CATALYTIC SYSTEMS FOR CARBOHYDRATE CONVERSIONS

by

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ABSTRACT

CATALYTIC SYSTEMS FOR CARBOHYDRATE CONVERSIONS

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Under the supervision of Professor Ronald T. Raines

At the University of Wisconsin–Madison

The fossil fuel reserves of the world are limited, and they are declining. To sustain modern civilization, the world must find an alternative resource to continue the supply of energy and chemicals. Lignocellulosic biomass is a resource that is both abundant and renewable. Using straightforward chemical methods, it can be transformed into 5-(hydroxymethyl)furfural (HMF), a platform chemical that can serve as an important intermediate to biofuels and commodity chemicals. This thesis describes novel processes developed to access HMF from carbohydrate materials.

In Chapter One, I review some recent developments in accessing HMF from carbohydrates using mineral acid, metal ion, and heterogeneous catalysts. The chapter also discusses a biofuel accessed from HMF, 2,5-dimethylfuran (DMF), and how it compares as a fuel to both gasoline and ethanol. In Chapter Two, I discuss my development of a method to convert fructose to HMF in the industrial solvent sulfolane. High yields of HMF are obtained using halide salts, with the highest yields accessed with hydrobromic acid.

My efforts to develop an environmentally benign catalyst system to convert glucose and cellulose to HMF are detailed in Chapter Three. Using a dual catalyst system of *ortho*-carboxyl phenylboronic acids and hydrated magnesium chloride, I achieved HMF yields comparable to those obtained from toxic chromium catalysts. The role of the boronic acids in the conversion of

carbohydrates to HMF is explored in Chapter Four. *Ortho*-carboxyl phenylboronic acids convert ketohexose and aldohexose sugars with the highest HMF yields obtained from sugars having high furanose isomeric compositions. An additional electron withdrawing substitution on the *ortho*-carboxyl phenylboronic acids was found to enhance HMF yields.

Ionic liquids are privileged solvents that enable the dissolution of cellulosic materials. I detail the application of fluorous labeling to ionic liquids for their recovery in Chapter Five. In Chapter Six, I describe a method to access pure monomer sugars from raw corn stover biomass. A two-stage hydrolysis provides high yields of glucose and xylose, which were recovered quantitatively from the ionic liquid solvent using simulated moving bed chromatography. Finally, in Chapter Seven I propose potential future directions for the research presented in this thesis.

ACKNOWLEDGEMENTS

It's funny, but in my final days of graduate school with my dissertation nearing completion, I find myself thinking more and more about the events and people that have gotten me here. While there is definitely a lot of work that has gone into my research, I truly believe that it is the support and guidance of others that has enabled me to come this far. I don't think that mere words can properly convey the depth of my gratitude, but hopefully they can at least provide a glimpse.

First of all, I am exceedingly grateful to my advisor, Professor Ron Raines. When I entered graduate school in the fall of 2007, I didn't have a clue what kind of research I wanted to do. However, I was thunderstruck when I heard Ron speak about his lab's research in using chemical techniques to solve biological problems. Upon meeting with him further to discuss a new project in the lab, the conversion of biomass materials to chemicals, I was sold. I felt this was a project that was made for me, allowing me to utilize knowledge from my farming background with cutting edge chemistry in developing novel conversion methods. Upon joining, I was impressed by the level of independence and freedom Ron gives to his students, even as first years. I am profoundly humbled by the trust Ron placed in me to push projects forward and by his encouragement to develop and pursue ideas of my own. The professional growth I achieved through Ron's faith in me has shaped me into the scientist I am today.

The diversity of research in the Raines Lab attracts many exceptional graduate students and postdocs, and it has been an honor to work alongside such incredible individuals. The collaborative environment of the lab oftentimes is the only reason a project moves past an obstacle. Furthermore, the level of camaraderie the lab fosters is truly remarkable, and quickly

changes graduate school from a seeming job to simply doing some science with your friends. I was fortunate to have excellent guidance when I started from Annie Tam, Luke Lavis, Matt Shoulders, Daniel Gottlieb, and Sayani Chattopadhyay. In particular, I am grateful for the opportunity to work with Joe Binder whose instruction and advice were indispensable in getting the biomass project started in the lab. Eddie Myers, Amit Choudhary, and Mike Palte were always willing to discuss ideas or troubleshoot problems, and it is discussions with them that allowed many initial obstacles to be overcome. Working alongside Mariëlle Delville, Nick McGrath, John Lukesh III, Katrina Jensen, Brett VanVeller, Ho-Hsuan Chou, Raso Biswas, Caglar Tanrikulu, Christine Bradford, Thom Smith, Matt Aronoff, and Rob Newberry in later years made for an exceptional setting in which to do research. I am grateful to Greg Ellis and Chelcie Eller for teaching me the basic fundamentals of biochemistry on how to keep cells alive. I was also fortunate to work alongside Tom Rutkoski, Jeet Kalia, Rebecca Turcotte, Margie Borra, Rex Watkins, Kelly Gorres, Nicole McElfresh, Cindy Chao, Greg Jakubczak, Mike Levine, Nadia Sundlass, Kevin Desai, Joelle Lomax, Sean Johnson, Kristen Andersen, Trish Hoang, Rob Presler, Jim Vasta, and Ian Windsor. I am especially appreciative of the enduring friendships I made, especially with Mike, Greg, Amit, John, and Nick. I am thankful for the opportunity to mentor high school student Kweku Brewoe and undergraduate Jackie Blank, and work with senior scientist Tom Van Oosbree.

The University of Wisconsin–Madison has been an ideal location to do my graduate school research. The outstanding quality of both faculty and staff ensures that students are given ample opportunity for success while exploring the frontiers of science. I am grateful to my committee members, Professors John Ralph, Jen Schomaker, Christos Maravelias, and Shannon Stahl, for their direction and guidance on my dissertation. I thank Mark Anderson of the

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Finally, and most importantly, I am eternally indebted to my family, whose unconditional love, encouragement, and support has been a source of constant inspiration. My parents, John and Jane Caes, never fail to tell me how proud they are. Their unwavering belief in me, especially when I fail to believe in myself, has given me the strength to push through obstacles and achieve things I never thought I could. My brother, Jonathan Caes, provided welcome respites by traveling to Madison for visits. While this began as an annual July 4th trip, it soon blossomed into four or five trips a year, although I think this may be due to the quality of food available in Madison… Regardless, it is only through the love and support of my family and friends that I am here today and I thank God for His blessings in surrounding me with such truly extraordinary people.

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LIST OF ABBREVIATIONS

[BMIM]Cl	1-butyl-3-methylimidazolium chloride
DMA	*N*,*N*-dimethylacetamide
DMF	dimethylfuran
DMSO	dimethylsulfoxide
DOE	Department of Energy
[EMIM]Cl	1-ethyl-3-methylimidzolium chloride
equiv	equivalent
FDCA	furan dicarboxylic acid
GLBRC	Great Lakes Bioenergy Research Center
h	hour
HMF	5-(hydroxymethyl)furfural
HPLC	high performance (pressure) liquid chromatography
HRMS	high resolution mass spectrometry
LB	Luria–Bertani medium
M	molar
min	minute
mol%	mole percent
NMR	nuclear magnetic resonance
s	second
SMB	simulated moving bed
SPE	solid phase extraction
T	temperature

wt%	weight percent

CHAPTER 1

5-(HYDROXYMETHYL)FURFURAL SYNTHESIS AND BIOFUEL APPLICATIONS

1.1 Abstract

The quest to achieve a sustainable supply of both energy and chemicals is one of the great challenges of this century. Renewable lignocellulosic biomass resources could alleviate this problem through conversion of its carbohydrate materials to valuable fuels and chemicals. 5-(Hydroxymethyl)furfural (HMF) is the dehydration product of hexose carbohydrates and could serve as a platform to access both fuels and chemicals. One such fuel is 2,5-dimethylfuran (DMF), which is accessed by hydrogenolysis of HMF and contains an energy density 40% greater than that of the bioethanol now in widespread use. Much work has been done in recent years to convert carbohydrate materials such as fructose, glucose, and cellulose to HMF in high yields using a variety of chemical methods. Here, an overview of synthetic methods to access HMF from carbohydrates is presented with additional methods discussed for accessing DMF from both HMF and carbohydrate materials.

1.2 Introduction

Energy is one of the most basic requirements of civilization. It supports technological development, scientific achievement, and cultural advancement. Petroleum reserves currently supply a vast majority of the requisite energy to maintain modern civilization.[1] Petroleum is comprised of a mixture of hydrocarbons and other organic compounds. A fossil fuel, petroleum was formed from organic matter that was chemically altered under intense heat and pressure over millions of years. As the world's population has increased, so too has its need for energy, and thus petroleum. The Earth, however, has a finite supply of petroleum, and it will not be able to serve as our energy source indefinitely.[2] In fact, we recently reached our maximal production of petroleum per year at nearly 40 billion metric tons.[3]

Biomass provides a potential alternative to petroleum as an energy resource.[4-5] The cellulose and hemicelluloses contained in biomass materials are the most abundant organic molecules in the world. Unfortunately, the recalcitrance of biomass severely limits its utility, but gaining access to its monosaccharide constituents could enable the realization of its potential. Glucose is a hexose sugar, and hexose sugars (Figure 1.1) are the most abundant

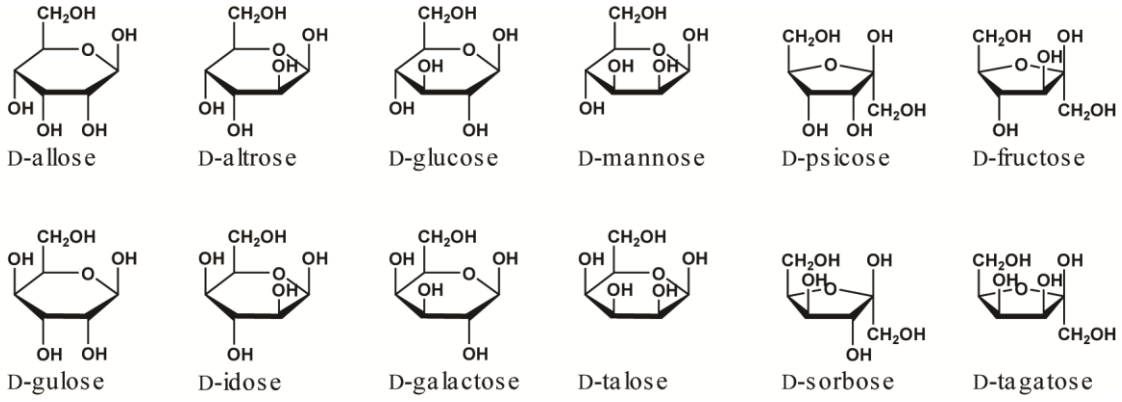

Figure 1.1 The structures of the D-hexose sugars.

monosaccharides in nature.[6] For biomass materials to be a viable substitute to petroleum, they must be able to match the wide array of products derived from petroleum. Furanics are heterocyclic compounds with an aromatic ring comprised of four carbon atoms and an oxygen atom that can be accessed from hexose sugars through a variety of chemical techniques. One such furanic that is becoming increasingly important is 5-(hydroxymethyl)furfural (HMF).

HMF is comprised of a furan ring system with an aldehyde and a hydroxymethyl group at the 2 and 5 positions. It is accessed from the furanose forms of hexose sugars by three dehydration reactions (Figure 1.2).[7-8] HMF has been shown to form when sugars are heated, typically under acidic conditions.[9] Additionally, HMF has been detected in foods such as dried fruits[10] and baking products,[11] and it is estimated that the daily intake of HMF is 30–150 mg per person.[12] HMF can be toxic to humans when ingested at concentrations of 75 mg per kg of body weight or greater. Beyond being a relatively benign contaminant in food, HMF has the potential to become an indispensable commodity.

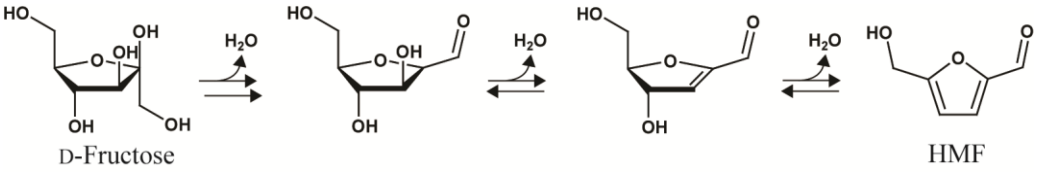

Figure 1.2 Dehydration of D-fructose to HMF.

The true value of HMF lies not in the compound itself, but rather in its capacity to be transformed into a number of other useful compounds through simple chemical techniques (Figure 1.3).[6,9,13-15] Rehydration of HMF causes it to decompose into levulinic acid and formic acid,[16-20] both valuable commodity chemicals. Furthermore, levulinic acid is a precursor to the

liquid fuel γ-valerolactone.[21-23] Oxidation of the hydroxymethyl group allows access to 2,5-diformylfuran and furan-2,5-dicarboxylic acid (FDCA). FDCA is of particular interest as it can be used as a polymeric substitute for terephthalic and isophthalic acids which are used to form polyamides, polyesters, and polyurethanes.[24] Reduction of the formyl moiety provides 2,5-bis(hydroxymethyl)furan while hydrogenation allows for the formation of 2,5-bis(hydroxymethyl)tetrahydrofuran and 2,5-diformyltetrahydrofuran. These types of products can undergo condensation to generate polymers that can ultimately become liquid alkanes.[25-27] HMF can also undergo undesirable degradation and polymerization to form insoluble polymers known as humins by reaction with itself and other monosaccharides.[28-30] Finally, hydrogenolysis can lead to 2,5-dimethylfuran (DMF), 2,5-dimethyltetrahydrofuran, and 2-methyltetrahydrofuran. DMF is of great interest as a biofuel with its high energy density, low volatility, and immiscibility with water.[31]

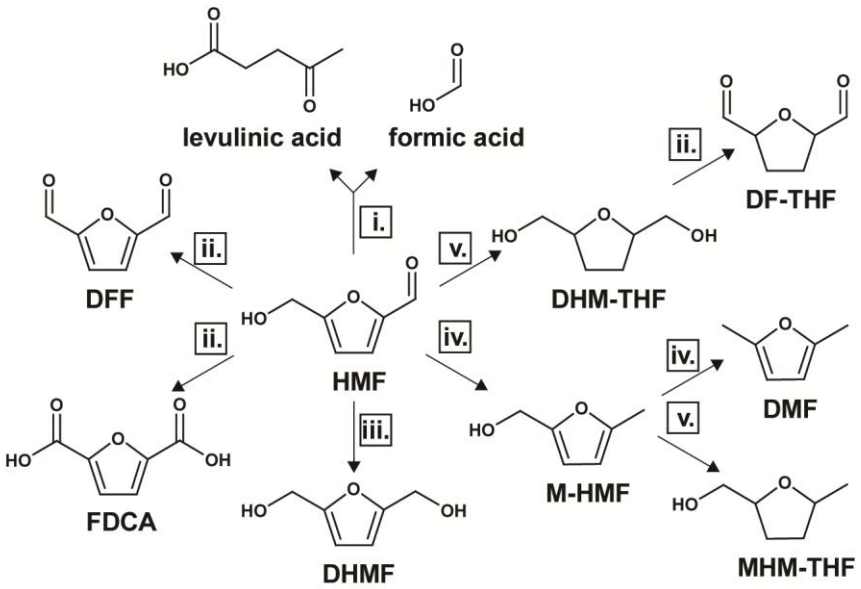

Figure 1.3 Synthetic routes from HMF by (i) rehydration, (ii) oxidation, (iii) reduction, (iv) hydrogenolysis, and (v) hydrogenation.

HMF holds great promise to match the array of compounds derived from petroleum, and thus biomass stands to become a viable replacement of petroleum as a primary energy resource. But, before this vision can be realized, conversion technologies must exist to enable the efficient, cost-effective conversion of tons of raw biomass to HMF. At present, no such process exists. Nonetheless, numerous extant processes convert mono- and polysaccharide materials into HMF in high yields. Here, I present an overview of developments in HMF synthesis in recent years and highlight the biofuel derived from HMF, DMF.

1.3 Ionic liquids

As carbohydrates serve as the source from which HMF is derived, a brief discussion of their characteristic properties is warranted. They are formed from carbon, hydrogen, and oxygen in a 1:2:1 ratio in various isomeric forms. By forming hydrogen bonds through their hydroxyl groups, carbohydrates are able to interact with other molecules and to dissolve in aqueous environments. Furthermore, carbohydrates can polymerize and form inter- and intra-strand hydrogen bonds, making them more recalcitrant towards dissolution, and hence insoluble in most solvents. A select few solvents are able to interact with the carbohydrates in a manner reminiscent of hydrogen bonding to accomplish dissolution.[32-33] Of these privileged few, ionic liquids are particularly noteworthy.

