EDGE ARTICLE

Organocatalytic conversion of cellulose into a platform chemical†

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The search for a source of fuels and chemicals that is both abundant and renewable has become of paramount importance. The polysaccharide cellulose meets both criteria, and methods have been developed for its transformation into the platform chemical 5-(hydroxymethyl)furfural (HMF). These methods typically employ harsh reaction conditions or toxic heavy metal catalysts, deterring large-scale implementation. Here, we describe a low-temperature, one-pot route that uses *ortho*-carboxyl-substituted phenylboronic acids as organocatalysts in conjunction with hydrated magnesium chloride and mineral acids to convert cellulose and cellulose-rich municipal waste to HMF in yields comparable to processes that use toxic heavy metal catalysts. Isotopic labeling studies indicate that the key aldose-to-ketose transformation occurs *via* an enediol intermediate. The route, which also allows for facile catalyst recovery and recycling, provides a green prototype for cellulose conversion.

Introduction

The dependence on fossil fuels for energy and chemicals has become unsustainable.[1] Abundant, renewable biomass resources could meet the fuel and chemical demands of the future,[2] but must recapitulate the wide array of products now derived from fossil fuels. The six-carbon furanic 5-(hydroxymethyl)furfural (HMF) has the potential to meet this challenge.[3] HMF can be transformed into a variety of useful products, such as common polyester building blocks[4] and the promising liquid fuel 2,5-dimethylfuran.[5] The carbon skeleton of HMF is identical to those of the hexose sugars that are the primary components of cellulose and hemicelluloses in biomass. Still, accessing this resource requires a process that efficiently transforms these carbohydrates into HMF.

The conversion of cellulose to HMF can proceed *via* three steps: hydrolysis of cellulose to glucose, isomerization of glucose to fructose, and dehydration of fructose to HMF (Fig. 1). Although several methods exist for transforming glucose and fructose into HMF,[6] few are capable of producing HMF in high yields directly from cellulose.[3] Solid acids[7] and heavy metals[6b,8]

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are the best extant catalysts for this conversion. The inefficiency of solid acid catalysts and the toxicity of heavy metals could diminish their impact.[9] Considering the ever-growing need for green chemistry, we sought a conversion process that uses benign and recyclable reagents, catalysts, and solvents, as well as mild reaction conditions. Here, we report on our discovery of such a process.

Results and discussion

Our initial experiments focused on discovering an alternative to heavy metals for accessing HMF from glucose. As a solvent, we choose *N,N*-dimethylacetamide (DMA), a polar aprotic solvent that has served as the medium for other biomass conversions.[8b,10] We screened a variety of metal chlorides (Table S1†) and found that magnesium, nickel, zinc, cerium, or lanthanum, like chromium, provides appreciable yields of HMF (Table 1). We chose to employ magnesium due to its being one of the most abundant elements in Earth's crust[11] and the human body.[12]

