15] However, the synthesis for the solid BA catalyst is both expensive and time-consuming, thus scalability is limited in addition to problems associated with including DMSO.

Fang *et al.* (entry 7) incorporated the LA Cr^{3+} into K10 clay in ionic liquid and DMSO for a high glucose conversion of 99% that yielded only 56% HMF. The highly charged LA unit appears to affect the conversion of glucose.[16] This is corroborated by Pagan-Torres *et al.* (entry 8) who found that the hardness/softness of the LA affected the conversion of glucose to fructose. They found that Al^{3+} (a hard Lewis acid) interacts strongly with the oxygen atoms of the hydroxyl groups in glucose, which are hard Lewis bases. This would also explain why glucose conversions are high when Cr^{3+} is used as the LA. $AlCl_3$ paired with HCl in a biphasic solution of $NaCl_{(aq)}+$*sec*-butylphenol (SBP) yielded 68% HMF with 91% glucose conversion[17] while entries 9 and 10 leave much to be desired.[18,19] More recently, Guo *et al.* was able to obtain a yield of 66% HMF using a biphasic system of H_2O/methyl isobutyl ketone (MIBK) with $AlCl_3$ and HCl catalysts.[20]

While much of this research shows promise, the current methods for producing HMF in high yield are neither economically feasible on a large scale nor do they use green methods of production. Reaction times are often several hours, and glucose concentration is extremely low, meaning large quantities of solvent will be required.

To develop an effective, low-cost strategy for HMF production directly from glucose with potential for large-scale application, our group has initiated several projects focusing on microwave-assisted isomerization and dehydration of monosaccharides. Different from conventional heating methods, microwave irradiation results in simultaneous and even heating of the reaction medium, which usually enables shorter reaction time and fewer side-products.[21] Because of its intrinsic advantages, microwave irradiation is widely recognized as a green heating approach that has been successfully applied in laboratory and industry.[22,23] Herein, we report a convenient and low-cost microwave-assisted strategy to produce HMF. Using an inexpensive biphasic solvent mixture, we obtained a respectable HMF yield (70%) from glucose with a concentration substantially higher than those typically adopted in previous studies.

Results and Discussion

Microwave-assisted glucose isomerization and dehydration

To effectively produce HMF from glucose while simultaneously minimizing its further interaction with catalysts most likely dissolved in the aqueous phase, it is advantageous to extract HMF from the aqueous phase to an organic phase during the reaction. Hence, an aqueous/organic biphasic solvent system is ideal. In addition, with the aim of convenient separation of HMF from the reaction mixture, organic solvents with high boiling points, such as DMA and DMSO, are unappealing options. We recently reported that THF coupled with a saturated NaCl aqueous solution could result in a biphasic solvent mixture which led to decent HMF yield from microwave-assisted fructose dehydration.[24] Herein, we demonstrate that a similar biphasic solvent system can also be used for HMF production from glucose under microwave irradiation. It should be noted that the presence of chloride anion is beneficial for the stabilization of reaction intermediates from glucose isomerization and dehydration to HMF.[25]

With the goal of large-scale production in mind, we aim to produce HMF from glucose at high concentration. Hence, 30% w/v glucose was chosen as the target concentration, which is substantially higher than those of all the previously reported systems (Table 1).

There are several factors that play critical roles in determining the final HMF yield from glucose. These are the catalyst, catalyst concentration, reaction duration, temperature, and the cation and anion of the inorganic salt. These factors have been systematically investigated in this study.

Inspired by previous reports and following the green chemistry principles, the low-cost and benign Lewis acid and Bronsted acid catalysts $AlCl_3$ and HCl were chosen for glucose isomerization and dehydration, respectively. We systematically varied the amounts of $AlCl_3$ and HCl relative to the mole of glucose to derive the optimal ratios of $AlCl_3$ and HCl versus glucose. The microwave-assisted reaction was set at 160 °C for 3 minutes and each reaction was performed at least in duplicate. As shown in Figure 1 and Table S1, the highest yield of HMF was 61 %, which could be obtained in two combinations of $AlCl_3$ and HCl: (i) 5 mol % $AlCl_3$ with 15 mol % HCl and (ii) 15 mol % $AlCl_3$ with 5 mol% HCl. To limit waste containing Al^{3+}, the subsequent optimization would focus on the former combination, 5 mol % $AlCl_3$ with 15 mol % HCl. An image of the reaction vessel post microwave irradiation (Figure S1) presents two distinct layers that show the separation of organic products in the top darker layer from the bottom aqueous layer primarily containing acid catalysts. It should be noted that such a yield of HMF from glucose at high concentrations (30 w/v%) has never been reported, strongly suggesting the potential of our microwave-assisted biphasic system for large-scale production of HMF from glucose.