Ionic liquids are water-soluble, polar salts that melt below 100 °C, giving them negligible vapor pressure.[34-35] As salts, they result from the pairing of a cation (*i.e.*, phosphonium, imidazolium, pyridinium, ammonium) with an anion (*i.e.*, chloride, bromide, acetate, hexafluorophosphate), making countless combinations of ionic liquids (Figure 1.4).[34] This staggering variety allows for customization of the ionic liquids to obtain specific properties

suited to specific tasks. One such task is the dissolution of polysaccharides, and a number of reviews specifically discuss dissolving cellulosic material in ionic liquids.[36-38]

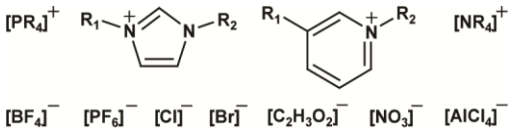

Figure 1.4 Common cations and anions of ionic liquids.

The recalcitrance of cellulose towards dissolution lies in its characteristic crystallinity, which is achieved through its network of inter- and intra-strand hydrogen bonds.[33] For a solvent to dissolve cellulose, it must out-compete the network for these hydrogen bonds. Ionic liquids are able to disrupt this network of hydrogen bonds as their charged constituents form electron donor–electron acceptor complexes with the hydroxyl groups of cellulose, causing de-aggregation of the polymer strands and allowing dissolution to occur.[36] Dialkylimidazolium chloride ionic liquids are especially well known for their capacity to dissolve high concentrations of cellulose,[38-40] and two of the best examples of this type of ionic liquid are 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) and 1-butyl-3-methylimidazolium chloride ([BMIM]Cl). Furthermore, ionic liquids themselves have been used as catalysts for the transformation of hexose sugars into HMF.[41]

1.4 Mineral acid catalysts

Of the methods used for HMF production, acid catalysis has perhaps been the most studied. HMF was first synthesized in 1895 from inulin[42] and sugar cane[43] using oxalic acid. Following these initial reports, more extensive work on HMF was done by Fenton and co-

workers,[44-46] and in 1919 Middendorp reported a detailed study on the synthesis, physical characteristics, and chemical behavior of HMF.[47] In subsequent years, Reichstein[48-49] and Haworth and Jones[50] described several immense contributions to HMF chemistry by proposing a modern synthetic method for its formation and studying its mechanism of transformation from fructose. Since then, numerous advancements have been made using mineral acid catalysts to transform carbohydrates (Table 1.1).

The inexpensive hydrochloric, sulfuric, and phosphoric mineral acids are most commonly used to catalyze the transformation of carbohydrate materials. Using H_2SO_4, Antal and co-workers reported the dehydration of fructose in subcritical water at 250 °C to access HMF in a 53% yield.[8] Furthermore, they were able to experimentally conclude that fructose dehydrates to HMF through closed ring intermediates due to ease of HMF formation from fructose and the fructosyl moiety of sucrose, as well as the facile conversion of 2,5-anhydro-D-mannose to HMF. Grin' and co-workers observed a kinetic isotope effect using HCl in D_2O for the dehydration of fructose to HMF, indicating that a proton participated in the rate limiting step of the reaction.[51] Kuster and co-workers used H_2SO_4 to access HMF from the fructose acetonide 1,2:4,5-di-*o*-isopropylidene-β-D-fructopyranose (prepared *via* the condensation of fructose with acetone).[52] As fructose has limited solubility in alcohols, transformation to the fructose acetonide enabled the volatile ethylene glycol dimethyl ether to be used as a solvent, providing a facile means for HMF recovery and solvent recycling.

In recent years, Dumesic and co-workers have investigated the use of biphasic reaction systems to both form HMF from fructose and extract the HMF using an organic solvent. Using HCl as a catalyst, fructose was dehydrated to HMF at 85% selectivity in an aqueous phase

Table 1.1. Conversion of carbohydrates to HMF using mineral acid catalysts

carbohydrate	catalyst	solvent	temp. (°C)	time	HMF molar yield (%)	ref.
fructose	H_2SO_4	subcritical H_2O	250	32 s	53	8
fructose	H_2SO_4	ethylene glycol dimethyl ether	200	3.3 h	70	52
fructose	HCl	7:3 (8:2 H_2O/DMSO)/PVP / 7:3 MIBK/2-butanol	200	3 min	75	53
fructose	HCl	5:5 H_2O/DMSO / 7:3 MIBK/2-butanol	170	4 min	85	54
glucose	HCl	4:6 H_2O/DMSO / 7:3 MIBK/2-butanol	170	10 min	23	54
sucrose	HCl	4:6 H_2O/DMSO / 7:3 MIBK/2-butanol	170	5 min	50	54
inulin	HCl	5:5 H_2O/DMSO / 7:3 MIBK/2-butanol	170	5 min	75	54
starch	HCl	4:6 H_2O/DMSO / 7:3 MIBK/2-butanol	170	11 min	26	54
cellobiose	HCl	4:6 H_2O/DMSO / 7:3 MIBK/2-butanol	170	10 min	27	54
fructose	H_3PO_4	subcritical H_2O	240	2 min	65	56
fructose	H_2SO_4	9:1 supercritical actone/H_2O	180 (20 MPa)	2 min	77	58
glucose	H_2SO_4	9:1 supercritical actone/H_2O	180 (20 MPa)	2 min	48	58
sucrose	H_2SO_4	9:1 supercritical actone/H_2O	180 (20 MPa)	2 min	56	58
inulin	H_2SO_4	9:1 supercritical actone/H_2O	180 (20 MPa)	2 min	78	58
fructose	HCl	H_2O	200	1 s	33	59
fructose	HCl	H_2O	200	1 min	53	59
fructose	HCl	H_2O	185 (17 bar)	1 min	54	60
fructose	HCl	1:5 H_2O/DMSO / MIBK/2-butanol	185 (20 bar)	1 min	83	60
fructose	HBr	sulfolane	100	1 h	93	151

containing dimethylsulfoxide (DMSO) and poly(1-vinyl-2-pyrrolidinone) (PVP), which were added to suppress unwanted side reactions.[53] HMF was extracted continuously into an organic phase of methylisobutylketone (MIBK), which was phase-modified with 2-butanol to improve

the partitioning of the HMF from the aqueous phase. They were also able to individually modify the biphasic system conditions for monomeric sugars and achieve HMF selectivities of 89% and 53% for fructose and glucose, and 91% selectivity for furfural from xylose.[54] Furthermore, these optimal conditions could be applied toward disaccharides sucrose (a glucose–fructose dimer) and cellobiose (a glucose dimer), along with polysaccharides inulin (a polyfructan), starch (a polyglucan), and xylan (a polyxylose). HMF selectivities were 77% from sucrose, 52% from cellobiose, 77% from inulin, and 43% from starch, with a furfural selectivity of 66% from xylan. Finally, the use of inorganic salts was shown to increase the partitioning of HMF in biphasic systems (NaCl being the most beneficial), and tetrahydrofuran (THF) was shown to have a superior extraction ability for HMF, with an attained selectivity of 83%.[55]

Asghari and Yoshida investigated the use of a variety acids in subcritical water to dehydrate fructose to HMF.[56] They found that a HMF yield of 65% was attained using H_3PO_4, although HMF was also formed even in the absence of acid catalysts at increased temperatures. They also used HCl to study the dehydration of fructose to HMF followed by a rehydration to form levulinic and formic acids in subcritical water, as well as the formation of decomposition products.[57] They determined that soluble polymer byproducts are formed not only from fructose, but HMF as well, and no soluble polymers are able to be formed from levulinic and formic acids. Vogel and co-workers used H_2SO_4 to investigate the dehydration of fructose in sub- and supercritical acetone–water mixtures.[58] They were able to access an HMF yield of 77% and observed no formation of humin byproducts. They further used their system to access HMF from glucose (48%), sucrose (56%), and inulin (78%).

Riisager and co-workers used HCl to catalyze a microwave-assisted dehydration of concentrated aqueous fructose solutions to access HMF.[59] Water, which normally results in low

HMF yields when used as the reaction medium, performed substantially better with microwave irradiation to give HMF rapidly with a selectivity of 63% and fructose conversion of 52%. A reaction time of 60 s gave 95% fructose conversion, but resulted in a decreased HMF selectivity of 55%. Loebbecke and co-workers also used HCl to dehydrate fructose in an aqueous solution at increased temperatures and pressures (185 °C and 17 bar) in a microreactor.[60] While a HMF yield of 54% was obtained in 1 min, addition of an organic co-solvent (DMSO) and extracting with a MIBK/2-butanol mixture increased the HMF yield to 83%. Unfortunately, DMSO is partly harmful to the environment and difficult to purify away from HMF.

Acid catalysis, while serving as a common method to access HMF from carbohydrates, also causes hydrolysis of cellulosic polysaccharides to access monomeric sugars. Amarasekara and Owereh used acidic ionic liquids 1-(1-propylsulfonic)-3-methylimidazolium chloride and 1-(1-butylsulfonic)-3-methylimidazolium chloride to both dissolve and hydrolyze cellulose to glucose and other reducing sugars in the presence of water.[61] The highest yields for reducing sugars (62%) and, specifically, glucose (14%) were obtained with 1 h of preheating at 70 °C and continued heating for 30 min after water addition. Seddon and co-workers used H_2SO_4 and methanesulfonic acid to study the rates of hydrolysis of cellobiose to glucose, and a linear dependence on acid concentration was observed.[62] The maximal amount of glucose obtained from cellobiose was 68%, although degradation of glucose occurred in the presence of the strong acids. Hydrolysis of lignocellulosic biomass (miscanthus grass) gave only 5% glucose, though if lignin were extracted first, 30% yields were obtainable, along with 25% yields of xylose. In another study, the Raines laboratory used HCl in the ionic liquid [EMIM]Cl to accomplish hydrolysis of corn stover, another lignocellulosic biomass source.[63] When untreated biomass was hydrolyzed with 10 wt% HCl with water added gradually to enhance glucose stability, the yields

of glucose and xylose were 42% and 71%, respectively. A second stage hydrolysis of the precipitated, unhydrolyzed residues allowed more sugar to be accessed, with final yields of 70% for glucose and 79% for xylose.

While HMF has great potential to serve as a platform chemical, another compound, 5-(chloromethyl)furfural (CMF), is also valuable for its ability to form furanic ethers, which are used as diesel additives. Mascal and Nikitin discovered a method for its conversion and isolation using a two-phase reaction medium.[64] By heating microcrystalline cellulose with 5 wt% LiCl in concentrated HCl at 65 °C, CMF was obtained as the major product. Continuous extraction in 1,2-dichloroethane gave a total recovered CMF yield of 71%.

1.5 Boron catalysts

Recently, researchers have utilized boron-containing compounds to facilitate the transformation of carbohydrates to HMF. Boric acid, which is known to dehydrate alcohols,[65-66] was shown by the Riisager laboratory to dehydrate glucose to HMF in a 42% yield in [EMIM]Cl.[67] Computational modeling suggested the formation of a glucose–borate complex to convert glucose to fructose though an enediol mechanism prior to dehydration to HMF.

1.6 Metal catalysts

Metal catalysts are also used for the transformation of carbohydrates into HMF (Table 1.2). A study by Chohan and Ansari used a variety of metal chlorides to test the conversion of glucose to HMF.[68] They found that all the metal ions they tested resulted in an enhancement in the rate of HMF production relative to acid catalysis, which became even more pronounced at increased catalyst concentrations and increased temperatures. Another study done by Tyrlik and

Table 1.2. Conversion of carbohydrates to HMF using metal ion catalysts

carbohydrate	catalyst	solvent	temp. (°C)	time	HMF molar yield (%)	ref.
glucose	Al_3•$6H_2O$	3:1 THF/H_2O	160	30 min	65	70
maltose	Al_3•$6H_2O$	3:1 THF/H_2O	160	10 min	57	70
cellobiose	Al_3•$6H_2O$	3:1 THF/H_2O	160	10 min	28	70
starch	Al_3•$6H_2O$	3:1 THF/H_2O	160	10 min	50	70
cellulose	Al_3•$6H_2O$	3:1 THF/H_2O	180	30 min	37	70
pine wood	Al_3•$6H_2O$	3:1 THF/H_2O	180	30 min	35	70
fructose	WCl_6	[BMIM]Cl/THF	50	4 h	72	71
cellulose	$MnCl_2$	[SA-BMIM]HSO_4	150	5 h	37	72
fructose	$SnCl_4$	[EMIM]BF_4	100	3 h	62	73
glucose	$SnCl_4$	[EMIM]BF_4	100	3 h	61	73
sucrose	$SnCl_4$	[EMIM]BF_4	100	3 h	65	73
inulin	$SnCl_4$	[EMIM]BF_4	100	3 h	40	73
cellobiose	$SnCl_4$	[EMIM]BF_4	100	3 h	57	73
starch	$SnCl_4$	[EMIM]BF_4	100	24 h	47	73
fructose	$CrCl_3$	[EMIM]Cl	80	3 h	70	74
glucose	$CrCl_2$	[EMIM]Cl	100	3 h	68	74
fructose	NaBr	DMA	100	2 h	93	76
glucose	$CrCl_2$	DMA–LiCl/[EMIM]Cl	100	6 h	62	76
glucose	$CrCl_3$	DMA–LiCl/[EMIM]Cl	100	6 h	67	76
cellulose	$CrCl_3$/HCl	DMA–LiCl/[EMIM]Cl	140	2 h	54	76
corn stover	$CrCl_3$/HCl	DMA–LiCl/[EMIM]Cl	140	2 h	48	76
mannose	$CrCl_2$	DMA–LiBr	100	2 h	69	77
galactose	$CrBr_3$	DMA	120	3 h	33	77
lactose	$CrBr_3$	DMA	120	3 h	41	77
tagatose	$CrCl_2$	DMSO	120	2 h	27	77
cellulose	$CrCl_2$/$CuCl_2$	[EMIM]Cl	120	8 h	59	82
cellulose	$CrCl_2$/$RuCl_3$	[EMIM]Cl	120	3 h	60	83
reed	$CrCl_2$/$RuCl_3$	[EMIM]Cl	120	2 h	41	83
sucrose	$CrCl_3$/NH_4Br	DMA	100	1 h	87	84
glucose	$CrCl_3$/NH_4Br	DMA	100	1 h	74	84
fructose	$CrCl_3$/NH_4Br	DMA	100	1 h	92	84
fructose	NHC/$CrCl_2$	[BMIM]Cl	100	6 h	96	85
glucose	NHC/$CrCl_2$	[BMIM]Cl	100	6 h	81	85
fructose	$LaCl_3$	DMSO	100	4 h	95	87
fructose	$NdCl_3$	DMSO	100	12 h	91	87
fructose	$EuCl_3$	DMSO	100	12 h	92	87
fructose	$DyCl_3$	DMSO	100	12 h	93	87
fructose	$LuCl_3$	DMSO	100	12 h	95	87
glucose	$YbCl_3$	[OMIM]	160	1 h	23	89
glucose	$Yb(OTf)_3$	[BMIM]Cl	140	6 h	24	89

co-workers used aluminum salts in various oxygenated solvents to serve as ligands to the metal center for the conversion of glucose to HMF.[69] The ligands were seen to influence both the yield and selectivity of HMF, with ethanol proving the most efficient.

The Abu-Omar laboratory used $AlCl_3 \cdot 6H_2O$ in a biphasic system of water and THF to transform glucose to HMF in 65% yield.[70] They also obtained good yields from other sugar sources such as maltose, cellobiose, starch, and cellulose. Their best HMF yields were only 35% from pine wood biomass materials, although furfural was obtained in yields greater than 60%. Chan and Zhang used another biphasic system of THF and [BMIM]Cl to transform fructose to HMF.[71] Using tungsten salts, notably WCl_6, they were able to achieve conversion to HMF with 72% yield at 50 °C, and even at room temperature achieved a 60% yield of HMF. Furthermore, they demonstrated the ability of the catalyst to be recycled.

Chou and co-workers used $MnCl_2$ in the acidic ionic liquid 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate ([SA-BMIM]HSO_4) to transform cellulose to HMF.[72] They reported HMF yields of 37%, although some levulinic acid was produced from the rehydration of the HMF product. Han and co-workers utilized $SnCl_4$ to transform carbohydrate materials into HMF in the ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM]BF_4).[73] Good HMF yields were obtained from fructose (62%) and glucose (61%). They also accessed HMF by applying their system to polysaccharides sucrose (65%), inulin (40%), cellobiose (57%), and starch (47%). They postulated that the formation of a five-membered ring chelate complex of the Sn with C1 and C2 hydroxyls of α-glucose facilitated an enolization of glucose to fructose before dehydration to HMF.

