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Efficient metal-free conversion of glucose to 5-hydroxymethylfurfural using a boronic acid

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Abstract 5-Hydroxymethylfurfural (HMF), which can be synthesized from hexose sugars without rearrangement of their carbon framework, is a key platform chemical that is readily convertible into fuels and chemicals that are now derived from petroleum. Methods to convert glucose, which is readily accessible from cellulose, to HMF typically rely on toxic heavy metals or harsh acidic conditions, and often give low yields or low selectivity. Here, we report on a mild, efficient, and metal-free process that uses an organocatalyst, 2-carboxyphenylboronic acid, along with small amounts of chloride ion to effect the selective transformation of glucose to HMF.

Keywords Biofuel · Boron · Cellulose · Green chemistry · Organocatalysis

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1 Introduction

Human society requires large amounts of energy. For much of history, energy was obtained exclusively from biomass sources, such as burning wood. More recently, the vast majority of our energy has come from the combustion of fossil fuels—petroleum, natural gas, and coal. These fuels are energy-rich and have been relatively easy to obtain. They are, however, non-renewable, and as the world population continues to grow and industrialize, more and more energy will be required to sustain human society. Indeed, petroleum reserves are estimated to become depleted during the 21st century and petroleum-based fuels are likely to become increasingly more expensive [1, 2]. Further, fossil fuels have a severe impact on the environment, both from extraction processes and from the pollutants produced from their combustion. Apart from energy, petroleum also currently supplies the vast majority of chemical feedstocks.

Lignocellulosic biomass, in the form of waste plant material and dedicated energy crops, represents a promising carbon source to replace petroleum as a source of both fuels and commodity chemicals [3-6]. In particular, 5-hydroxymethylfurfural (HMF), which is produced from the dehydration of hexose sugars, can be transformed into a wide variety of chemicals currently produced from petroleum, including fuels, solvents, and monomers for plastic production [7-12]. For example, 2,5-dimethylfuran, which is formed by the facile hydrogenolysis of HMF, is a liquid with higher energy density than ethanol (29.3 MJ/L versus 21 MJ/L), lower volatility (bp 92 °C versus 78 °C), and immiscibility with water, and serves well as an additive to or even a replacement for gasoline in engines [13, 14].

The production of HMF from fructose is facile. Glucose, however, represents a more practical and sustainable feedstock due to its accessibility from cellulose [15]. The transformation from glucose to HMF requires the isomerization of glucose to fructose, followed

by dehydration (Scheme 1). A number of catalysts have been developed to promote this transformation. Inexpensive mineral acids are effective at inducing sugar dehydration, though continuous extraction is often required to obtain high HMF yields [16-18]. Transition metal salts are more effective at promoting glucose isomerization and achieve higher yields [19-21]. Recently, solid acids, many of which combine Lewis acidic and Brønsted acidic sites, have received significant attention and have shown promise as easily recyclable catalysts for HMF production, achieving particularly high yields from fructose [22-30]. Still, these catalytic systems suffer from drawbacks that have prevented large-scale adoption, especially toxicity of the transition metals, requirements for expensive ionic liquid solvents or high temperatures, and relatively moderate yields from glucose for most solid-acid systems. Further, reactions to produce HMF entice side reactions, including the formation of complex polymeric byproducts, known as humins [31-35], and the hydrolysis of HMF to form levulinic and formic acids [36-38].

In 2011, Riisager and coworkers reported on the use of boric acid in ionic liquids as a metal-free method to convert glucose to HMF [39]. The reaction likely proceeds through borate esters with the 1,2- and 1,3-diols in glucose. In 2013, our group found that the methyl ester of 2-carboxyphenylboronic acid (2-CPBA) together with 2–3 equiv of magnesium chloride hexahydrate provides up to a 57% yield of HMF from glucose in dimethylacetamide [40]. Since then, boric and boronic acids, which have low toxicity and are milder reagents than are solid acids or mineral acids, have received only scant attention for HMF production [40-44]. Here, we report on a boronic acid catalyst that affords HMF in yields comparable to those from metal-catalyzed processes.