Next, we attempted to increase the efficiency of the conversion while maintaining environmental benignancy. To do so, we turned to organocatalysis,[13] which had not been employed previously in a biomass conversion process.[2,3] We were aware that boronic acids readily form boronate esters with 1,2- and 1,3-diols, and bind to furanose sugars with greater affinity than to pyranose sugars.[14] We reasoned that these organoboranes would alter the equilibrium between glucose and fructose (which exist primarily in the pyranose and furanose forms, respectively), and thereby enhance HMF production. The precedents were discouraging, however, as phenylboronic acid had been reported to inhibit the hydrolysis of cellulose and the dehydration of sugar monomers.[15,16]
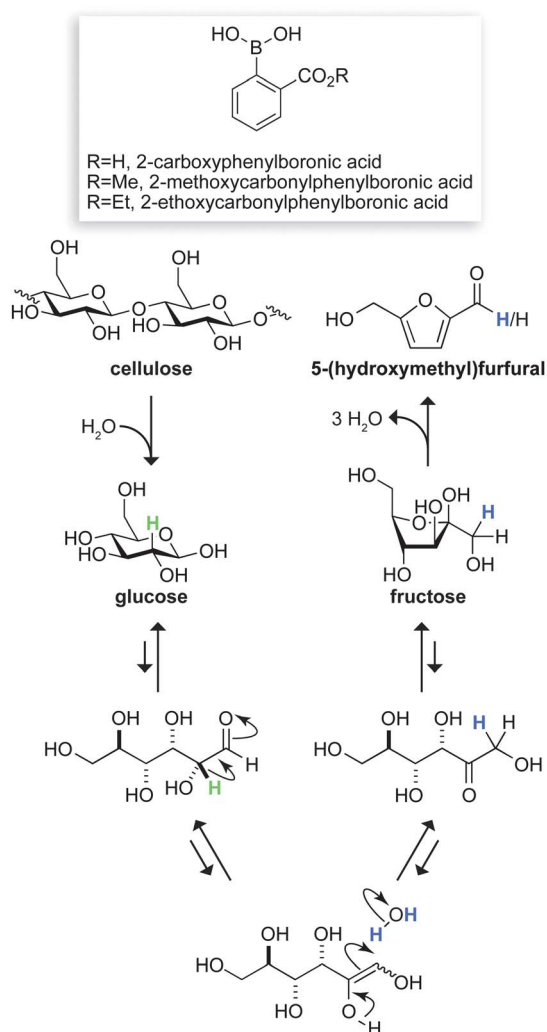
Fig. 1 Putative route for the conversion of cellulose to 5-(hydroxymethyl)furfural, mediated by the depicted boronic acids. Labeled hydrogens in glucose (green) and water (blue) have the indicated fates.

Table 1 Conversion of glucose to HMF in DMA[a]

Metal chloride, mol%	Boronic acid, wt%	T (°C)	Time (h)	HMF yield (%)
—	—	100	6	0
CrCl$_2$, 25	—	100	6	58
MgCl$_2$·6H$_2$O, 200	—	120	6	29
NiCl$_2$·6H$_2$O, 300	—	120	3	32
ZnCl$_2$, 300	—	120	6	21
CeCl$_3$·7H$_2$O, 300	—	120	3	22
LaCl$_3$·7H$_2$O, 300	—	120	6	22
—	2-Carboxyphenyl, 100	120	6	2
MgCl$_2$·6H$_2$O, 200	2-Carboxyphenyl, 100	120	4	54
MgCl$_2$·6H$_2$O, 200	2-Carboxyphenyl, 50	120	6	48
MgCl$_2$·6H$_2$O, 200	2-Carboxyphenyl, 25	120	6	46
MgCl$_2$·6H$_2$O, 200	2-Carboxyphenyl, 10	120	6	31
NiCl$_2$·6H$_2$O, 300	2-Carboxyphenyl, 100	105	4	24
ZnCl$_2$ + 6H$_2$O, 300	2-Carboxyphenyl, 100	105	4	18
CeCl$_3$·7H$_2$O, 300	2-Carboxyphenyl, 100	120	3	51
LaCl$_3$·7H$_2$O, 300	2-Carboxyphenyl, 100	120	3	49
—	2-Methoxycarbonylphenyl, 100	100	6	22
MgCl$_2$·6H$_2$O, 200	2-Methoxycarbonylphenyl, 100	120	4	57
—	2-Ethoxycarbonylphenyl, 100	100	6	15
MgCl$_2$·6H$_2$O, 200	2-Ethoxycarbonylphenyl, 100	120	4	52

[a] Glucose was at 10 wt% relative to DMA. Mol% and HMF yield (HPLC) are relative to glucose.