Chromium catalysis has rapidly become one of the most well established methods to transform carbohydrates into HMF. From an initial report by the Zhang laboratory in 2007 in

which numerous metal chloride catalysts were screened, $CrCl_2$ and $CrCl_3$ emerged as the premier transition metal catalysts for carbohydrate dehydration.[74] By dissolving the catalysts in [EMIM]Cl, fructose was dehydrated to HMF in yields of 70%, and glucose in yields at 68%. The kinetics of the reaction with $CrCl_2$ paired with other metal chloride catalysts to convert glucose provided some mechanistic insight into the reaction. In the presence of $CrCl_2$, the β-anomer of glucose could coordinate with the metal to facilitate a hydride transfer through a chromium enolate intermediate (Figure 1.5). Work done by Hensen and co-workers supported the complexation of a Cr(II) ion with sugar hydroxyl groups.[75]

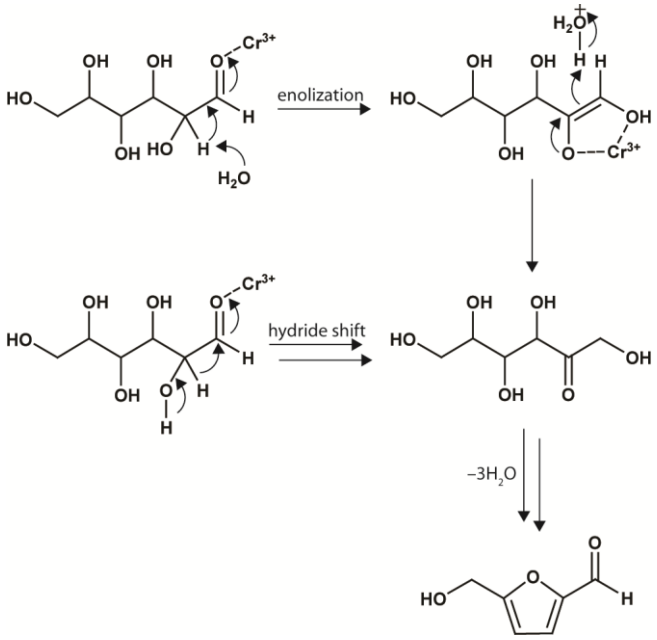

Figure 1.5 Mechanisms for the chromium(III) catalyzed conversion of an aldose into HMF.

Work by the Raines laboratory again used $CrCl_2$ and $CrCl_3$ in a solvent mixture of *N,N*-dimethylacetamide (DMA)–LiCl and [EMIM]Cl.[76] In this solvent system, glucose was transformed into HMF in a yield of 62% using $CrCl_2$ and 67% using $CrCl_3$. These yields were increased further by using the chromium bromide salts. Importantly, the system was amenable to

cellulose dissolution, and by using $CrCl_3$ an HMF yield of 48% was attained from corn stover biomass materials, along with a 37% yield of furfural. Further work in the same group demonstrated that the catalytic system could be applied to convert other sugars such as mannose, galactose, lactose, and tagatose to HMF,[77] and transform xylose and xylan to furfural.[78] Interestingly, however, isotopic labeling studies suggested a formal 1,2-hydride shift occurred to transform an aldose (glucose) to a ketose (fructose) without formation of an enolate intermediate (Figure 1.5). This mechanism was consistent with previous reports by Harris and Feather.[79-81]

The success of chromium chloride catalysts to convert carbohydrates to HMF prompted groups to investigate enhancement of its transformative properties by pairing it with other metal chlorides. Further work by the Zhang laboratory used $CrCl_2$ and $CuCl_2$ in [EMIM]Cl to convert cellulose to HMF with yields consistently near 57%.[82] The HMF was able to be extracted and the system recycled for repeated use while maintaining catalytic performance. Furthermore, they demonstrated that the bi-catalyst system was able to depolymerize cellulose more rapidly than typical acid hydrolysis procedures. Cho and co-workers paired $CrCl_2$ with $RuCl_3$ in [EMIM]Cl to access HMF from cellulose in yields of 60%, and from reed biomass in a 41% yield with a 26% furfural yield.[83] A pairing of $CrCl_3$ with ammonium halides, notably NH_4Br, in DMA by Zhang and co-workers was used to transform sucrose, glucose, and fructose into HMF at 87%, 74%, and 92% yields.[84] They observed a halide effect by varying chloride, bromide, and iodide as the anion of the ammonium salt for glucose conversion to HMF, with bromide being the best. This halide effect is consistent with that observed previously by Raines and co-workers.[76] Yong *et al.* used *N*-heterocyclic carbenes (NHC) as ligands to complex with Cr(II) and Cr(III) in an effort to enhance their catalytic activity.[85] They were able to convert fructose and glucose to HMF at 96%

and 81% yields using 1,3-bis(2,6-diisopropylphenyl)imidazolylidene as the NHC ligand. Both the catalysts and the ionic liquid in this system were able to be recycled for continued use.

The lanthanide metals have been found to serve as Lewis acids in their ionic forms to catalyze the conversion of saccharide materials into HMF. Ishida and Seri found that glucose could be dehydrated to HMF by lanthanide(III) ions, potentially due to the high affinity of these ions for oxygen atoms.[86] HMF was, however, observed to decompose in the reactions. In further work, they demonstrated that high yields of HMF (>90%) could be obtained from fructose using the chloride salts of the lanthanides in DMSO.[87] It was similarly shown that all the lanthanide (III) ions could dehydrate hexoses in water without rehydration to levulinic and formic acids.[88] A kinetic analysis indicated that the rate-determining step in the dehydration is the reaction of the hexose–catalyst complex rather than the association of the two to form the complex.

The activity of the lanthanides was also investigated in ionic liquids. Ståhlberg *et al.* demonstrated the conversion of glucose to HMF in ionic liquids with ytterbium chloride ($YbCl_3$) and ytterbium triflate ($Yb(OTf)_3$).[89] They achieved their best yield for $YbCl_3$ (23%) in 1-octyl-3-methylimidazolium chloride ([OMIM]Cl) and for $Yb(OTf)_3$ (24%) in [BMIM]Cl. While these yields are modest in comparison to chromium catalysts, the ytterbium catalysts tended to give the higher HMF yields in hydrophobic ionic liquids, whereas chromium preferred less hydrophobic ionic liquids such as [EMIM]Cl. Another study by Beckerle and Okuda compared lanthanum chloride ($LaCl_3$) to the rare earth salts ytterium chloride (YCl_3) and scandium chloride ($ScCl_3$) for the conversion of glucose and cellobiose to HMF in the organic solvent DMA.[90] They concluded that the conversion and selectivity have a dependence on the ionic radii of the metal center, with the smaller radius giving greater activity.

1.7 Heterogeneous catalysts

Heterogeneous catalysts are also used to convert carbohydrates to HMF. Their use in conversion reactions can be advantageous for several reasons: facile product separation, catalyst recyclability, high temperature tolerance, and modulation of surface properties (acidity, basicity, and pore size) to achieve maximal HMF selectivities and yields. Here, we discuss ion-exchange resins, heteropolyacids, zirconia compounds, and H-form zeolites (Table 1.3).

Smith and co-workers investigated the dehydration of fructose to HMF using the ion-exchange resin DOWEX 50WX8–100 with microwave heating.[91] Although initial work had used pure DMSO as the solvent, they were interested in using acetone as a co-solvent to serve as a promotor for higher HMF selectivities. In only 10 min, HMF yields of 82% could be obtained in this system while the catalytic activity of the resin was maintained over multiple runs. In another study by the same group, Amberlyst-15 ion-exchange resin was used to dehydrate fructose to HMF in [BMIM]Cl with the addition of various co-solvents.[92] All of the co-solvents tested (acetone, DMSO, methanol, ethanol, ethyl acetate, and super critical CO_2) accessed HMF yields between 78–82%.

Lansalot-Matras and Moreau compared the effect of two ionic liquids, the hydrophilic 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) and the hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF_6), on the dehydration of fructose to HMF using Amberlyst-15.[93] Using DMSO as a co-solvent to assist with sugar solubility, they observed similar HMF yields in both systems of ~80%. But without the DMSO co-solvent, HMF yields dropped to 52% in [BMIM]BF_4, and fructose was not soluble in pure [BMIM]PF_6. Still, the Smith group was able to access HMF yields as high as 83% in only 10 min using the same catalyst in [BMIM]Cl with microwave heating at 80 °C.[94] When the temperature was increased

Table 1.3. Conversion of carbohydrates to HMF using heterogeneous catalysts

carbohydrate	catalyst	solvent	temp. (°C)	time	HMF molar yield (%)	ref.
fructose	DOWEX ion-exchange resin	70:30 acetone/DMSO	150	10 min	82	91
fructose	Amberlyst 15	[BMIM]Cl/acetone	25	6 h	78	92
fructose	Amberlyst 15	[BMIM]Cl/DMSO	25	6 h	78	92
fructose	Amberlyst 15	[BMIM]Cl/methanol	25	6 h	82	92
fructose	Amberlyst 15	[BMIM]Cl/ethanol	25	6 h	80	92
fructose	Amberlyst 15	[BMIM]Cl/ethyl acetate	25	6 h	81	92
fructose	Amberlyst 15	[BMIM]Cl/$scCO_2$	35 (15 MPa)	6 h	79	92
fructose	Amberlyst 15	[BMIM]BF_4/DMSO	80	32 h	87	93
fructose	Amberlyst 15	[BMIM]PF_6/DMSO	80	24 h	78	93
fructose	Amberlyst 15	[BMIM]Cl	80	10 min	83	94
fructose	Amberlyst 15	[BMIM]Cl	80	1 min	82	94
fructose	$[MIMPS]_3PW_{12}O_{40}$	*sec*-butanol	120	2 h	99	95
fructose	$Ag_3PW_{12}O_{40}$	1:2.25 H_2O/MIBK	120	1 h	78	96
glucose	$Ag_3PW_{12}O_{40}$	1:2.25 H_2O/MIBK	130	4 h	76	96
cellulose	$Cr[(OSO_3C_{12}H_{25})H_2PW_{12}O_{40}]_3$	H_2O	150	2 h	53	97
corn stover	$Cr[(OSO_3C_{12}H_{25})H_2PW_{12}O_{40}]_3$	H_2O	150	2 h	31	97
husk	$Cr[(OSO_3C_{12}H_{25})H_2PW_{12}O_{40}]_3$	H_2O	150	2 h	36	97
fructose	SO_4^{2-}–ZrO_2	[BMIM]Cl	100	30 min	88	98
fructose	SO_4^{2-}–ZrO_2	H_2O	200	5 min	36	99
fructose	SO_4^{2-}–ZrO_2	acetone/DMSO	180	20 min	73	99
fructose	CSZ	DMSO	130	4 h	68	100
fructose	CSZA	DMSO	130	4 h	56	100
glucose	CSZ	DMSO	130	4 h	18	100
glucose	CSZA	DMSO	130	4 h	48	100
fructose	a-TiO_2	hot-compressed H_2O	200	5 min	24	101
glucose	a-TiO_2	hot-compressed H_2O	200	5 min	23	101
glucose	ZrO_2	hot-compressed H_2O	200	5 min	18	101
fructose	a-TiO_2	3:1 H_2O/*n*-butanol	200	2 min	18	102
glucose	a-TiO_2	1:10 H_2O/MIBK	180	2 min	29	102
glucose	ZrO_2	1:10 H_2O/MIBK	180	2 min	21	102
starch	a-TiO_2	1:10 H_2O/MIBK	180	2 min	15	102
cellulose	a-TiO_2	1:5 H_2O/MIBK	270	2 min	35	102
fructose	TiO_2 NPs	H_2O	120	5 min	34	103
fructose	TiO_2 NPs	DMSO	140	5 min	54	103
glucose	TiO_2 NPs	H_2O	120	2 min	22	103
glucose	TiO_2 NPs	DMSO	140	5 min	37	103
fructose	DAHM	1:5 H_2O/MIBK	165	2 h	68	104

to 120 °C, a similar yield could be accessed in only 1 min. Furthermore, they demonstrated that 5 wt% water content or lower in the ionic liquid had no adverse effects on HMF yields.

As HMF can be difficult to separate from ionic liquids, Huang and co-workers used the heteropolyacid salt of an ionic liquid cation as a catalyst to convert fructose in *sec*-butanol.[95] Using 1-(3-sulfonicacid)propyl-3-methylimidazolium phosphotungstate ($[MIMPS]_3PW_{12}O_{40}$), they achieved an HMF yield as high as 99% in 2 h. Furthermore, simple precipitation of the catalyst enabled its recycling in further reactions with no loss in activity. Wang and co-workers used another heteropolyacid salt, $Ag_3PW_{12}O_{40}$, to transform both fructose and glucose to HMF.[96] Using a biphasic system of water and MIBK to extract the HMF product, HMF yields of 78% and 76% were obtained from fructose and glucose, respectively. The catalyst was recycled easily, demonstrated no loss of activity over multiple reactions, and was observed to be tolerant to high feedstock concentrations with minimal byproduct formation. Wang and co-workers further used the Brønsted–Lewis–surfactant-combined heteropolyacid $Cr[(OSO_3C_{12}H_{25})H_2PW_{12}O_{40}]_3$ to achieve both cellulose depolymerization and conversion to HMF.[97] A 53% HMF yield was obtained in 2 h at 150 °C using pure cellulose, and HMF yields of 31% and 36% were obtained from corn stover and *Xanthoceras sorbifolia* Bunge husk (a Chinese biomass energy tree), respectively. The catalyst existed as an emulsion during extraction of HMF using MIBK, allowing facile recovery for reuse. The group attributed the catalyst's high activity to its duel Brønsted and Lewis acidities.

A number of groups have also used heterogeneous zirconia (ZrO_2) compounds to facilitate dehydration of carbohydrates to HMF. Qi and co-workers impregnated ZrO_2 with H_2SO_4 to serve as a catalyst for conversion of fructose to HMF in [BMIM]Cl.[98] An 88% yield was obtained in only 30 min at 100 °C. The solid catalyst and ionic liquid were able to be

recycled with constant activity for multiple runs. Another study by Qi and Smith used the sulfated zirconia with microwave heating to dehydrate fructose to HMF in an acetone–DMSO mixture.[99] At 180 °C, a HMF yield of 73% was attained in 20 min. Yet, when the reaction was carried out in water, the HMF yield was only 36%, demonstrating that ZrO_2 has little activity in aqueous systems. Hu and co-workers used an ethylene dichloride solution of chlorosulfonic acid to impregnate $Zr(OH)_4$ (CSZ) and $Zr(OH)_4$–$Al(OH)_3$ (CSZA) to serve as catalysts for fructose and glucose conversion to HMF with maximal respective yields of 68% and 48%.[100] The Zr contained both Brønsted and Lewis acid sites, while the Al contained basic sites. They found that increased basicity promoted isomerization of glucose to fructose, and an ideal mole ratio of 1:1 Zr:Al resulted in their highest HMF yield. The catalyst was also able to be recovered with minimal loss of activity.

Inomata and co-workers used both TiO_2 (anatase and rutile) and ZrO_2 to convert glucose and fructose to HMF in hot-compressed water.[101] They found that rutile TiO_2 was inactive in glucose conversion, while both anatase TiO_2 and the ZrO_2 were able to isomerize glucose to fructose. The anatase TiO_2 was also able to dehydrate fructose to HMF, consistent with ZrO_2 acting as a base while anatase TiO_2 acts as both an acid and a base. McNeff and co-workers again used anatase TiO_2 and ZrO_2 in a fixed bed reactor to access HMF from a variety of carbohydrates (*i.e.*, fructose, glucose, starch, and cellulose).[102] An HMF yield of 35% was obtained from cellulose and extracted with MIBK, and the catalysts were regenerated when they demonstrated diminished activity upon heating to 450 °C for 5 h. Mesoporous TiO_2 nanoparticles (NPs) were used by Bhaumik and Saha to convert carbohydrate materials with microwave heating in aqueous and organic solvents.[103] The maximal HMF yields from fructose

were 34% and 54% in water and DMSO, respectively, and 37% from glucose in DMSO. The nanoparticles were shown to retain their catalytic activity over 4 cycles.

The Moreau laboratory used dealuminated H-form mordenites (DAHM) in a biphasic system of water and MIBK to transform fructose to HMF.[104] They achieved a HMF yield of 68% with the maximal reaction rate achieved using H-mordenites with an 11:1 Si:Al ratio. A correlation was observed between HMF selectivity and the bidimensional structure of the H-mordenites, particularly the absence of cavities within the structure that prevented secondary product formation. Continuous extraction of HMF using MIBK for countercurrent circulation in a continuous heterogeneous pulsed column reactor resulted in an increase in HMF selectivity.

Heterogeneous catalysts have also been used to accomplish the depolymerization and hydrolysis of cellulose. Schüth and co-workers used Amberlyst 15DRY in [BMIM]Cl to produce reducing sugars and cellooligomers from microcrystalline cellulose and wood biomass after an induction period of 1 h.[105] Yet, when they used *p*-toluenesulfonic acid, they observed no induction period. The Shimizu laboratory used the heteropolyacids $H_3PW_{12}O_{40}$ and $H_4SiW_{12}O_{40}$ to access reducing sugars from cellulose in an aqueous phase.[106] They found that a stronger Brønsted acidity resulted in more active reactions. Sulfonated silica/carbon nanocomposites were investigated by Jacobs and Sels to access high glucose yields from cellulose.[107] They attributed the high yields to the hybrid surface facilitating the adsorption of the β-1,4 glucan. Hara and co-workers used amorphous carbon with sulfuric acid, hydroxyl, and carboxylic acid groups to directly hydrolyze solid cellulose in water.[108] They too attributed the activity of the catalysts on their ability to adsorb the cellulose glucan onto the catalytic surface.