2. Methodology

2.1 General

Commercial chemicals were of reagent grade or better, and were used without further purification. All chemicals were from Sigma–Aldrich except for boronic acids, which were from Combi-blocks, and [BMIM]Cl, which was a generous gift of Merck KGaA. Reactions were performed in 1-dram glass vials heated in a VWR temperature-controlled shaker with shaking at 650 rpm.

2.2 Analytical methods

Reaction products were identified by HPLC and quantified using calibration curves generated from commercial samples. The concentrations of reactants and products were calculated from HPLC-peak integrations. In this analysis, an aliquot containing a known mass was removed from a reaction mixture. The aliquot was diluted with a known mass of deionized water, mixed thoroughly, and subjected to centrifugation at 10,000 RCF for 10 min to remove humins, and the supernatant was analyzed by HPLC. HPLC was performed with an Agilent 1200 system equipped with refractive index and photodiode array detectors. Analytes were applied to a Bio-Rad Aminex HPX-87H ion-exchange column (300 × 7.8 mm) with a 5 mM H₂SO₄ aqueous mobile phase at a flow rate of 0.6 mL/min and a column temperature of 65 °C.

2.3 Representative procedure for the synthesis of HMF from glucose

General procedure: Dextrose (99.6 mg, 0.553 mmol), 2-carboxyphenylboronic acid (92.4 mg, 0.557 mmol) were added to a 1-dram vial. A 1.0-mL solution of 0.19 M [BMIM]Cl in DMSO was added to the vial. The vial was capped, and the reaction mixture was heated at 95 °C for 2 h

in a heating block with shaking at 650 rpm. No effort was made to dry solvents or exclude O₂(g) from reaction mixtures.

Conversion of other sugars: The general procedure was followed, replacing dextrose with 0.55 mmol of the sugar.

Reactions in ionic liquid: The general procedure was followed, replacing the DMSO solution with 1.0 g of [BMIM]Cl.

Optimization screens: For the salt screen, sufficient salt to produce 1.0 mL of a 0.19 M solution was added to the vial along with the boronic acid and glucose prior to the addition of 1.0 mL DMSO. For the solvent screen, sufficient [BMIM]Cl to produce 1.0 mL of a 0.19 M solution was added to the vial, and the appropriate solvent was added instead of DMSO. For the catalyst screen, the general procedure was followed, replacing 2-CPBA with an equimolar amount of another catalyst. Reactions in the solvent screen, salt screen, and catalyst screen were run for 1 h to observe differences in glucose conversion, as conversion was typically complete after 2 h.

3 Results and discussion

3.1 Effect of boronic acids in [BMIM]Cl

At the outset, we were motivated by finding that unesterified 2-CPBA in the absence of Mg(II) facilitated the conversion of glucose in the ionic liquid 1-butyl-3-methylimidazolium chloride ([BMIM]Cl). The yields of HMF were, however, modest. Specifically, 1 equiv of 2-CPBA afforded HMF in 43% and 21% yield from fructose and glucose, respectively. Nonetheless, a screen of boric acid and 20 boronic acids revealed that 2-CPBA did afford the highest HMF yields (Table S1).

We surmised that the modest yield afforded by 2-CPBA in [BMIM]Cl even at high glucose conversion was indicative of the formation of humins. A temperature-screen led to a small gain in selectivity upon running reactions at 95 °C (Fig. S1). In an attempt to improve selectivity further, we turned to the well-known ability of polar aprotic solvents to reduce humin formation [45-47]. Screening the reaction in varying concentrations of [BMIM]Cl in DMSO (Fig. 1) showed a maximal HMF yield of 70% at 3% w/v [BMIM]Cl in DMSO (corresponding to 0.19 M chloride ion). Lower concentrations of [BMIM]Cl led to lower glucose conversion, whereas higher concentrations led to rapid humin formation. At [BMIM]Cl concentrations >50% w/v, the reaction produced yields similar to those in neat [BMIM]Cl. These results indicated that ionic liquids limit HMF yield, discouraging their use as solvents for the production of HMF in our system. Importantly, only traces of levulinic and formic acids were detected in any of the reaction mixtures, even at quantitative glucose conversion, indicating that hydrolytic damage to the HMF product was insignificant.