Phenylboronic acids have an affinity for carbohydrates that is tunable based on substituents.[14] We assessed the ability of twenty derivatives of phenylboronic acid to promote the conversion of glucose to HMF (Tables S2–S4 in the ESI†). Our data corroborated the earlier work with phenylboronic acid itself,[15] which is not a catalyst in our hands, but revealed that adding an *ortho* carboxyl group engenders catalysis, especially in the presence of MgCl$_2$·6H$_2$O (Table 1). Further optimization revealed prospects for catalytic turnover. For example, adding 25 mol% of 2-carboxyphenylboronic acid to the magnesium increases the HMF yield from 29% to 46%.

Water can counter the dehydration of fructose (Fig. 1). Accordingly, we attempted to increase our HMF yields by using anhydrous MgCl$_2$. We found, however, that anhydrous MgCl$_2$ provides lower HMF yields than does the hydrated salt (Table S4†). To determine how much water is beneficial for HMF production, we added water to reaction mixtures containing the anhydrous salt (Table S5 in the ESI†) and found that HMF yields increase steadily up to an H$_2$O : Mg(II) ratio of ∼6 (Fig. S1†).

Other anhydrous metal chlorides that work synergistically with 2-carboxyphenylboronic also have a similar reliance on water (Table S5†).

Encouraged by the successful conversion of glucose to HMF, we next attempted to convert cellulose to HMF using boronic acids in 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl), an ionic liquid that dissolves cellulose[17] and enables a mineral acid to catalyze its hydrolysis.[18] We observed that phenylboronic acids with an *ortho* carboxylic acid or ester promote the conversion of cellulose to HMF (Tables S6 and S7 in the ESI†), and that MgCl$_2$·6H$_2$O is necessary to maximize HMF production (Table 2). The observed yields of HMF (*e.g.*, 41% in 1 h at 105 °C with 2-methoxycarbonylphenyl boronic acid) are comparable to those attainable with a heavy metal.[8] Boronic acid/MgCl$_2$·6H$_2$O also promote the conversion of cotton, paper towels, and newspaper (Table 2), which are cellulose-rich components of municipal waste. The HMF yields correlate with the purity of the cellulose in these materials. Thus, HMF can be produced efficiently from cellulosic material in a single, one-pot process that is devoid of heavy metals.

The high boronate loadings necessary to turnover cellulose rapidly (≤2 h) led us to search for a recovery method that enables boronate recovery. Our initial separation strategy

Table 2 Conversion of cellulosic substrates into HMF in ionic liquids[a]

cellulose   catalyst(s) / ionic liquid →   HMF
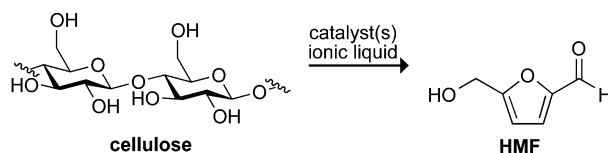
Substrate	Ionic liquid	Acid, wt%	Metal chloride, mol%	Boronic acid, mol%	T (°C)	Time (h)	HMF yield (%)
Cellulose	[EMIM]Cl	HCl, 0.61	—	—	105	2	10
Cellulose	[EMIM]Cl	HCl, 0.61	$MgCl_2 \cdot 6H_2O$, 300	—	105	3	15
Cellulose	[EMIM]Cl	HCl, 0.61	—	2-Methoxycarbonylphenyl, 120	105	2	12
Cellulose	[EMIM]Cl	HCl, 0.61	$MgCl_2 \cdot 6H_2O$, 300	2-Methoxycarbonylphenyl, 120	105	2	39
Cellulose	[EMIM]Cl	H_2SO_4, 0.88	$MgCl_2 \cdot 6H_2O$, 300	2-Methoxycarbonylphenyl, 120	105	1	41
Cellulose	[EMIM]Cl	HCl, 0.61	—	2-Ethoxycarbonylphenyl, 160	105	1	21
Cellulose	[EMIM]Cl	HCl, 0.61	$MgCl_2 \cdot 6H_2O$, 300	2-Ethoxycarbonylphenyl, 160	105	2	38
Cellulose	[EMIM]Cl	H_2SO_4, 0.88	$MgCl_2 \cdot 6H_2O$, 300	2-Ethoxycarbonylphenyl, 160	105	1	36
Cotton	[BMIM]Cl	—	$MgCl_2 \cdot 6H_2O$, 300	2-Ethoxycarbonylphenyl, 160	105	2	40
Paper towel	[EMIM]Cl	HCl, 0.61	$MgCl_2 \cdot 6H_2O$, 300	2-Ethoxycarbonylphenyl, 160	105	2	31
Newspaper	[BMIM]Cl	—	$MgCl_2 \cdot 6H_2O$, 300	2-Ethoxycarbonylphenyl, 160	105	2	18