1.8 2,5-Dimethylfuran

Currently, the biofuel ethanol is used in blends with gasoline in an effort to supplement petroleum-derived fuels. Nevertheless, the chemical properties of ethanol such as miscibility with water and low enthalpy of vaporization leave much to be desired for an ideal biofuel.[109] Even with substantial progress being made into accessing ethanol from cellulosic materials, the question of its ultimate viability and sustainability as a biofuel remains unanswered.[110] DMF, formed by catalytic hydrogenolysis of HMF, could serve as an alternative to ethanol as a biofuel for gasoline blends. It has an increased energy density compared to ethanol (31.5 MJ/L vs. 23 MJ/L), lower volatility (b.p. 92–94 °C vs. 78 °C), and is immiscible with water (Table 1.4).[111]

Table 1.4. Comparison of base fuel properties

property	gasoline	ethanol	DMF
motored octane number	88.5	89.7	88
heat of combustion (volumetric, MJ/L)	31.82	21.22	29.55
density (kg/L)	0.742	0.789	0.888
boiling point (°C)	31 (initial) 203 (final)	78	93
heat of vaporization (289 K, kJ/kg)	~349	931.1	380.7
water solubility (g/L)	0	> 1000 (miscible)	1.47

Xu and co-workers have done extensive analyses of DMF as a fuel compared to both gasoline and ethanol. One such study was to compare the combustion performance of DMF in a gasoline direct-injection (GDI) engine to gasoline and ethanol.[112] They found that using pure DMF did not adversely affect the performance of the research engine. Different loads of DMF gave different initial combustion durations (though gasoline had a longer duration) and engine knock was induced at 7.1 bar indicated mean effective pressure (IMEP). Furthermore, emissions

of CO, hydrocarbons, NO_x, and particulate matter were all similar to those from gasoline (though emissions from ethanol were lower). Similar conclusions were reached using dual-injection of DMF or ethanol with gasoline in a spark-ignition engine.[113] High performance gains were attained with increased direct injection fractions of both DMF and ethanol, and emissions were mostly reduced using the dual-injection strategy (although CO_2 and NO_x emissions increased for DMF blends with gasoline). They concluded that the dual-injection strategy was most effective at lower fractions of the biofuels for port fuel injection.

In another study by Xu and co-workers, the effect of spark timing and load of DMF was analyzed on a direct-injection spark-ignition (DISI) engine.[114] As compared to gasoline, they found DMF to be more resistant to engine knock, have a lower initial and total combustion duration (as did ethanol, indicating the rapid combustion rate of oxygenated fuels), have a similar volumetric consumption rate (allowing for a similar driving range). Additionally, DMF had a greater loss of thermal energy due to higher combustion temperatures and similar engine-out emissions to gasoline. Ethanol combustion was not limited by engine knock, but it has a lower volumetric consumption rate than both gasoline and DMF. Unsurprisingly, they also found that ethanol had the highest laminar burning velocity, followed by gasoline and then DMF.[115] This indicates that a laminar flame propagates most quickly in ethanol, though the velocities of gasoline and DMF were most similar.

The Rothamer group compared the knocking propensity of blends of DMF and ethanol with gasoline to base gasoline in a single-cylinder direct-injection research engine.[111] The five blends tested were 5, 10, and 15% DMF in gasoline, 10% ethanol in gasoline, and a blend of 10% DMF and 10% ethanol in gasoline. While all the blends showed improvement in the knock-limited spark advance relative to gasoline, ethanol had a greater capacity than DMF to reduce

engine knock at the same volumetric blend. The blend of both DMF and ethanol, however, showed the greatest performance. The greater knock resistance of ethanol versus DMF is hypothesized to be due to ethanol's higher heat of vaporization. They concluded that while ethanol could be more effective at reducing engine knock than DMF, the higher energy density of DMF could make it a competitive blending additive. Additionally, co-blending of DMF and ethanol in gasoline could give a greater benefit than either biofuel blended with gasoline alone.

With the potential advantages of DMF as a biofuel, technologies must exist to enable its accessibility from biomass materials. The Dumesic laboratory developed a two-step process to transform fructose to DMF.[31] Acid-catalyzed dehydration of fructose in a biphasic reactor led to the formation of HMF, which was then extracted into 1-butanol. The HMF was subjected to hydrogenolysis using a 3:1 atomic ratio copper–ruthenium (Cu:Ru/C) catalyst to access DMF in 71% yield. The Cu:Ru/C catalyst was more resistant to poisoning by chloride anions than copper catalysts, and could be regenerated by flowing hydrogen at the reaction temperature of 220 °C. The Raines laboratory used the same catalyst to access DMF from corn stover biomass in a two-step process.[76] Using $CrCl_3$ in a [EMIM]Cl/DMA–LiCl mixture, they converted untreated corn stover to HMF, which was purified with ion-exclusion chromatography to remove chloride anions and prevent poisoning of the Cu:Ru/C catalyst. The recovered HMF was subjected to hydrogenolysis in 1-butanol to give DMF in 49% yield, with an overall 9% yield from corn stover.

Maat and van Bekkum used a palladium (Pd/C) catalyst to access DMF from HMF in 1-propanol.[116] By GC-MS, they observed formation of 5-hydroxymethyl-2-(propyloxymethyl)furan during the initial stages of hydrogenolysis. The alcohol bond was the first to be hydrogenolyzed, followed by the ether bond to access DMF. Similar reactivity was

observed in 2-propanol, but 2,5-bishydroxymethylfuran became the major product in 1,4-dioxane (Figure 1.6). Thananatthanachon and Rauchfuss developed a one-pot process to convert fructose to DMF using formic acid.[117] The formic acid served to dehydrate the fructose to HMF, which upon addition of a Pd/C catalyst in tetrahydrofuran, underwent hydrogenolysis using the formic acid as a hydrogen source to access 2,5-bishydroxymethylfuran before deoxygenation to DMF. Chidambaram and Bell also used a Pd/C catalyst to access DMF from glucose in an ionic liquid/acetonitrile mixture in a two-step process.[118] Glucose was converted to HMF using the heterocatalyst 12-molybdophosphoric acid, after which the catalyst could be replaced with the Pd/C without isolation of HMF to access DMF in a 16% yield. The lower yield was attributed to decreased reaction temperature, duration, and solubility of H_2 in ionic liquids.

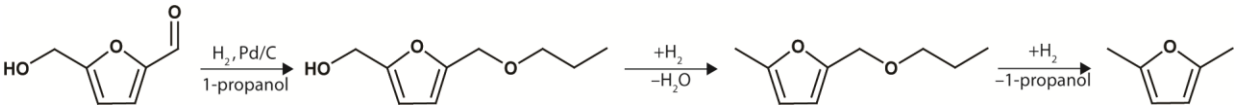

Figure 1.6 Catalytic hydrogenolysis of HMF to DMF.

1.9 Conclusions

HMF has the potential to serve as a renewable platform for fuels and chemicals in place of fossil fuel reserves. Considerable work has been done to access HMF from carbohydrate resources, although more remains to be done. Much progress has been reported for the conversion of fructose, yet the conversions of other carbohydrates such as glucose and cellulose remain difficult. The barrier is due primarily to the isomerization of glucose to fructose, which requires more complex catalytic materials than those used for fructose dehydration to HMF. Transition metals, lanthanide metals, and heterogeneous catalysts are some of the most studied

catalysts for glucose isomerization to fructose. These types of catalysts are, however, often harsh or toxic, and with today's emphasis on green chemistry, it is imperative that processes for the transformation of carbohydrates be environmentally benign. Furthermore, they must be amenable to implementation on a large-scale that will be required to meet the demands of the future. As ionic liquids are typically costly, it is essential that processes involving them mitigate costs by using high carbohydrate loadings and facilitate their recovery for continued use.

2,5-Dimethylfuran is a biofuel that is accessed from HMF with great promise to meet our fuel demands. Studies have shown it has the capacity to be used as a fuel or part of a fuel blend in our existing fuel infrastructure. While it has very similar properties to existing gasoline, more work must be done in order to obtain it in high yields from carbohydrate materials. Initial studies have focused on converting fructose and HMF to DMF, but almost no work has been done to access it from biomass resources. Furthermore, it often requires specific reaction conditions to hydrogenolyze HMF to DMF, although some work has been done to better enable this transformation using more robust and simplified reagents and catalysts.

The road to using carbohydrate materials as a sustainable energy and fuel resource is long, and there is still a long way to go. Many challenges and obstacles have yet to be overcome, or even realized. HMF may indeed help to realize this goal, but it is only by continuing to seek new and better alternatives to fossil fuels that we shall develop a green, sustainable energy economy.

1.10 Thesis Summary

Rapid progress has been made toward the conversion of carbohydrate materials in recent years. In Chapter Two, I describe a process I invented to produce HMF from fructose using

hydrobromic acid (HBr) in the industrial solvent sulfolane. In research presented in Chapter Three, I developed a conversion method that was not reliant on toxic chromium to transform glucose, cellulose, and cellulosic municipal waste to HMF using *ortho*-carboxyl phenylboronic acids with hydrated magnesium chloride in ionic liquids. I expanded the scope of the bicatalytic system in Chapter Four to transform all the D-hexose sugars and varying cellodextrins to HMF, and explored the effect of additional substituents on the boronic acids on HMF yields. Work reported in Chapter Five details my development of novel fluorous labeled ionic liquids that enable cellulose dissolution. I further used one of the ionic liquids to perform cellulose hydrolysis and separated the ionic liquid from the reaction mixture using a fluorous phase. In research presented in Chapter Six, I detail the scale-up of a process using acid to hydrolysis biomass to sugars and recover the sugars using simulated moving bed chromatography. The sugars were found to be suitable for consumption by microbial ethanologens. Finally, I highlight potential future directions of my research in Chapter Seven.

CHAPTER TWO*

CONVERSION OF FRUCTOSE TO 5-(HYDROXYMETHYL)FURFURAL IN SULFOLANE

2.1 Abstract

Sulfolane, an industrial solvent, allows for the efficient conversion of fructose into 5-(hydroxymethyl)furfural (HMF), a key platform chemical. Yields of ≥90 % are attainable with catalytic HBr in 1 h at 100 °C. The use of an inexpensive catalyst at a low concentration, low temperature, and short reaction time makes the process amenable for large-scale access to HMF.

2.2 Author Contributions

R.T.R. proposed using sulfolane as a solvent for fructose conversion to HMF. B.R.C. performed the research and drafted the manuscript. B.R.C. and R.T.R. designed experiments, analyzed the data, and edited the manuscript and figures.

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2.3 Introduction

Population growth has created an expanding gap between the supply and demand of both energy and chemicals. Non-renewable fossil sources such as coal, natural gas, and petroleum are the source of nearly 86% of the world's energy and 96% of its organic chemicals.[1] Diminishing reserves of these sources, rising atmospheric CO_2 levels, and socioeconomic concerns require a reduction in our dependence on these sources.[2,4,119]

Furanics, such as 5-(hydroxymethyl)furfural (HMF), hold special promise. Their carbon skeletons are identical to those in cellulose and hemicellulose, which are the most abundant organic molecules on our planet. HMF could serve as a sustainable source of liquid fuels and chemicals (Figure 2.1).[8,13-14,26,31,53] For example, HMF is already a feedstock for common polyester building blocks, including 2,5-furandicarboxylic acid (**1**), 2,5-bis(hydroxymethyl)furan (**2**), and 2,5-bis(hydroxymethyl)tetrahydrofuran (**3**).[13-14,26,53] In addition, HMF is a precursor to 2,5-dimethylfuran (**4**), which is a promising alternative liquid transportation fuel.[112,114-115] Obtaining HMF from biomass would help to bridge the growing gap between the supply and

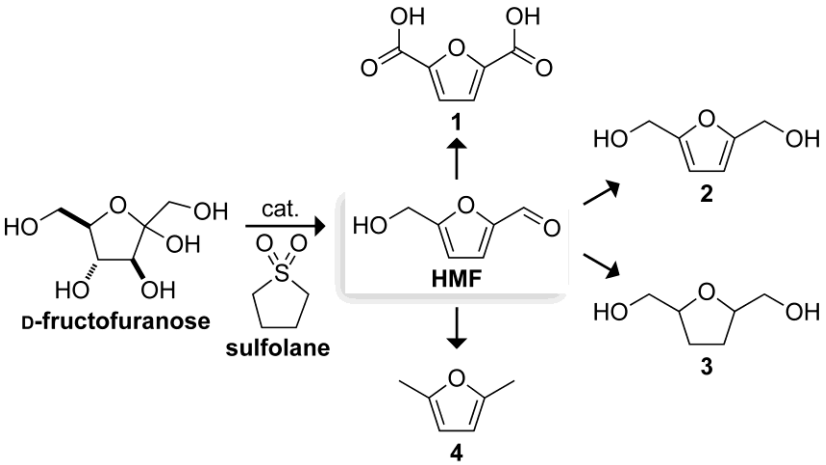

Figure 2.1 Production of HMF from D-Fructose. HMF serves as a platform molecule for a range of other molecules.

demand of energy and chemicals. Doing so requires processes to convert carbohydrates to HMF selectively and efficiently.[74,76-78]

Rapid progress has been made in the synthesis of HMF from simple sugars. Most notably, multiple conditions are now known to enable the dehydration of D-fructose to HMF.[120-124] This reaction can be performed in acidified water[51,59-60,81] (including sub- and supercritical states[56-57,125]), organic solvents,[7,52,58,99,126] multi-component mixtures,[53,55,71,76,91,104] and ionic liquids.[74,92-94,127] The aqueous reactions typically entail high temperatures or pressures that lead to energetic inefficiency and substantial degradation of HMF.

Organic solvents and ionic liquids provide advantages. First, they discourage the formation of acyclic fructose, which can polymerize along with HMF into an insoluble, amorphous polymer known as humin.[28] Second, they limit the water content in the reaction mixture, thereby diminishing HMF decomposition into levulinic and formic acids.[16-20,29] Nevertheless, the expense of ionic liquids and the limited industrial applicability of most organic solvents can be problematic. For example, dimethyl sulfoxide (DMSO; bp 189°C) has been used to access high yields of HMF from fructose.[126,128-129] Heating DMSO to >150°C, however, leads to its decomposition, as does exposure to acid.[130] This instability limits the utility of DMSO in industrial processes.

We envisioned that tetramethylene sulfone ("sulfolane") could be a superior solvent for HMF production. Sulfolane is a polar, aprotic solvent that is non-volatile (bp 285°C) and miscible with both water and hydrocarbons. Developed by the Shell Oil Company in the late 1950s, sulfolane is a preferred industrial solvent for the extraction of aromatics and purification of natural gas.[131-133] In addition, sulfolane has been used for the pyrolysis of cellulose to access HMF and furfural.[134-137] We view sulfolane as a robust congener of dimethyl sulfoxide. For

example, unlike DMSO, sulfolane is stable at temperatures up to 240°C and under acidic conditions. Herein, we report that sulfolane supports the high-yielding, energy-efficient transformation of D-fructose into HMF using low loading of an inexpensive catalyst, HBr.

2.4 Results and Discussion

We realized that the yield of HMF from the dehydration of fructose should depend on the catalyst identity, concentrations of the reacting species, and the reaction temperature and duration. We began our investigations by screening for an efficient catalyst. Previously, high yields of HMF from fructose had been reported using $CrCl_2$ in ionic liquids (65%)[74] and LiCl in dimethylacetamide (65%).[74,76] Upon using these two metal chlorides as catalysts, we found that HMF yields with LiCl alone (67%) exceeded those with added $CrCl_2$ (53%). We tested other metal chlorides, both alone (Table 2.1) and with LiCl (Table 2.2), but did not find an additive effect. Hence, we designated LiCl as a preferred catalyst. Next, we investigated the effect of LiCl loading on HMF yields. Optimization of HMF yields with variable LiCl concentrations soon demonstrated that increasing the concentration of LiCl above a 1:1 w/w ratio with fructose provided no improvement in either conversion rates or yields (Table 2.3). Conversely, decreasing the concentration of LiCl below a 1:1 w/w ratio with fructose led to decreased HMF conversion rates and yields.