3.2 Effect of salt type

To elucidate the role of salt type in the reaction, we screened a panel of salts (Fig. 2), including both coordinating and non-coordinating cations, and nucleophilic and non-nucleophilic anions, as well as an amine base. All of the additives were able to promote the reaction to some degree. Organizing the data by cation showed no clear pattern (Fig. 2A); however, organizing by anion showed similar yields for a particular anion, regardless of its cation (Fig. 2B). The pattern of halide reactivity ($\text{Cl}^- > \text{F}^- > \text{Br}^- > \text{I}^-$) is consistent with a role as a nucleophile or base, with fluoride ion giving anomalous results due to its propensity to form strong covalent bonds with boron. The ability of non-nucleophilic ions, such as sulfate, and an amine to promote the reaction

favor a role as base. These data provide further support that chloride ion in MgCl_2 , rather than the magnesium ion, is the active catalyst in process. Previously, we proposed a similar role for halides in the metal-catalyzed conversion of sugars to HMF [48]. This interpretation is also consistent with the results of Riisager and coworkers [39], who showed that chloride ionic liquids performed best in the boric acid-promoted production of HMF.

DMSO is problematic as a reaction solvent because its high boiling point makes product isolation difficult and because of its proclivity to act as an oxidizing agent. A solvent screen (Fig. 3A) showed that strongly electron-donating polar aprotic solvents gave the best selectivity, with DMF, DMA, and NMP performing comparably to DMSO. The results of a further screen of the most active solvents but omitting the chloride emphasized further the vital role of chloride for reactivity, as all solvents showed dramatically lower yields without that ion (Fig. 3B). As DMSO is known to be able to catalyze fructose dehydration at high temperature [49], we tested whether HMF could be produced without boronic acid or chloride present (Fig. S2). Glucose showed no conversion to HMF without the boronic acid, whereas fructose showed a low yield in neat DMSO and a significantly improved yield in DMSO with added chloride, indicating that chloride catalyzes fructose dehydration. Importantly, HMF showed no detectable degradation under the reaction conditions, in both the absence and presence of boronic acid. Other hexose and pentose sugars gave furanic yields similar to those from glucose (Fig. 4), and yields from the disaccharides sucrose and cellobiose were significant, indicating that glycosidic bonds can be cleaved under the reaction conditions. Cellulose afforded little HMF (1% yield), as expected from its insolubility in the reaction solvent.

3.3 Effect of catalyst loading

A screen of boronic acid-loading at constant reaction time showed that HMF yield and glucose conversion correlated well with catalyst loading, and led to yields as high as 79%. Allowing a reaction with a 20% loading of boronic acid to react for 19 h gave quantitative glucose conversion and 52% yield of HMF (Fig. 5), indicating that the boronic acid was indeed catalytic, though the longer reaction time decreased selectivity for HMF.

3.4 Effect of boronic acids in DMSO and DMF

Many boronic acids demonstrated catalytic activity in [BMIM]Cl (Table S2). Accordingly, we screened a number of boronic acids and other similar molecules in DMSO and DMF under the new reaction conditions (Fig. S3 and Table S2). Phenylboronic acid produced no HMF, and boric acid gave only a few percent yield of product. The methyl and ethyl esters of 2-CPBA showed significantly lower yields compared to the free acid, and benzoic acid and salicylic acid showed insignificant conversion, as did a mixture of phenylboronic acid and benzoic acid. Interestingly, only 2-carboxy-substituted phenylboronic acids showed any activity in the conversion of glucose to HMF. Moving the carboxy group to the 3- or 4-position nullified catalysis, and other oxygen-containing substituents at the 2-position did not engender catalysis. The esters of 2-CPBA, which showed some activity, are likely hydrolyzed to 2-CPBA *in situ*. These data indicate that the binding of phenylboronic acid to a sugar is not sufficient—an *ortho* carboxylic acid is necessary for reactivity. Intramolecular coordination of the carboxylic acid with the Lewis-acidic boron likely modulates the reactivity of both the boron and the carboxylic acid, leading to the unique reactivity of these molecules, though internal coordination is clearly insufficient for catalysis, as other boronic acids which would be expected to exhibit this