[a] Substrates were at 5 wt% relative to the ionic liquid. Wt% is relative to the ionic liquid. Mol% and HMF yield (HPLC) are relative to glucose monomers within the substrate, which was assumed to be pure cellulose.

focused on isolating 2-carboxyphenylboronic acid from a reaction mixture using an anion-exchange resin. The reaction mixture was diluted with water, filtered to remove any humins (which are insoluble byproducts from aldol addition and condensation[19]), extracted with ethyl acetate to remove HMF, and passed through a column of resin. The anionic boronate was retained on the resin and eluted with aqueous NH_4HCO_3 (1 M) to yield purified boronate, which retained catalytic activity (Fig. S2†). This strategy was, however, inapplicable to the *o*-esterphenylboronic acids, which have low solubility in water and high solubility in ethyl acetate.

Boronic acid moieties become anionic at high pH and partition completely into an aqueous phase. Hence, we added basic water to reaction mixtures containing 2-ethoxycarbonylphenylboronic acid, filtered to remove any humins, and extracted with ethyl acetate (Fig. S3†). Removing solvent from the organic phase provided HMF. Evaporating water from the aqueous phase recovered the boronic acid and $MgCl_2$. The recovered catalysts provided HMF in comparable yield through four reaction cycles.

Additional data provided insight on the chemical mechanism of our conversion (Fig. 1). Chromium is known to mediate the isomerization of aldose to ketose sugars by a 1,2-hydride shift.[10,20] To probe the mechanism of our conversion, we performed two deuterium-labeling experiments. In the first, glucose-2-*d* was converted into HMF by 2-ethoxycarbonylphenylboronic acid and $MgCl_2 \cdot 6H_2O$. ^{1}H NMR spectroscopy revealed that virtually no deuterium was retained in the HMF product. In the second, unlabeled glucose was converted in the presence of D_2O, and a substantial quantity of deuterium was found at C-1 of HMF (Fig. S4†). These results are compatible with a mechanism that avails an enediol intermediate (Fig. 1). A similar mechanism is used by the enzyme phosphoglucose isomerase, which catalyzes the interconversion of glucose 6-phosphate and fructose 6-phosphate.[21]

Boronate ester-formation is known to be more favorable with fructose than glucose.[14] We found that boronic acids also serve by catalyzing fructose dehydration (Table S8†). We suspect that the organocatalyst relies on an *ortho* carboxyl group because its oxygen can donate electron density into the empty p-orbital of boron, thereby decreasing the strength of the fructose–boronate complex in the nearly water-free medium.[14b] Finally, we propose that water attenuates the reactivity of Mg(II), allowing its participation in catalysis, but deterring reaction pathways that can lead to humins.[22]

Concluding remarks

In summary, we have discovered novel reactivity mediated by a simple boronic acid composed of hydrogen, boron, carbon, and oxygen—four of the first eight elements in the periodic table. This organocatalyst mediates the transformation of fructose, glucose, and cellulose into the platform chemical HMF. Although boronate loadings for rapid (≤2 h) conversions are high, this liability is overcome by the facility of its recovery (or, potentially, by its immobilization). This discovery, which is the first to link two highly active areas of research: organocatalysis and biomass conversion, could facilitate the transition from fossil-based fuels and chemicals to a more sustainable biomass-based society.

Acknowledgements

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