Table 2.1 Effect of chloride salts on the conversion of D-fructose to HMF in sulfolane

catalyst	amount, wt%[a]	HMF yield (%)[b]
—	0	14
LiCl	**100**	**67**
$CrCl_2$	100	5
CuCl	100	6
$CuCl_2$	100	7
$AlCl_3$	100	6
KCl	100	22
$MgCl_2 \cdot 6H_2O$	100	35
$MnCl_2 \cdot 4H_2O$	100	11
NaCl	100	19
RbCl	100	31
$ZnCl_2$	100	1
$BaCl_2 \cdot 2H_2O$	100	17
$CdCl_2 \cdot 2.5H_2O$	100	2
$CaCl_2 \cdot 2H_2O$	100	8
CsCl	100	25
$CoCl_2 \cdot 6H_2O$	100	11
$PdCl_2$	100	0
$NiCl_2 \cdot 6H_2O$	100	21
$RuCl_3(H_2O)_3$	100	0
$FeCl_3$	100	0
$VaCl_3$	100	21
$MoCl_3$	100	0
$PtCl_2$	100	1
$LaCl_3 \cdot 7H_2O$	100	7

[a]Catalyst wt% is relative to fructose (83 mg/g) in the reaction mixture.
[b]Yields are based on HPLC analysis of reactions for 2 h at 90 °C.

Table 2.2 Effect of metal chlorides on the conversion of D-fructose to HMF in sulfolane

catalyst, wt%[a]	LiCl additive, wt%[a]	HMF yield (%)[b]
LiCl, 100	**0**	**67**
$CrCl_2$, 5	100	52
CuCl, 5	100	59
$CuCl_2$, 5	100	56
$AlCl_3$, 5	100	49
KCl, 5	100	58
$MgCl_2 \cdot 6H_2O$, 5	100	59
$MnCl_2 \cdot 4H_2O$, 5	100	60
NaCl, 5	100	59
RbCl, 5	100	60
$ZnCl_2$, 5	100	60
$BaCl_2 \cdot 2H_2O$, 5	100	26
$CdCl_2 \cdot 2.5H_2O$, 5	100	51
$CaCl_2 \cdot 2H_2O$, 5	100	44
CsCl, 5	100	44
$CoCl_2 \cdot 6H_2O$, 5	100	46
$PdCl_2$, 5	100	62
$NiCl_2 \cdot 6H_2O$, 5	100	39
$RuCl_3(H_2O)_3$, 5	100	64
$FeCl_3$, 5	100	62
$VaCl_3$, 5	100	56
$MoCl_3$, 5	100	51
$PtCl_2$, 5	100	63
$LaCl_3 \cdot 7H_2O$, 5	100	50

[a]Catalyst and additive wt% are relative to fructose (83 mg/g) in the reaction mixture.
[b]Yields are based on HPLC analysis of reactions in sulfolane for 2 h at 90°C.

Table 2.3. Effect of LiCl:fructose on the conversion of D-fructose to HMF in sulfolane

LiCl:fructose, w/w[a]	HMF yield (%)[b]
1.0:1.0	**58**
1.5:1.0	60
2.0:1.0	55
2.5:1.0	57

[a]The concentration of fructose was 83 mg/g in the reaction mixture.
[b]Yields are based on HPLC analysis of reactions in sulfolane for 2 h at 90°C.

We then sought to identify the optimal fructose loading in sulfolane. We also varied the LiCl:fructose ratio during these trials. The effect of that ratio on HMF yield was negligible (Table 2.4). Hence, we employed a 1:1 w/w LiCl:fructose ratio in a wider range of fructose:sulfolane ratios. Again, changes in HMF yield were negligible (Table 2.5), indicating that the yield of fructose attainable from HMF in sulfolane is not highly sensitive to reagent concentrations.

Having explored the effects of catalyst type and concentration, we next sought to optimize the reaction temperature and duration. These reaction conditions are especially crucial, as HMF decomposes at elevated temperatures. Yet, high HMF yields are obtainable at short times only at elevated temperatures. Hence, a variety of temperatures were screened by taking aliquots at 30- or 60-min intervals. At 90–100°C, HMF reached a peak at 2 h (Figure 2.2). Achieving the same HMF yields at <90°C required reaction times of at least 5 h, whereas temperatures >100°C gave lower HMF yields, even at a reaction time of 1.5 h. Hence, we found that reactions were best performed at 90 or 100°C for 1–2 h. The temperature and duration of this process provides a method for fructose to HMF conversion at a more energy efficient temperature with a short reaction time without any adverse effects on overall HMF yields.

Knowing that the dehydration of fructose is acid-catalyzed in aqueous systems,[51,59-60,81] we sought benefts from acid catalysts. So, we tested HCl, HNO_3, H_2SO_4, and HOAc as additives to the LiCl catalyst. Of the four, HCl and HOAc provided HMF yields over 60% (Table 2.6). Interestingly, these two were the strongest and weakest, respectively, of the four acids. The high HMF yields from these two acids led us to vary their molar concentrations in the absence of LiCl. Interestingly, only HCl availed HMF yields comparable to those obtained using LiCl alone. The conversion of fructose to HMF appeared to benefit from the presence of a halide ion. Using

Table 2.4. Effect of LiCl:fructose and sulfolane:fructose ratios on the conversion of D-fructose to HMF in sulfolane

LiCl:fructose, mol/mol	sulfolane:fructose, mol/mol	time (h)	HMF yield (%)[a]
4.25:1.00	16.5:1.0	2	65
4.25:1.00	16.5:1.0	3	65
4.25:1.00	16.5:1.0	4	58
3.25:1.00	16.5:1.0	2	62
3.25:1.00	16.5:1.0	3	62
3.25:1.00	16.5:1.0	4	60
2.25:1.00	16.5:1.0	2	62
2.25:1.00	16.5:1.0	3	62
2.25:1.00	16.5:1.0	4	60
1.25:1.00	16.5:1.0	2	56
1.25:1.00	16.5:1.0	3	59
1.25:1.00	16.5:1.0	4	60
4.25:1.00	13.5:1.0	2	63
4.25:1.00	13.5:1.0	3	62
4.25:1.00	13.5:1.0	4	58
3.25:1.00	13.5:1.0	2	60
3.25:1.00	13.5:1.0	3	60
3.25:1.00	13.5:1.0	4	59
2.25:1.00	13.5:1.0	2	60
2.25:1.00	13.5:1.0	3	60
2.25:1.00	13.5:1.0	4	59
1.25:1.00	13.5:1.0	2	58
1.25:1.00	13.5:1.0	3	59
1.25:1.00	13.5:1.0	4	59
4.25:1.00	10.5:1.0	2	60
4.25:1.00	10.5:1.0	3	60
4.25:1.00	10.5:1.0	4	58
3.25:1.00	10.5:1.0	2	60
3.25:1.00	10.5:1.0	3	60
3.25:1.00	10.5:1.0	4	59
2.25:1.00	10.5:1.0	2	59
2.25:1.00	10.5:1.0	3	59
2.25:1.00	10.5:1.0	4	58
1.25:1.00	10.5:1.0	2	54
1.25:1.00	10.5:1.0	3	58
1.25:1.00	10.5:1.0	4	59

[a]Yields are based on HPLC analysis of reactions in sulfolane at 90°C.

LiBr as the halide source increased HMF yields by ~10% (Table 2.7). Remarkably, the analogous bromide source, HBr, provided HMF with a yield of 93%. A likely byproduct was humin, as evidenced by the formation of insoluble material in the reaction vessel. To our knowledge, this HMF yield is the highest for a conversion at ambient pressure and ≤100°C. To complete this analysis, we tested the iodide sources HI, LiI, and NaI as catalysts, and obtained yields of ≤30%.

Table 2.5 Effect of sulfolane:fructose ratio on the conversion of D-fructose to HMF in sulfolane

sulfolane:fructose, mol/mol	time (h)	HMF yield (%)[a]
13.5:1.0	2	63
13.5:1.0	3	62
15.0:1.0	2	63
15.0:1.0	3	62
16.5:1.0	2	65
16.5:1.0	3	65
21.0:1.0	2	67
21.0:1.0	3	66
22.5:1.0	2	67
22.5:1.0	3	66
24.0:1.0	2	67
24.0:1.0	3	65
25.5:1.0	2	65
25.5:1.0	3	66
27.0:1.0	2	65
27.0:1.0	3	63

[a]Yields are based on HPLC analysis of reactions containing LiCl:fructose 1/1 at 90°C.

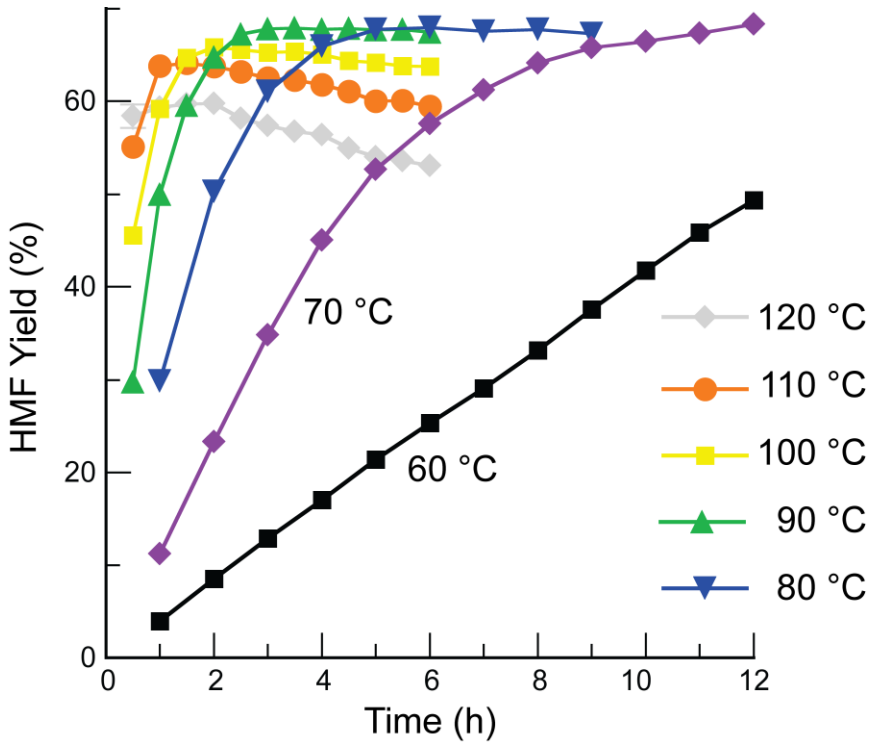

Figure 2.2 Effect of temperature on the production of HMF from D-fructose in sulfolane containing LiCl (100 wt%). Yields are based on HPLC analysis.

Table 2.6 Effect of acid on the conversion of D-fructose to HMF in sulfolane

acid, mol%[a]	time (min)	LiCl, mol%[b]	HMF yield (%)[c]
HCl, 3	**120**	**250**	**60**
HCl, 6	**60**	**250**	**61**
H_2SO_4, 3	120	250	46
H_2SO_4, 6	120	250	48
HNO_3, 3	120	250	24
HNO_3, 6	120	250	23
HOAc, 3	**60**	**250**	**66**
HOAc, 6	60	250	56
HCl, 9	**15**	**0**	**68**
HCl, 9	**30**	**250**	**60**
HCl, 12	**15**	**0**	**65**
HCl, 12	**15**	**250**	**63**
HCl, 15	**15**	**0**	**62**
HCl, 15	**15**	**250**	**63**
HOAc, 9	45	0	0
HOAc, 9	60	250	21
HOAc, 12	45	0	2
HOAc, 12	**60**	**250**	**61**
HOAc, 15	45	0	3
HOAc, 15	15	250	32

[a]Mol% is relative to the solvent.
[b]Mol% is relative to fructose.
[c]Yields are based on HPLC analysis of reactions at 90°C.

Table 2.7 Effect of bromide and iodide on the conversion of D-fructose to HMF in sulfolane

catalyst, wt%[a]	time (h)	HMF yield (%)[b]
LiBr, 100	2	78
LiBr, 100	4	79
HBr, 2	1	80
HBr, 2	**2**	**91**
HBr, 5	**1**	**93**
HBr, 5	2	82
HBr, 7	1	86
HBr, 7	2	81
HBr, 9	**0.5**	**90**
HBr, 9	1	79
HBr, 28	0.5	66
HBr, 28	1	64
LiI, 100	2	8
LiI, 100	4	18
LiI, 100	6	30
NaI, 100	2	34
NaI, 100	4	45
HI, 3.75	0.5	28
HI, 3.75	1	28
HI, 7.5	0.5	29
HI, 7.5	1	22

[a]Catalyst wt% is relative to fructose (67 mg/g) in the reaction mixture.
[b]Yields are based on HPLC analysis of reactions at 100°C.

What is the basis for the superior catalytic activity of HBr? We suspect that the Brønsted acid facilitates formation of a fructofuranosyl oxocarbenium ion that suffers nucleophilic attack by a bromide ion to form a 2-deoxy-2-bromo intermediate.[76] This intermediate, which would have a lower tendency than the oxocarbenium ion to undergo deleterious side reactions, then loses HBr to form an enol. Two subsequent dehydration steps catalyzed by the Brønsted acid and bromide base would lead to HMF.

Next, we explored the breadth of our conversion process. Only ketohexoses gave appreciable furanic yields (Table 2.8). In addition, HBr in DMSO did support the conversion of fructose into HMF (Table 2.9), but at lower yields than obtainable in sulfolane (Table 2.7).

Table 2.8 Conversion of sugars to a furanic in sulfolane

substrate	time (h)	HMF yield (%)[a]	furfural yield (%)[a]
Cellobiose	1.5	4	—
Lactose	1.5	3	—
Glucose	1	6	—
Galactose	2	0	—
Mannose	0.5	2	—
Sorbose	0.5	41	—
Tagatose	0.5	43	—
Arabinose	0.5	—	2
Xylose	0.5	—	30

[a]Reaction mixtures contained 5 wt% HBr relative to sugar (100 mg/g) at 100°C. Yields are based on HPLC analysis of reactions.

Table 2.9 Conversion of D-fructose to HMF in DMSO

HBr (wt%)[a]	time (h)	HMF yield (%)[b]
2	0.5	66
5	**2**	**71**
7	2	64
9	1.5	52

[a]HBr wt% is relative to fructose (100 mg/g) in the reaction mixture.
[b]Yields are based on HPLC analysis of reactions at 100°C.

Additionally, we sought to isolate HMF from sulfolane by adapting a known extraction procedure.[53] Our results were encouraging in that the organic and aqueous phases can be modified such that HMF favors the organic layer of methylisobutylketone (MIBK) and 2-butanol over the aqueous layer of water and sulfolane while sulfolane favors the aqueous phase (Table 2.10). We achieved the best partitioning by using a H_2O:sulfolane 9/1 aqueous phase and

MIBK:2-butanol 8/2 organic phase. Optimization of a continuous extraction process could lead to even greater partitioning of HMF into the organic layer.

Table 2.10 Extraction of HMF from sulfolane[a]

aqueous phase composition	organic phase composition	R_{HMF}[b]	$R_{sulfolane}$[c]
H_2O:sulfolane 9/1	MIBK	1.01	0.60
H_2O:sulfolane 9/1	MIBK:2-butanol 9/1	1.32	0.67
H_2O:sulfolane 9/1	**MIBK:2-butanol 8/2**	**1.50**	**0.73**
H_2O:sulfolane 8/2	MIBK	0.95	0.61
H_2O:sulfolane 8/2	MIBK:2-butanol 9/1	1.24	0.69
H_2O:sulfolane 8/2	MIBK:2-butanol 8/2	1.40	0.76
H_2O:sulfolane 7/3	MIBK	0.91	0.66
H_2O:sulfolane 7/3	MIBK:2-butanol 9/1	1.14	0.74
H_2O:sulfolane 7/3	MIBK:2-butanol 8/2	1.28	0.81
H_2O:sulfolane 6/4	MIBK	0.85	0.70
H_2O:sulfolane 6/4	MIBK:2-butanol 9/1	1.06	0.78
H_2O:sulfolane 6/4	MIBK:2-butanol 8/2	1.26	0.83

[a]Water was added to sulfolane containing HMF, followed by MIBK and 2-butanol.
[b]$R_{HMF} = [HMF]_{org}/[HMF]_{aq}$
[c]$R_{sulfolane} = [sulfolane]_{org}/[sulfolane]_{aq}$

Finally, we tested the scalability of our optimized conditions for HMF production by performing reactions on 5 g of fructose. These conditions (sulfolane containing 5 wt% HBr, 1 h, 100°C) consistently provided HMF in yields near 90%, instilling optimism for their utility in an industrial-scale process.

2.5 Conclusions

We have developed a high-yielding process to access HMF from D-fructose in sulfolane. The use of an inexpensive catalyst (HBr) at a low concentration (5 wt%), low temperature (100°C), and short reaction time (1 h) makes our process amenable for large-scale access to

HMF. We propose that transformation of the nascent HMF in sulfolane, which is among the most versatile of solvents, could be the basis for an advantageous route to liquid fuels and chemicals (Figure 2.1).

2.6 Acknowledgments

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2.7 Materials and Methods

2.7.1 Materials

Commercial chemicals were reagent grade or better obtained from Sigma–Aldrich (Milwaukee, WI) and were used without further purification. Reactions were performed in 4-mL glass vials heated in a temperature-controlled oil bath with magnetic stirring or in a temperature-controlled VWR Mini Shaker at 600 rpm.