coordination showed no activity. Investigation of the mechanism of catalysis by 2-CPBA are ongoing in our laboratory.

The high boiling point of DMSO and other polar aprotic organic solvents complicates isolation of the HMF product. Vacuum distillation can theoretically separate the solvent and HMF, but the process is energy intensive and inefficient [45]. Alternatively, HMF could be isolated by adsorption onto a solid support [50], or the HMF in the crude reaction mix could be functionalized further to form more easily isolated products. Overall, however, the large-scale isolation of HMF from reaction mixtures remains an unsolved problem [51].

The high loading of boronic acid required to obtain good yields necessitates an effective method for recycling the boronic acid catalyst. The large-scale use of [BMIM]Cl would require recycling of the ionic liquid, which could be achieved through ion-exchange; however, our results indicate that any inexpensive chloride salt could be used in its place in our process, eliminating the need for recycling. 2-CPBA can be isolated from reaction mixtures by using an anion-exchange resin [40]. The recycling of the boronic acid could also be achieved by its immobilization on a solid support, which could allow as well for the production of HMF in a flow reactor. Efforts towards these goals are underway in our laboratory, along with means to integrate HMF into the bioenergy and bioproduct pipeline.

4 Conclusions

In this study, we link two highly active areas of sustainability research: biomass conversion and organocatalysis. Specifically, we report on an environmentally benign catalytic process for the transformation of glucose and other sugars into a key platform chemical that is readily convertible into a wide variety of useful fuels and commodity chemicals, improving the

economics of lignocellulosic biomass conversion relative to reliance on the limited products available from microbial fermentation. With additional effort, our process could serve as the basis for an efficient, renewable route to expedite the transition away from an unsustainable society based on petroleum.

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Figure Legends

Scheme 1 Synthetic route to HMF and its further reactions.

Fig. 1 Graph showing the effect of [BMIM]Cl concentration on the yield of HMF in DMSO. Reaction conditions: 1.0 mL of DMSO containing glucose (10% w/v), [BMIM]Cl, and 2-CPBA (1 equiv); shaken (650 rpm) at 95 °C for 1 h.

Fig. 2 Bar graphs showing the yield of HMF from glucose in DMSO containing different salts as catalyzed by 2-CPBA. (A) Salts grouped by cation. (B) Salts grouped by anion. Bars are rendered in CPKnew colors for the relevant atom and listed by atomic number. Reaction conditions: 1.0 mL of DMSO containing glucose (10% w/v), a salt (0.19 M), and 2-CPBA (1 equiv); shaken (650 rpm) at 95 °C for 1 h.

Fig. 3 Bar graphs showing the effect of solvent and chloride ion on the yield of HMF and conversion of glucose as catalyzed by 2-CPBA. (A) Higher selectivity is obtained in polar aprotic solvents that are strong electron donors, such as DMSO, DMF, DMA, and NMP. Reaction conditions: 1.0 mL of a solvent containing glucose (10% w/v), [BMIM]Cl (0.19 M), and 2-CPBA (1 equiv); shaken (650 rpm) at 95 °C for 1 h. (B) In DMSO, DMF, DMA, and NMP, a higher HMF yield and glucose conversion is obtained in the presence of chloride ion. Reaction conditions: 1.0 mL of a solvent containing glucose (10% w/v) and 2-CPBA (1 equiv), with or without [BMIM]Cl (0.19 M); shaken (650 rpm) at 95 °C for 1 h. Data with [BMIM]Cl are reproduced from panel A to facilitate comparisons.