Effect of the reaction duration and temperature on HMF yield

Next, we varied the duration of microwave irradiation and the reaction temperature to further improve the yield of HMF. Different from fructose dehydration to produce HMF, higher temperature is required due to the better stability of the six-member ring in glucose. We varied the microwave treatment from 1 minute to 10 minutes spanning the temperature range from 150 °C to 170 °C. This two-dimensional optimization allowed us to obtain HMF yields shown in Figure 2 and Table S2. It is apparent that reaction time and temperature have much more linear effects on HMF yield compared to the concentrations of acid catalysts. The maximum HMF yield (70 %) was achieved at 165 °C for 2.5 minutes microwave irradiation. There is a sharp decrease in HMF yield if the reaction temperature is lower than 160 °C or reaction time less than 2 minutes. Increasing reaction temperature to 170 °C will also lead to a decrease in HMF yield, probably due to more side reactions taking place at high temperature. In addition, elongating the reaction time beyond 2.5 minutes also resulted in decreased HMF yield, most likely because of the further reaction of produced HMF with acid catalysts to form by-products such as insoluble humins. It agrees with the observation that more precipitates were produced at higher temperature and longer reaction time.

Salt effects on HMF yield

Inorganic salts likely play two important roles in the microwave-assisted production of HMF from glucose. First, the aqueous solution of inorganic salts helps to create a biphasic solvent mixture, which facilitates the separation of HMF in the organic phase from the aqueous phase. Second, inorganic cations may also act as Lewis acids while inorganic anions may stabilize carbocation intermediates or catalyze side reactions.[26,27] Furthermore, it has been recently proposed that inorganic salts contribute to the increase in HMF yield by enhancing the fructose dehydration step in organic solvents.[28,29] In order to elucidate whether a certain combination of inorganic cation and anion would result in an optimal HMF yield in our microwave-assisted transformation from glucose, we decided to systematically vary the inorganic cations and anions used in the reaction.

Acting as a Lewis acid, alkaline and alkaline earth cations can interact with oxygen atoms in glucose, fructose, and HMF

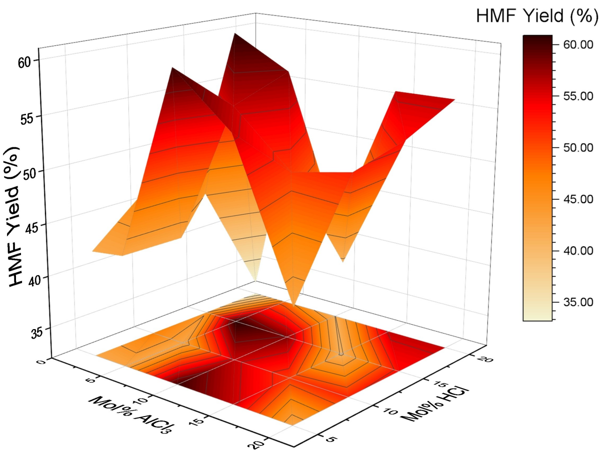

Figure 1. HMF yields from microwave-assisted glucose conversion with varying concentrations of $AlCl_3$ and HCl.

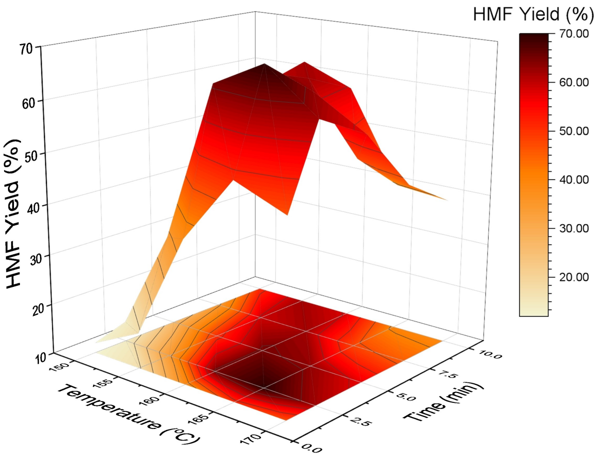

Figure 2. HMF Yields from microwave-assisted glucose conversion with varying time and temperature.

to different extent depending on their size, charge density, and hardness. Because the concentrations of these inorganic salts are substantially larger than that of $AlCl_3$, these inorganic cations will have higher chance to interact with organic substrates than Al^{3+} does. As shown in Figure 3, keeping the chloride anion unchanged, Na^+ exhibited the best performance in HMF yield. Li^+ has the smallest size and its strong interaction with oxygen atoms in organic substrates may prohibit their further interaction with other catalysts for the desirable isomerization and dehydration steps. K^+ is larger in size and may sterically hinder Al^{3+} from interacting with organic substrates effectively. Mg^{2+} has been reported to favour HMF degradation to levulinic acid, which may also explain the significant drop in yield.[29] Consistent with this hypothesis, reducing the Mg^{2+} to 0.5 M substantially boosted the HMF yield to 52 %, albeit still lower than that using Na^+. Among these tested cations, Na^+ has less charge density than Li^+, Mg^{2+}, and Al^{3+}, and therefore may be the right size not to hinder the interaction of Al^{3+} with organic substrates, collectively leading to the best HMF yield.