2.7.2 Analytical Methods

At known times, reaction mixtures were diluted with a known mass of deionized water, subjected to centriguation at 12,000 rpm for 5 min to remove insoluble products, and analyzed by HPLC. Product concentrations were calculated from HPLC-peak integrations, which were then used to calculate yields. HPLC was performed using either a Waters system equipped with two 515 pumps, a 717 Plus autosampler, and a 996 photodiode array detector, or an Agilent 1200 system equipped with refractive index and photodiode array detectors. HMF was analyzed by either reversed-phase chromatography with a Varian Microsorb-MV 100-5-C18 column (250 ×

4.6 mm) using a 93:7 water/acetonitrile mobile phase at a flow rate of 1 mL/min and 25°C, or by ion-exclusion chromatography with a Bio-Rad Aminex HPX-87H column (300 × 7.8 mm) using a 5 mM H_2SO_4 mobile phase at a flow rate of 0.6 mL/min at 65°C.

2.7.3 Representative Procedure for Conversion of D-Fructose to HMF

D-Fructose (0.10 g, 0.563 mmol) was dissolved in sulfolane (1.40 g, 11.7 mmol). Hydrobromic acid (4.7 mg, 0.058 mmol) was added, and the reaction mixture was heated at 100°C for 2 h. At 30-min intervals, aliquots were removed, quenched with deionized water, and analyzed by HPLC. Any humins were removed prior to HPLC analysis. Only low levels of colored products, other than HMF, were detected by HPLC. For reaction mixtures containing salts rather than acid, the salts and fructose were dissolved in sulfolane prior to heating.

Experiments to isolate HMF were done after using the optimized reaction conditions (67 mg/g fructose in sulfolane containing 5 wt% HBr for 1 h at 100°C). Water was added to the reaction mixture, followed by the MIBK and 2-butanol. Aliquots of the organic and aqueous layers were analyzed by HPLC to determine values of $R_{org/aq}$.

CHAPTER THREE*

ORGANOCATALYTIC CONVERSION OF BIOMASS INTO FURANICS

3.1 Abstract

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 employ harsh reaction conditions or toxic heavy metal catalysts, deterring large-scale implementation of a cellulose-conversion process. 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 to HMF in yields comparable to processes that use toxic heavy metal catalysts. The route, which also allows for facile catalyst recovery and recycling, provides a green prototype for cellulose conversion technologies.

3.2 Author Contributions

M.J.P. proposed using phenylboronic acids for carbohydrate conversion to HMF. B.R.C. designed the dual-catalyst system of *ortho*-carboxyl phenylboronic acids and magnesium chloride, performed the research, and drafted the manuscript. B.R.C., M.J.P., and R.T.R. designed experiments, analyzed the data, and edited the manuscript and figures.

*This chapter will be published, in part, under the same title. Reference: Caes, B.R.; Palte, M.J.; Raines, R.T. *In preparation*.

3.3 Introduction

The dependence on fossil fuel resources for energy and chemicals has become unsustainable.[1] Abundant, renewable biomass resources hold great promise to meet the fuel and chemical demands of the future,[4,138] but must recapitulate the wide array of products derived from fossil fuels. The six-carbon furanic 5-(hydroxymethyl)furfural (HMF) has the potential to meet this challenge.[13] HMF can be transformed into a variety of useful products, such as common polyester building blocks[14] and the promising liquid fuel 2,5-dimethylfuran.[112,114-115] The carbon skeleton of HMF is identical to those of the hexose sugars that are the primary components of cellulose and hemicelluloses in biomass. Accessing this resource requires a process that efficiently transforms these carbohydrates into HMF.

The conversion of cellulose to HMF proceeds through three steps: hydrolysis of cellulose to glucose, isomerization of glucose to fructose, and dehydration of fructose to HMF (Figure 3.1). Although numerous methods exist for transforming glucose and fructose into HMF,[53,74] few

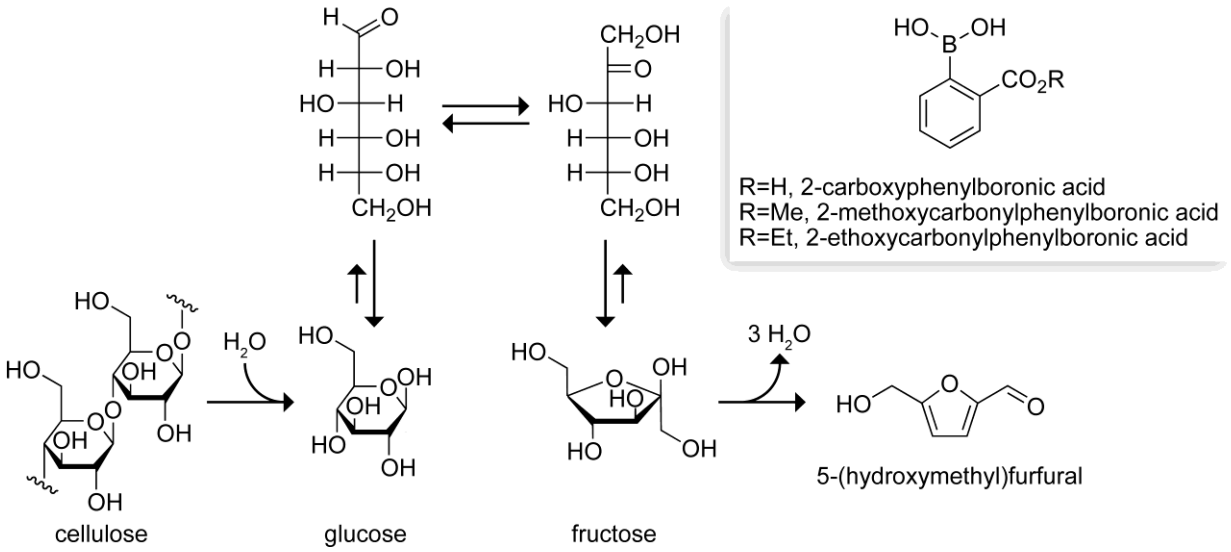

Figure 3.1 Route for the conversion of cellulose to 5-(hydroxymethyl)furfural (HMF). Inset: Structures of organocatalysts for the conversion.

are capable of producing HMF in high yields directly from cellulose. Solid acids[102,139] and heavy metals[74,76,82-83,140] are the best known catalysts for this conversion. The inefficiency of solid acid catalysts and the environmental toxicity of heavy metals diminish their potential impact.[141-142] 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.

3.4 Results and Discussion

Our initial experiments focused on discovering an alternative to heavy metals for accessing HMF from glucose. As a solvent, we choose dimethylacetamide (DMA), a polar aprotic solvent that has served as the medium for other biomass conversions.[76-78] We screened a variety of metal chlorides (Table 3.1) and found that magnesium, nickel, zinc, cerium, or lanthanum, like chromium, provides appreciable yields of HMF (Table 3.2). We chose to employ magnesium, due to its low toxicity and its low cost as one of the most abundant elements in Earth's crust.[143]

To increase the efficiency of the conversion while maintaining environmental benignancy, we turned to organocatalysis.[138,144] 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.[145-147] We reasoned that these attributes could 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.[137] Boric

Table 3.1 Screen of metal halides for the conversion of glucose to HMF in DMA

metal halide	*T* (°C)	time (h)	HMF yield (%)
$CaCl_2 \cdot 2H_2O$	120	6	13
LiCl	120	6	5
LiBr	120	6	1
NaCl	120	6	0
KCl	120	6	0
CuCl	120	6	12
$CuCl_2$	120	6	9
CsCl	120	6	0
$FeCl_2$	120	4.5	7
$FeCl_3$	120	4.5	4
$MoCl_3$	120	1.5	12
VCl_3	120	1.5	16
RbCl	120	6	0
$BaCl_2 \cdot 2H_2O$	120	6	0
$CoCl_2 \cdot 6H_2O$	120	3	11
$PdCl_2$	120	6	4
$MnCl_2 \cdot 4H_2O$	120	6	10

Metal halides were at 3 equiv relative to glucose. Glucose was at 10 wt% relative to DMA. HMF yield (HPLC) is relative to glucose.

Table 3.2 Conversion of glucose to HMF in DMA

metal chloride, mol%	boronic acid	*T* (°C)	time (h)	HMF yield (%)
—	—	100	6	0
$CrCl_2$, 25	**—**	**100**	**6**	**58**
$MgCl_2 \cdot 6H_2O$, 200	**—**	**120**	**6**	**29**
$NiCl_2 \cdot 6H_2O$, 300	—	120	3	32
$ZnCl_2$, 300	—	120	6	21
$CeCl_3 \cdot 7H_2O$, 300	—	120	3	22
$LaCl_3 \cdot 7H_2O$, 300	—	120	6	22
—	2-carboxyphenyl	120	6	2
$MgCl_2 \cdot 6H_2O$, 200	**2-carboxyphenyl**	**120**	**4**	**54**
$NiCl_2 \cdot 6H_2O$, 300	2-carboxyphenyl	105	4	24
$ZnCl_2 + 6H_2O$, 300	2-carboxyphenyl	105	4	18
$CeCl_3 \cdot 7H_2O$, 300	2-carboxyphenyl	120	3	51
$LaCl_3 \cdot 7H_2O$, 300	2-carboxyphenyl	120	3	49
—	2-methoxycarbonylphenyl	100	6	22
$MgCl_2 \cdot 6H_2O$, 200	**2-methoxycarbonylphenyl**	**120**	**4**	**57**
—	2-ethoxycarbonylphenyl	100	6	15
$MgCl_2 \cdot 6H_2O$, 200	**2-ethoxycarbonylphenyl**	**120**	**4**	**52**

Glucose and boronic acid were 10 wt% relative to solvent. Mol% and HMF yield (HPLC) are relative to glucose.

acid can catalyze the dehydration of alcohols,[65] but its efficiency as a catalyst of sugar dehydration was not clear.[67,137]

Unlike boric acid, phenylboronic acids have an affinity for carbohydrates that is tunable based on substituents.[145-147] We assessed the ability of numerous derivatives of phenylboronic acid to catalyze the conversion of glucose to HMF (Table 3.3). Our data corroborated the earlier work with phenylboronic acid itself,[137] which is not a catalyst in our hands, but revealed that adding a 2-carboxyl group engenders catalysis, especially in the presence of $MgCl_2 \cdot 6H_2O$ (Table 3.2). Further optimization revealed that the conversion requires only catalytic amounts of the boronic acid but is best with a slight excess of $MgCl_2 \cdot 6H_2O$ (Table 3.4).

Water can counter the dehydration of fructose (Figure 3.1). 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 3.5). To determine how much water is beneficial for HMF production, we added water to reaction mixtures containing the anhydrous salt (Table 3.6) and found that HMF yields increase steadily up to an H_2O:Mg(II) ratio of ~6 (Figure 3.2). Other anhydrous metal chlorides that work synergistically with 2-carboxyphenylboronic also have a similar reliance on water (Table 3.5).

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 and enables a mineral acid to catalyze its hydrolysis.[63] We observed that phenylboronic acids with an *ortho* carboxyl group catalyze the conversion of cellulose to HMF (Table 3.7), and that $MgCl_2 \cdot 6H_2O$ is necessary to obtain maximal yields (Table 3.8) using optimal catalyst concentrations (Table 3.9). These co-catalysts

Table 3.3 Screen of boronic acids for the conversion of glucose to HMF in DMA

boronic acid	metal halide	*T* (°C)	time (h)	HMF yield (%)
phenylboronic acid	—	105	4	0
phenylboronic acid	$MgCl_2 \cdot 6H_2O$	105	4	4
2-(hydroxymethyl)phenyl	—	100	6	0
2-(hydroxymethyl)phenyl	$MgCl_2 \cdot 6H_2O$	100	6	6
2-formylphenyl	—	105	4	0
2-formylphenyl	$MgCl_2 \cdot 6H_2O$	105	4	4
2-acetylphenyl	—	105	4	0
2-acetylphenyl	$MgCl_2 \cdot 6H_2O$	105	4	2
2-aminocarbonylphenyl	—	105	4	0
2-aminocarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	4	8
2-nitrophenyl	—	105	4	0
2-nitrophenyl	$MgCl_2 \cdot 6H_2O$	105	4	7
2-(*N,N*-dimethylaminomethyl)phenyl	—	120	6	0
2-(*N,N*-dimethylaminomethyl)phenyl	$MgCl_2 \cdot 6H_2O$	120	6	2
2-methoxyphenyl	—	120	6	6
2-methoxyphenyl	$MgCl_2 \cdot 6H_2O$	120	5	33
2,4-bis(trifluoromethyl)phenyl	—	100	9	ND
2,4-bis(trifluoromethyl)phenyl	$MgCl_2 \cdot 6H_2O$	100	9	ND
5-amino-2-hydroxymethylphenyl	—	120	1	6
5-amino-2-hydroxymethylphenyl	$MgCl_2 \cdot 6H_2O$	120	1	3
2,6-dimethoxyphenyl	—	120	6	0
2,6-dimethoxyphenyl	$MgCl_2 \cdot 6H_2O$	120	6	28
2,6-dimethylphenyl	—	120	6	8
2,6-dimethylphenyl	$MgCl_2 \cdot 6H_2O$	120	6	27
3-carboxyphenyl	—	100	7.5	24
3-carboxyphenyl	$MgCl_2 \cdot 6H_2O$	100	7.5	25
3-carboxy-5-nitrophenyl	—	100	4.5	5
3-carboxy-5-nitrophenyl	$MgCl_2 \cdot 6H_2O$	100	9	36
3,5-bis(trifluoromethyl)phenyl	—	100	6	18
3,5-bis(trifluoromethyl)phenyl	$MgCl_2 \cdot 6H_2O$	100	9	25
4-carboxyphenyl	—	100	6	1
4-carboxyphenyl	$MgCl_2 \cdot 6H_2O$	100	9	28
4-methylphenyl	—	120	6	0
4-methylphenyl	$MgCl_2 \cdot 6H_2O$	120	9	23
Benzoic acid	$MgCl_2 \cdot 6H_2O$	100	9	22
Phthalic acid	$MgCl_2 \cdot 6H_2O$	100	9	18

Boronic acids were at 1 equiv and $MgCl_2 \bullet 6H_2O$ was at 2 equiv relative to glucose. Glucose was at 10 wt% relative to DMA. Mol% and HMF yield (HPLC) are relative to glucose. ND = not determined (because HMF and the boronic acid have the same retention time during HPLC).

Table 3.4 Screen of catalyst concentrations for the conversion of glucose to HMF in DMA

boronic acid, mol%	metal halide, mol%	*T* (°C)	time (h)	HMF yield (%)
2-carboxyphenyl, 50	$MgCl_2 \cdot 6H_2O$, 200	120	6	48
2-carboxyphenyl, 25	$MgCl_2 \cdot 6H_2O$, 200	120	6	46
2-carboxyphenyl, 10	$MgCl_2 \cdot 6H_2O$, 200	120	6	31
2-carboxyphenyl, 100	**$MgCl_2 \cdot 6H_2O$, 250**	**110**	**6**	**55**
2-carboxyphenyl, 100	**$MgCl_2 \cdot 6H_2O$, 200**	**110**	**5**	**51**
2-carboxyphenyl, 100	$MgCl_2 \cdot 6H_2O$, 150	110	5	48
2-carboxyphenyl, 100	$MgCl_2 \cdot 6H_2O$, 100	110	5	43

Glucose was at 10 wt% relative to DMA. Mol% and HMF yield are relative to glucose.

Table 3.5 Screen of boronic acids and metal halides for the conversion of glucose to HMF in DMA

boronic acid	metal halide, mol%	*T* (°C)	time (h)	HMF yield (%)
2-carboxyphenyl	$CrCl_2$, 25	100	6	37
2-carboxyphenyl	$CrCl_2 + 6H_2O$, 25	100	6	48
2-methoxycarbonylphenyl	$CrCl_2$, 25	100	1.5	39
2-methoxycarbonylphenyl	$CrCl_2 + 6H_2O$, 25	100	1.5	28
2-ethoxycarbonylphenyl	$CrCl_2$, 25	100	3	33
2-ethoxycarbonylphenyl	$CrCl_2 + 6H_2O$, 25	100	1.5	26
2-carboxyphenyl	**$MgCl_2$, 200**	**120**	**1**	**19**
2-carboxyphenyl	**$MgCl_2 \cdot 6H_2O$, 200**	**120**	**4**	**54**
2-methoxycarbonylphenyl	**$MgCl_2$, 200**	**120**	**1**	**19**
2-methoxycarbonylphenyl	**$MgCl_2 \cdot 6H_2O$, 200**	**120**	**4**	**57**
2-ethoxycarbonylphenyl	**$MgCl_2$, 200**	**120**	**1**	**18**
2-ethoxycarbonylphenyl	**$MgCl_2 \cdot 6H_2O$, 200**	**120**	**4**	**52**
2-carboxyphenyl	$CaCl_2 \cdot 2H_2O$, 300	120	3	38
2-carboxyphenyl	$LiCl + 6H_2O$, 300	105	4	16
2-carboxyphenyl	$LiBr + 6H_2O$, 300	105	4	4
2-carboxyphenyl	$NaCl + 6H_2O$, 300	105	4	2
2-carboxyphenyl	$KCl + 6H_2O$, 300	105	4	2
2-carboxyphenyl	$CuCl + 6H_2O$, 300	105	4	0
2-carboxyphenyl	$CuCl_2 + 6H_2O$, 300	105	4	4
2-carboxyphenyl	$CsCl + 6H_2O$, 300	105	4	7
2-carboxyphenyl	$FeCl_2 + 6H_2O$, 300	105	4	10
2-carboxyphenyl	$FeCl_3 + 6H_2O$, 300	105	4	4
2-carboxyphenyl	$MoCl_3 + 6H_2O$, 300	105	1	15
2-carboxyphenyl	$VCl_3 + 6H_2O$, 300	105	4	29
2-carboxyphenyl	$RbCl + 6H_2O$, 300	105	4	2
2-carboxyphenyl	$BaCl_2 \cdot 2H_2O$, 300	105	4	1
2-carboxyphenyl	$CoCl_2 \cdot 6H_2O$, 300	105	4	17
2-carboxyphenyl	$PdCl_2 + 6H_2O$, 300	105	4	3
2-carboxyphenyl	$MnCl_2 \cdot 4H_2O$, 300	105	4	5

Boronic acids were at 1 equiv relative to glucose. Glucose was at 10 wt% relative to DMA. Mol% and HMF yield (HPLC) are relative to the glucose. Added water is relative to the metal halide. Entries highlighted in gray are also listed in Table 3.2.