Fig. 4 Bar graph showing the effect of sugar type on furanic yield as catalyzed by 2-CPBA.

HMF was recovered quantitatively, indicating its stability under the reaction conditions.

Reaction conditions: 1.0 mL of DMSO containing a sugar (10% w/v), [BMIM]Cl (0.19 M), and 2-CPBA (1 equiv); shaken (650 rpm) at 95 °C for 1 h.

Fig. 5 Catalysis of the conversion of glucose to HMF by 2-CPBA. **(A)** Graph of HMF yield as a function of 2-CPBA concentration. Reaction conditions: 1.0 mL of DMSO containing glucose (10% w/v), [BMIM]Cl (0.19 M), and 2-CPBA (0.11–1.95 equiv); shaken (650 rpm) at 95 °C for 2 h. **(B)** Graph of HMF yield and glucose conversion afforded by 2-CPBA (0.2 equiv) as a function of time ($n = 2$). Reaction conditions: 1.0 mL of DMSO containing glucose (10% w/v), [BMIM]Cl (0.19 M), and 2-CPBA; shaken (650 rpm) at 95 °C for 2, 5, or 19 h.

Scheme 1

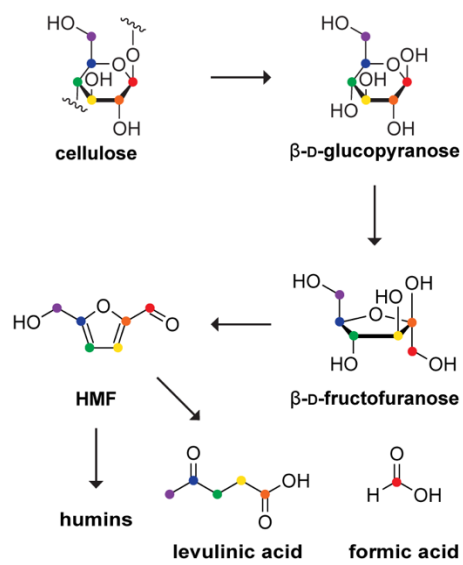


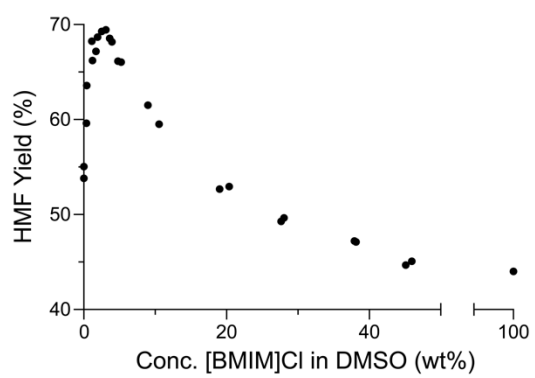
Fig. 1

Fig. 2

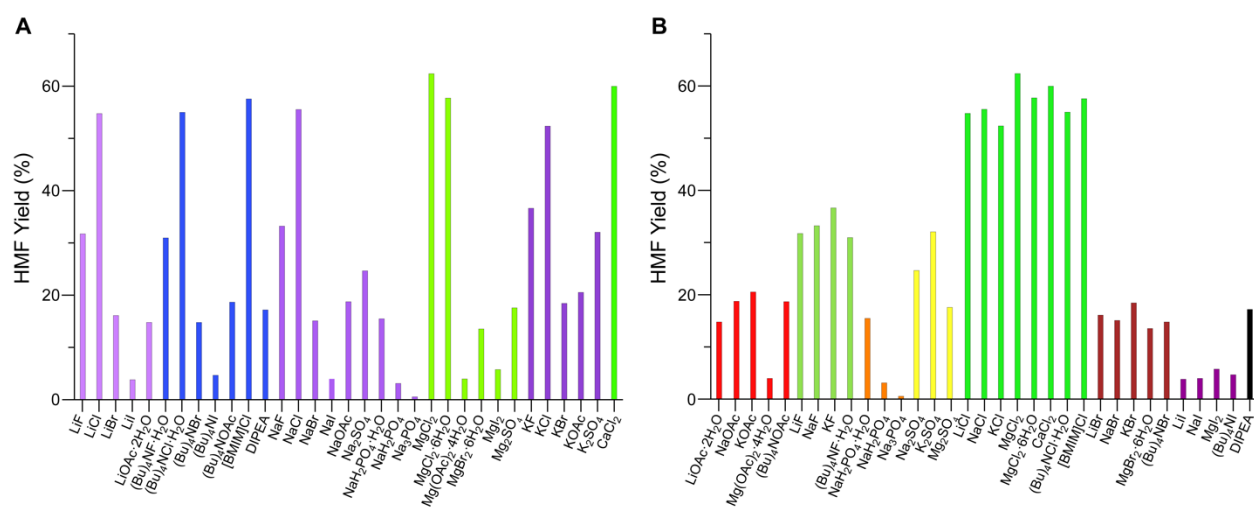


Fig. 3

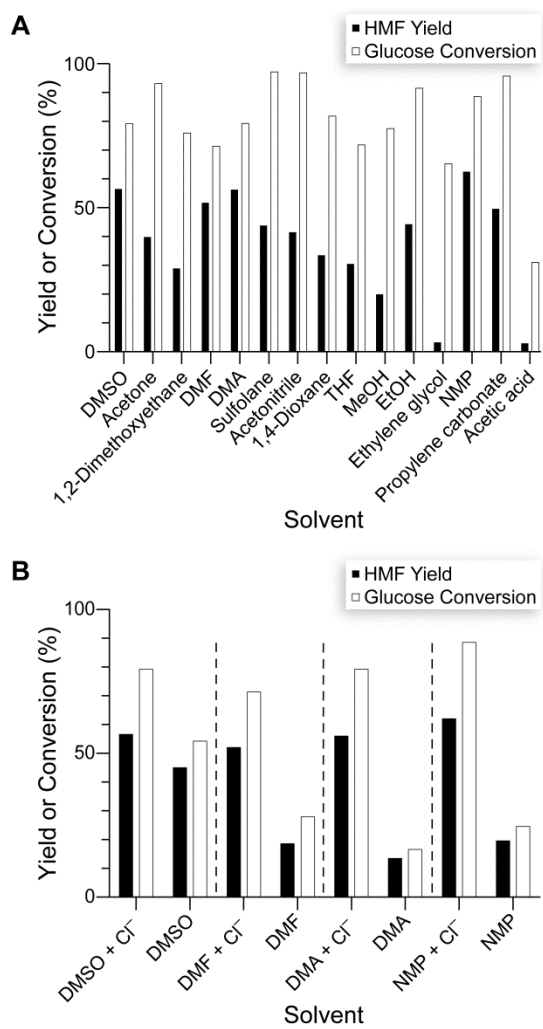


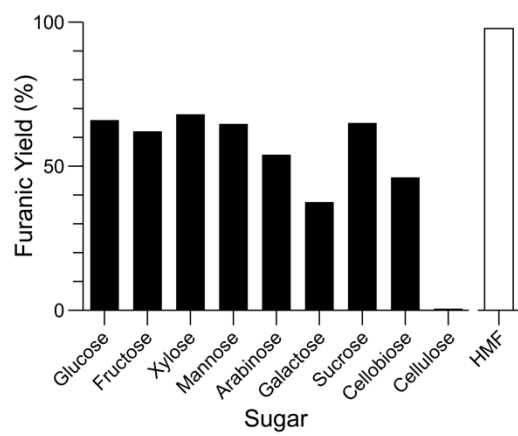
Fig. 4

Fig. 5