Previous research also indicates inorganic anions play an important role in the transformation of glucose, fructose, and HMF.[30] Therefore, we next investigated the impact of inorganic anions for glucose conversion to HMF while keeping the cation Na^+ unchanged (Figure 4). The use of $NaHCO_3$ resulted in a significant increase in pH which suppressed the solubility of Al^{3+}. It would effectively deactivate this Lewis acid and hence is detrimental to HMF production, supporting the idea that pH plays a key role in controlling the Lewis acidity of metal halides in aqueous solution.[31] Overall, no HMF was detected when $NaHCO_3$ aqueous solution was used. Similar result was obtained when $Na_2S_2O_3$ was used, but for different reasons. $Na_2S_2O_3$ degrades in the presence of HCl according to the following reaction:

$$Na_2S_2O_3 + 2\ HCl \rightarrow 2\ NaCl + S + SO_2 + H_2O$$

Not only does the anion degrade but it also consumes HCl which is the Bronsted acid catalyst for fructose dehydration to HMF. The relatively low HMF yield resulting from the use of Na_2SO_4 may be due to the stronger interaction of sulfate anion with hydrogen atoms in the alcohol groups of glucose, fructose, and HMF. While this could be beneficial for their solvation, it might slow the formation of the carbocation intermediate and hence dehydration, consequently resulting in a lower HMF yield. It is also possible the sulfate anion may favor other side-reactions. Out of the selected anions, it is apparent halogen anions exhibit the best performance, for which chloride is better than bromide. The ^1H NMR spectrum of the final HMF product obtained from the microwave reaction mixture is shown in Figure S2, confirming the identity of the desirable product.

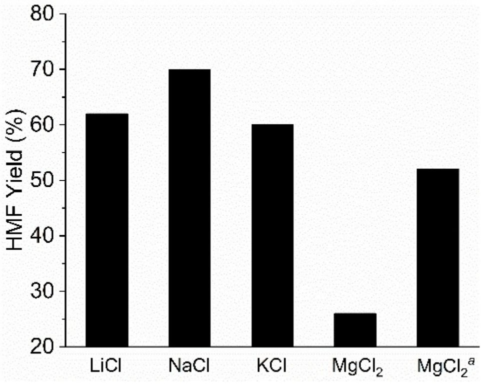

Figure 3. HMF yields obtained in the presence of varying inorganic cations with a concentration of 1.0 M unless otherwise stated. Reaction condition: 30 % w/v glucose, 165 °C, 2.5 min, 5 mol % $AlCl_3$ and 15 mol % HCl. ^{a}0.5 M.

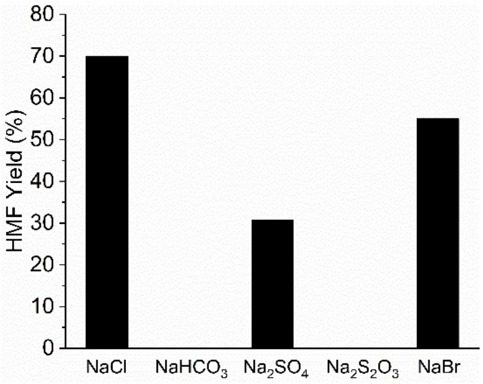

Figure 4. HMF yields obtained in the presence of varying inorganic anions with a concentration of 1.0 M. Reaction condition: 30 % w/v glucose, 165 °C, 2.5 min, 5 mol % $AlCl_3$ and 15 mol % HCl.

Conclusion

A green microwave-assisted strategy has been developed for the direct synthesis of HMF from glucose. With the unique advantages of microwave irradiation coupled with biphasic solvent mixture, after a systematic optimization of reaction conditions including time, temperature, and inorganic salts, we achieved superior HMF yields from highly concentrated glucose solution within minutes, representing a promising method for large-scale application. Our ongoing efforts focus on the downstream electrocatalytic upgrading of HMF to more valuable products, directly utilizing the microwave reaction mixture without HMF separation and purification.

Supporting Information Summary

Details on experimental procedure are outlined in the supporting information. A visual representation of the microwave reaction vessel after the reaction is complete, tables outlining collected reaction optimization data, and ^1H NMR data are presented.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 5-HMF · glucose · conversion · microwave · biphasic

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