Table 3.6 Screen of water concentrations for the conversion of glucose to HMF in DMA

metal halide	added water (equiv)	total water (equiv)	*T* (°C)	time (h)	HMF yield (%)
$MgCl_2$	0	0	100	3	22
$MgCl_2$	1	1	100	3	24
$MgCl_2$	2	2	100	4.5	28
$MgCl_2$	3	3	100	6	30
$MgCl_2$	4	4	100	6	33
$MgCl_2$	5	5	100	6	36
$MgCl_2$	6	6	100	6	40
$MgCl_2$	7	7	100	6	43
$MgCl_2$	8	8	100	6	43
$MgCl_2$	9	9	100	6	46
$MgCl_2$	10	10	100	6	46
$MgCl_2$	**11**	**11**	**100**	**6**	**56**
$MgCl_2$	**12**	**12**	**100**	**6**	**54**
$MgCl_2 \cdot 6H_2O$	1	13	100	3	54
$MgCl_2 \cdot 6H_2O$	2	14	100	4.5	56
$MgCl_2 \cdot 6H_2O$	3	15	100	6	57
$MgCl_2 \cdot 6H_2O$	4	16	100	4.5	57
$MgCl_2 \cdot 6H_2O$	5	17	100	4.5	58

Glucose was at 10 wt% relative to DMA. Mol%, HMF yield (HPLC), and water equiv are relative to glucose. 2-Carboxyphenylboronic acid was at 1 equiv, and $MgCl_2$ and $MgCl_2 \bullet 6H_2O$ were at 2 equiv relative to glucose.

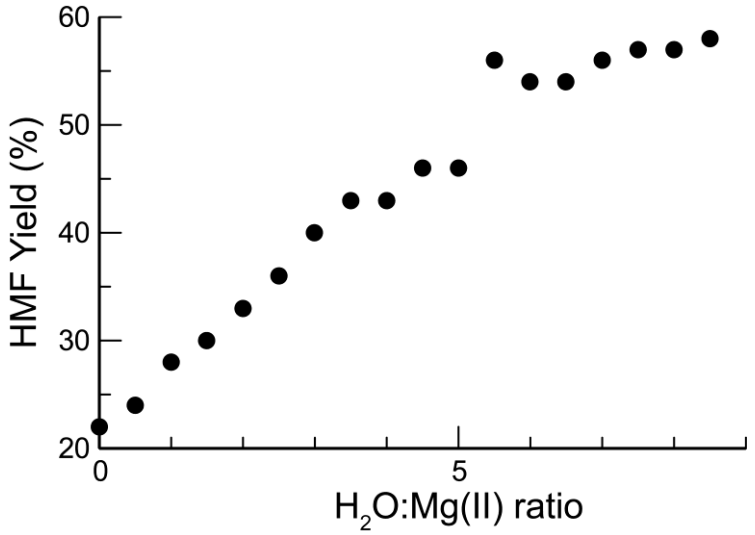

Figure 3.2 Dependence of HMF yield on H_2O:Mg(II) ratio. Data are from Table 3.6.

Table 3.7 Initial screens of catalysts for the conversion of cellulose to HMF in [EMIM]Cl

acid, wt%	boronic acid	additive	*T* (°C)	time (h)	HMF yield (%)
—	2-carboxyphenyl	—	120	4.5	0
—	2-methoxycarbonylphenyl	—	120	4.5	0
—	2-ethoxycarbonylphenyl	—	120	3.8	12
HCl, 0.88	—	—	105	2	10
HCl, 0.88	—	$MgCl_2 \cdot 6H_2O$	105	3	16
HCl, 0.88	2-methoxycarbonylphenyl	—	105	2	16
HCl, 0.88	2-methoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	1	26
HCl, 0.88	2-ethoxycarbonylphenyl	—	105	1	22
HCl, 0.88	2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	1	29
HCl, 0.88	2-methoxycarbonylphenyl	—	120	2	12
HCl, 0.88	2-methoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	120	2	28
HCl, 0.88	2-ethoxycarbonylphenyl	—	120	1	21
HCl, 0.88	**2-ethoxycarbonylphenyl**	**$MgCl_2 \cdot 6H_2O$**	**120**	**1**	**30**
HCl, 0.8	2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	1	27
H_2SO_4, 0.8	**2-ethoxycarbonylphenyl**	**$MgCl_2 \cdot 6H_2O$**	**105**	**1**	**32**
H_3PO_4, 0.8	**2-ethoxycarbonylphenyl**	**$MgCl_2 \cdot 6H_2O$**	**105**	**2**	**31**
AcOH, 0.8	2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	3	29

Boronic acids were at 2 equiv, and $MgCl_2 \bullet 6H_2O$ was at 4 equiv relative to glucose monomers within the cellulose. Wt% is relative to the [EMIM]Cl. Cellulose was at 5 wt% to [EMIM]Cl. HMF yield (HPLC) is relative to the glucose monomers within cellulose.

Table 3.8 Conversion of cellulose to HMF in ionic liquids

substrate	ionic liquid	acid	boronic acid	metal chloride	time (h)	HMF yield (%)
cellulose	[EMIM]Cl	HCl	—	—	2	10
cellulose	[EMIM]Cl	HCl	—	$MgCl_2 \cdot 6H_2O$	3	15
cellulose	[EMIM]Cl	HCl	2-methoxycarbonylphenyl	—	2	12
cellulose	**[EMIM]Cl**	**HCl**	**2-methoxycarbonylphenyl**	**$MgCl_2 \cdot 6H_2O$**	**2**	**39**
cellulose	**[EMIM]Cl**	**H_2SO_4**	**2-methoxycarbonylphenyl**	**$MgCl_2 \cdot 6H_2O$**	**1**	**41**
cellulose	[EMIM]Cl	HCl	2-ethoxycarbonylphenyl	—	1	21
cellulose	[EMIM]Cl	HCl	2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	2	38
cellulose	[EMIM]Cl	H_2SO_4	2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	1	36
cotton	[BMIM]Cl		2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	2	40
paper towel	[EMIM]Cl	HCl	2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	2	31
newspaper	[BMIM]Cl		2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	2	18

Substrates were at 5 wt%, HCl was at 0.61 wt%, and H_2SO_4 was at 0.88 wt% relative to the ionic liquid. $MgCl_2 \bullet 6H_2O$ was at 3 equiv, 2-methoxycarbonylphenylboronic acid was at 1.2 equiv, and 2-ethoxycarbonylphenylboronic acid was at 1.6 equiv relative to glucose monomers within the substrate. Reactions were done at 105 °C and HMF yield (HPLC) is relative to glucose monomers within the substrate, which was assumed to be pure cellulose.

Table 3.9 Catalyst concentration determination for cellulose to HMF conversion in [EMIM]Cl

acid, wt%	boronic acid, mol%	additive, mol%	*T* (°C)	time (h)	HMF yield (%)
HCl, 0.33	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 400	105	2	26
HCl, 0.61	**2-ethoxycarbonylphenyl, 200**	**$MgCl_2·6H_2O$, 400**	**105**	**1**	**30**
HCl, 0.88	**2-ethoxycarbonylphenyl, 200**	**$MgCl_2·6H_2O$, 400**	**105**	**1**	**30**
H_2SO_4, 0.33	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 400	105	1	27
H_2SO_4, 0.61	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 400	105	1	30
H_2SO_4, 0.88	**2-ethoxycarbonylphenyl, 200**	**$MgCl_2·6H_2O$, 400**	**105**	**1**	**32**
H_3PO_4, 0.33	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 400	105	2	32
H_3PO_4, 0.61	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 400	105	2	28
H_3PO_4, 0.88	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 400	105	1	26
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 940	105	1	32
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 720	105	1	32
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 500	105	1	33
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 260	105	1	29
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 400	$MgCl_2·6H_2O$, 400	105	1	29
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 340	$MgCl_2·6H_2O$, 400	105	1	35
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 260	$MgCl_2·6H_2O$, 400	105	1	33
H_2SO_4, 0.88	**2-methoxycarbonylphenyl, 160**	**$MgCl_2·6H_2O$, 400**	**105**	**1**	**36**
H_2SO_4, 0.88	**2-methoxycarbonylphenyl, 120**	**$MgCl_2·6H_2O$, 400**	**105**	**0.5**	**39**
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 80	$MgCl_2·6H_2O$, 400	105	2	29
H_2SO_4, 0.88	2-methoxycarbonylphenyl, 40	$MgCl_2·6H_2O$, 400	105	2	22
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 940	105	1	32
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 720	105	1	32
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 500	105	1	33
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 200	$MgCl_2·6H_2O$, 260	105	1	29
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 400	$MgCl_2·6H_2O$, 400	105	1	26
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 340	$MgCl_2·6H_2O$, 400	105	1	25
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 260	$MgCl_2·6H_2O$, 400	105	1	26
H_2SO_4, 0.88	2-ethoxycarbonylphenyl, 160	$MgCl_2·6H_2O$, 400	105	1	30

Wt% is relative to [EMIM]Cl. Cellulose was at 5 wt% relative to [EMIM]Cl. Mol% and HMF yield (HPLC) are relative to glucose monomers within the cellulose.

also mediate the conversion of cotton, paper towels, and newspaper, which are cellulose-rich components of municipal waste (Table 3.8). Thus, HMF can be produced efficiently from cellulosic material in a single, one-pot process that is devoid of heavy metals.

The expense of boronic acids led us to search for a recovery method that enables catalyst recycling. Our initial separation strategy 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, 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 (Figure 3.3). This strategy was, however, inapplicable to the *o*-esterphenylboronic acids, which have low solubility in water and high solubility in ethyl acetate.

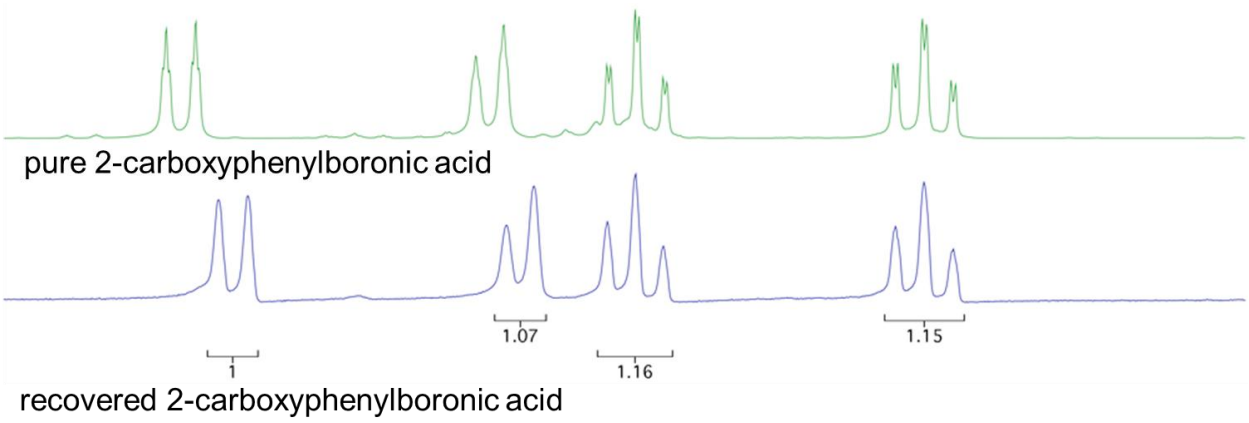

Figure 3.3 Comparison of ^{1}H NMR spectra of pure 2-carboxyphenylboronic acid with that after use in a glucose conversion reaction. Slight differences in chemical shifts are a result of NH_4HCO_3 being added to the sample during recovery from the reaction mixture. Recovered material has HRMS (ESI) *m/z* 192.0701 [calculated for $C_9H_{10}BO_4$ $(M - H)^-$ 192.0703].

Boronic acid moieties become anionic at high pH. Hence, we added basic water to reaction mixtures containing *o*-esterphenylboronic acids, filtered to remove any humins, and extracted with ethyl acetate (Figure 3.4). Removing solvent from the organic phase provided HMF. Evaporating water from the aqueous phase recovered the boronic acid/$MgCl_2$ catalysts, which provided HMF in comparable yield through four reaction cycles.

Additional data provided some insight on the chemical mechanism of our conversion (Figure 3.1). Chromium is known to catalyze the isomerization of aldose to ketose sugars by a

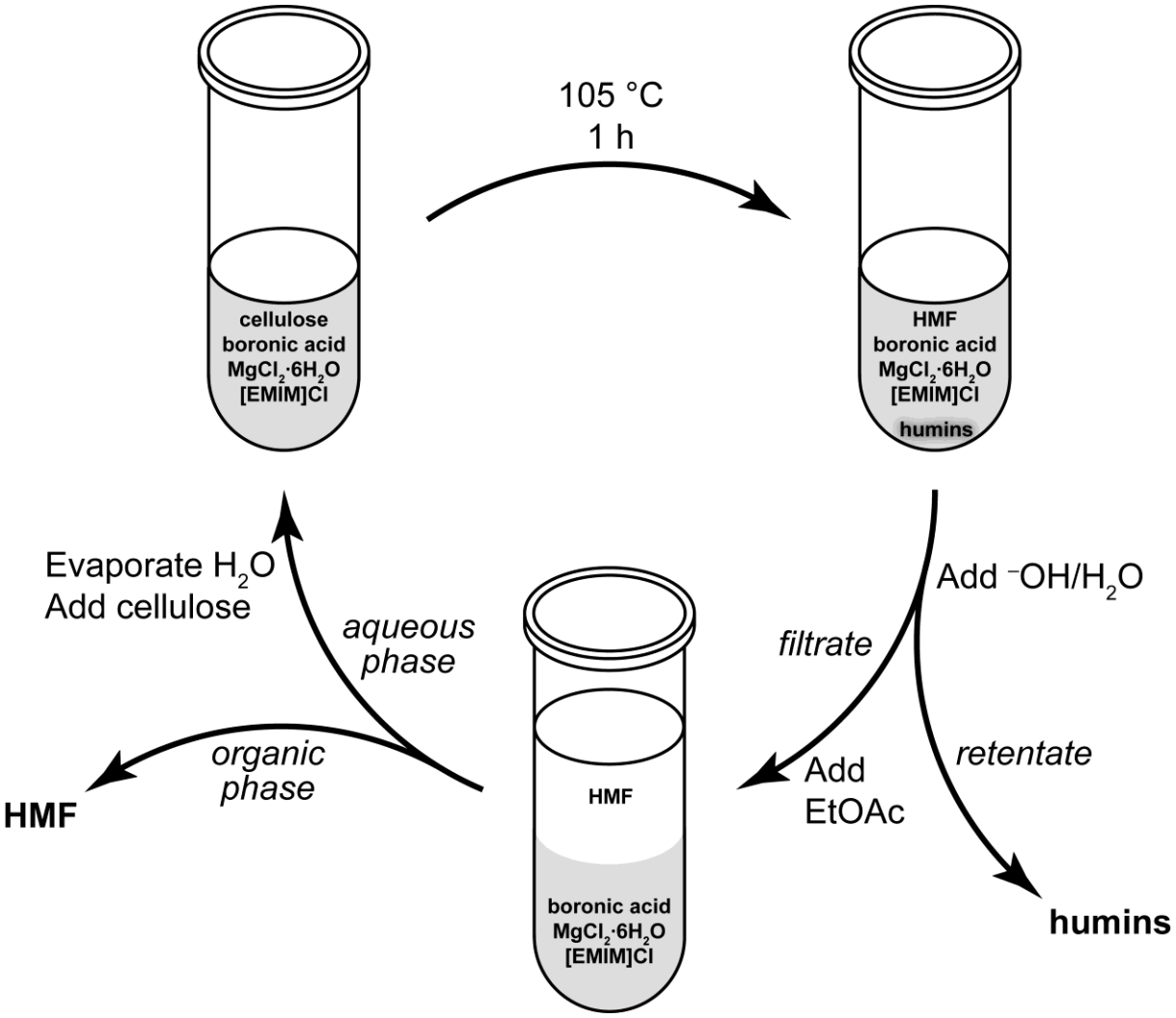

Figure 3.4 Scheme for the recovery and recycling of catalysts for the conversion of cellulose to HMF.

1,2-hydride shift.[77-78] 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 $MgCl_2 \cdot 6H_2O$. ^1H 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 (Figure 3.5). These results are compatible with a mechanism that avails an enediol intermediate, like that used by the enzyme phosphoglucose isomerase.

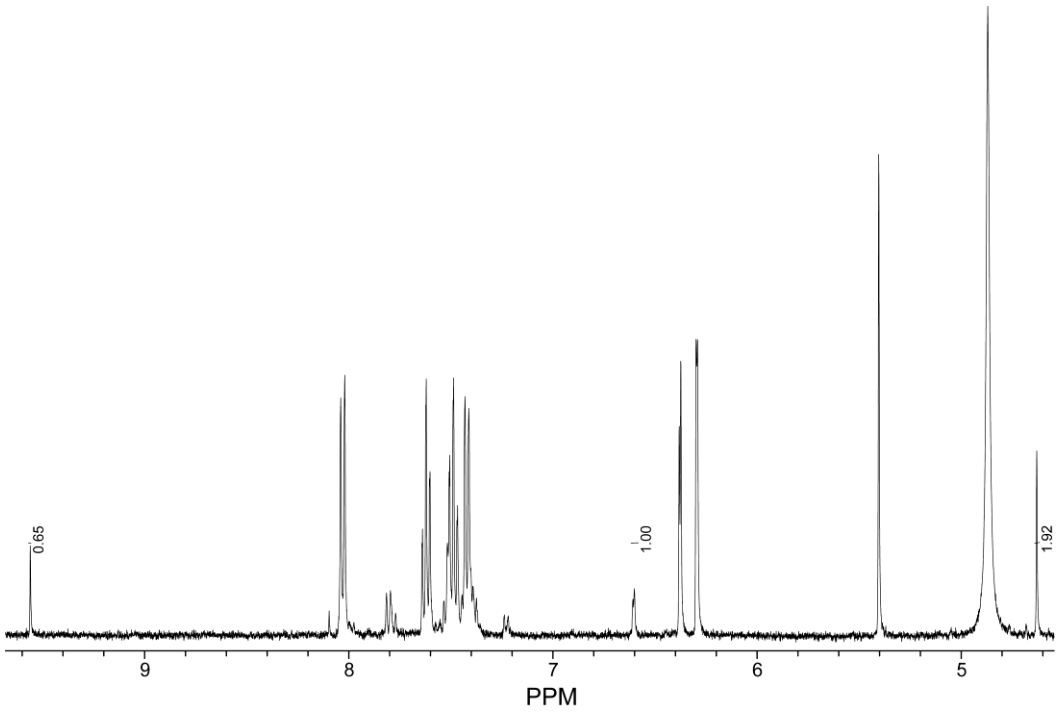

Figure 3.5 ^{1}H NMR spectrum showing peak integrations of HMF after its conversion from glucose in DMA containing D_2O. The aldehyde peak at 9.56 ppm integrates to only $^{2}/_{3}$ that expected from the two diagnostic peaks. The incorporation of solvent deuterium is consistent with the isomerization of glucose to fructose occurring via an enolization mechanism.

Boronate ester-formation is known to favor fructose over glucose.[145-147] We found that boronates also serve by catalyzing fructose dehydration (Table 3.10). 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 aqueous-free medium.[145] Finally, we propose that water attenuates the

reactivity of Mg(II), allowing its participation in catalysis, but deterring reaction pathways that lead to humins.[28]

Table 3.10 Screen of catalysts for the conversion of fructose to HMF in DMA

boronic acid	additive	*T* (°C)	time (h)	HMF yield (%)
2-carboxyphenyl	—	105	4	13
2-carboxyphenyl	**$MgCl_2 \cdot 6H_2O$**	**105**	**2**	**61**
2-methoxycarbonylphenyl	—	105	4	40
2-methoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	4	52
2-ethoxycarbonylphenyl	**—**	**105**	**3**	**84**
2-ethoxycarbonylphenyl	$MgCl_2 \cdot 6H_2O$	105	4	59

Boronic acids were at 1 equiv and $MgCl_2 \bullet 6H_2O$ was at 2 equiv relative to fructose. Fructose was at 10 wt% to the DMA. HMF yield (HPLC) is relative to fructose.

3.5 Conclusions

Thus, we have discovered a simple organocatalytic system for the transformation of glucose and cellulose into the platform chemical, HMF. The process, including the isolation of the HMF product and the recovery and recycling of the catalysts, is rapid and economical. This discovery could facilitate the transition from fossil-based fuels and chemicals to a more sustainable biomass-based society.

3.6 Acknowledgments

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3.7 Materials and Methods

3.7.1 Materials

Commercial chemicals were of reagent grade or better and were used without further purification. 1-Ethyl-3-methylimidazolium chloride (99.5%, [EMIM]Cl) was from Solvent-Innovation (Cologne, Germany). Glucose was from J. T. Baker (Phillipsburg, NJ). Cellulose (medium cotton linters, C6288), fructose, *N,N*-dimethylacetamide (DMA), and metal chlorides were from Sigma Chemical (St. Louis, MO). Magnesium chloride hexahydrate was from Fisher Scientific (Pittsburgh, PA). Boronic acids were from either Synthonix (Doylestown, PA) or Combi-Blocks (San Diego, CA). All reactions were performed in 4-mL glass vials heated in a temperature-controlled VWR Mini Shaker at 600 rpm.

The term “concentrated under reduced pressure” refers to the removal of solvents and other volatile materials with a rotary evaporator under reduced pressure provided by a Welch 2025 self-cleaning dry vacuum system while maintaining the water-bath temperature below 50 °C except where noted. The term “high vacuum” refers to a vacuum of <0.1 torr achieved by a Welch mechanical belt-drive oil pump. The term “speed vacuum” refers to spinning samples in a UVS400 Universal Vacuum System from Thermo Scientific (Waltham, MA) under reduced pressure provided by a Welch 2042 DryFast vacuum system.

3.7.2 Analytical Methods

Reaction products were analyzed by HPLC and quantified using calibration curves generated from commercially available standards. Product concentrations were calculated from HPLC-peak integrations, which were then used to calculate molar yields. During a reaction, an aliquot of the reaction mixture was taken, diluted with a known mass of deionized water, cooled to 4 ˚C, centrifuged at 12,000 rpm for 5 min to sediment insoluble products, and analyzed. HPLC was performed using an Agilent 1200 system equipped with refractive index and photodiode array detectors. HMF was analyzed by ion-exclusion chromatography with a Bio-Rad Aminex HPX-87H column (300 x 7.8 mm) using a 5 mM H_2SO_4 mobile phase at a flow rate of 0.6 mL/min at 65 °C.

NMR spectra were acquired with a Bruker DMX-400 Avance spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) at the National Magnetic Resonance Facility at Madison (NMRFAM). NMR spectra were obtained at ambient temperature unless indicated otherwise. Values of the coupling constant *J* are given in Hertz. Mass spectrometry was performed with a Micromass LCT (electrospray ionization, ESI) in the Mass Spectrometry Facility in the Department of Chemistry.

3.7.3 Representative Procedure for Synthesis of HMF from Glucose

Glucose (51.6 mg, 286 μmol), 2-carboxyphenylboronic acid (47.3 mg, 285 μmol), and $MgCl_2$•$6H_2O$ (145.5 mg, 716 μmol) were mixed in DMA (500 mg). The reaction mixture was heated at 120 °C for 4 h. At 1 h intervals, aliquots of the reaction mixture were removed for HPLC analysis. For reactions using [EMIM]Cl, approximately 500 mg of the ionic liquid was added to the vial in place of DMA. Other boronic acids were also used. Reactions were also performed using anhydrous $MgCl_2$ and adding 1–12 molar equivalents of H_2O.

3.7.4 Representative Procedure for Synthesis of HMF from Cellulose

Cellulose (21.6 mg, 133 μmol of glucose units in cellulose) and [EMIM]Cl (493.4 mg) were mixed and heated at 105 ˚C for 3 h. 2-Methoxycarbonylphenylboronic acid (48.4 mg, 269 μmol), $MgCl_2$•$6H_2O$ (115 mg, 566 μmol), and concentrated HCl (3.4 μL, 109 μmol) were added and the reaction was heated for 4 h. At 1 h intervals, aliquots of the reaction mixture were removed for HPLC analysis. Other boronic acids and mineral acids were also used.

3.7.5 Catalyst Recovery and Recycling

Cellulose (248.2 mg, 1.531 mmol of glucose units in cellulose) and [EMIM]Cl (2.5173 g) were mixed and heated at 105 °C for 3 h. 2-Ethoxycarbonylphenylboronic acid (488.7 mg, 2.519 mmol), $MgCl_2 \cdot 6H_2O$ (973.0 mg, 4.786 mmol), and concentrated H_2SO_4 (12.0 μL, 0.225 mmol) were added, and the reaction mixture was heated for 1 h. The reaction mixture was then cooled to 4 °C and dissolved *via* sonication in basic H_2O prepared from an NH_4OH solution (15 mL). Vacuum filtration was done to remove insoluble humins and unreacted cellulose. Five extractions were done with ethyl acetate (7.5 mL) to remove HMF from the aqueous phase. The extracts were combined and concentrated under reduced pressure to yield HMF (50.1 mg, 26.0% recovered HMF yield). The reaction mixture was subjected to speed vacuum overnight, and then to high vacuum overnight. Cellulose (233.2 mg) was added to the reaction mixture, which was heated at 80 °C for 4 h. The temperature was then increased to 105 °C. Concentrated H_2SO_4 (11.0 μL, 0.206 mmol) was added, and the reaction mixture was heated for 1 h. Work-up of the reaction mixture and isolation of HMF were done as described above. The reaction mixture was recycled for a total of four reactions with a final recovered HMF yield of 18% (*i.e.*, 201.9 mg of cellulose yielded 28.0 mg of HMF).

3.7.6 Isotopic Labeling Experiments

2-Deuteroglucose (48.5 mg, 268 μmol), 2-ethoxycarbonylphenylboronic acid (54.1 mg, 279 μmol), and $MgCl_2 \cdot 6H_2O$ (126.2 mg, 621 μmol) were dissolved in DMA (532 μL). The reaction mixture was heated at 105 °C for 4 h, placed under high vacuum overnight to remove DMA, extracted with ethyl acetate, concentrated under reduced pressure, and analyzed by ^1H NMR spectroscopy. The aldehyde peak of HMF (9.56 ppm) showed <5% deuterium retention, indicating that the isomerization mechanism from glucose to fructose is not a 1,2-hydride shift.

Glucose (100.5 mg, 558 μmol) and 2-ethoxycarbonylphenylboronic acid (120.0 mg, 619 μmol) were dissolved in DMA (1064 μL), and D_2O (500 μL) was added to exchange any labile protons with deuterons. This mixture was then concentrated under reduced pressure to remove D_2O and H_2O. The D_2O exchange was repeated. Anhydrous $MgCl_2$ (123.2 mg, 1.29 mmol) and D_2O (150.8 mg, 7.53 mmol) were then added, and the reaction mixture was heated at 105 °C for 4 h, placed under high vacuum overnight to remove DMA, extracted with ethyl acetate, concentrated under reduced pressure, and analzyed by ^1H NMR spectroscopy. The aldehyde peak of HMF (9.56 ppm) showed 35% deuterium incorporation relative to other HMF peaks (Figure 1S), consistent with the isomerization of glucose to fructose proceeding by an enolization mechanism.

CHAPTER FOUR*

ELUCIDATING THE ROLE OF PHENYBORONIC ACIDS AS ORGANOCATALYSTS FOR THE CONVERSION OF SUGARS TO 5-(HYDROXYMETHYL)FURFURAL

4.1 Abstract

Biomass resources have the potential to serve as the foundation for a renewable energy economy. Carboxyl phenylboronic acids can serve in conjunction with a magnesium salt to convert cellulosic biomass to 5-(hydroxymethyl)furfural (HMF), an important intermediate for biofuels and commodity chemicals. The nature of this conversion is unclear as boronic acids are known to bind to sugars and prevent their transformation to HMF. Here, we probe the interaction between these boronic acids with glucose and fructose. The influence of D-hexose sugar conformation on the catalytic capacity of the boronic acid is noted as is their ability to hydrolyze polysaccharides. Further substitution on the aryl ring of the boronic acids to fine tune the electronics was also used to enhance overall HMF yields. These studies help to elucidate how boronic acids transform carbohydrates to HMF and inform the design of specialized boronic acids for carbohydrate conversion.

4.2 Author Contributions

B.R.C. and M.J.P. performed the research. B.R.C. drafted the manuscript. B.R.C., M.J.P., and R.T.R. designed experiments, analyzed the data, and edited the manuscript and figures.

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4.3 Introduction

Since the beginning of the Industrial Revolution in the 1860s, fossil fuels have become the primary energy and chemical resources of modern civilization.[148-149] Today, they provide the substantial majority of our world's energy.[1] As the world's population continues to grow, even greater demand will be placed on diminishing fossil fuel reserves. Moreover, as we reach peak oil production[3] and as CO_2 emissions continue to rise,[2] a reduction in the dependence on fossil fuels is imperative. Abundant and renewable biomass could serve as a viable, carbon-neutral alternative to fossil fuels and help to alleviate these concerns.[4,119]

The six-carbon furanic 5-(hydroxymethyl)furfural (HMF) is an important intermediate in the chemical conversion of biomass.[150] This bifunctional compound could serve as a platform chemical to access multiple useful products,[14] such as the polyester building block 2,5-furandicarboxylic acid[24] and 2,5-dimethylfuran,[31] a liquid biofuel.[111-115] HMF can be obtained from cellulosic biomass in three steps: hydrolysis (I), isomerization (II), and dehydration (III) (Figure 4.1). While a variety of processes exist to synthesize HMF from fructose in high yields,[53,55,92,94,98,151-152] it is only in recent years that HMF has been accessed efficiently from glucose and cellulose using chromium catalysts.[74,76,82-83,85] Chromium catalysts have since been

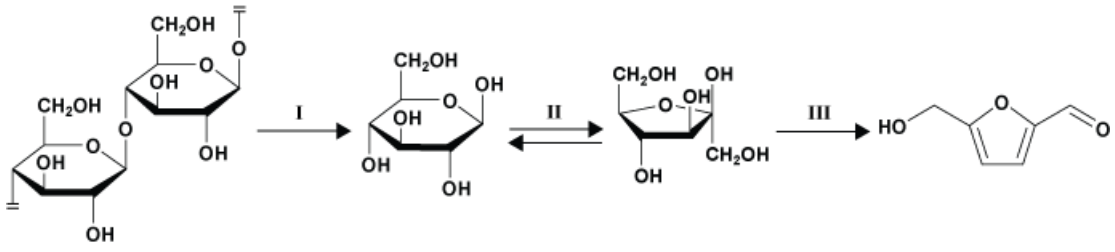

Figure 4.1 Conversion of cellulose to HMF in three steps: (I) hydrolysis, (II) isomerization, and (III) dehydration.

employed to transform a variety of other carbohydrate materials as well.[77-78] Cellulose dissolves in the presence of a high concentration of chloride ions,[33,36,63] such as that found in ionic liquids like 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) or organic/salt mixtures such as *N,N*-dimethylacetamide–lithium chloride (DMA–LiCl). Chromium ions are hypothesized to catalyze the isomerization of glucose to fructose, allowing for rapid dehydration to HMF. Unfortunately, the reported environmental toxicity of chromium inhibits the implementation of these processes on the industrial scale. Hence, it is crucial that a biomass conversion process utilize recyclable and environmentally benign reaction constituents.

Boronic acids bind to 1,2- and 1,3-diols to form cyclic boronate esters, and have a high binding affinity for furanose sugars relative to pyranose sugars.[145-146,153-155] The strength of this binding allowed boronic acids to inhibit cellulose hydrolysis and degradation of sugar monomers,[136-137] and to facilitate monosaccharide extraction from saccharide mixtures.[156] Functionalization of the aryl ring of phenylboronic acids with electron-donating or -withdrawing groups allows the strength of this binding to be tuned.[145,153]

Recently, we reported a novel conversion method to transform cellulosic materials to HMF using carboxyl phenylboronic acids with magnesium chloride in ionic liquids.[157] The unique reactivity of the phenylboronic acids in our reaction system inspired us to investigate the mechanism of carbohydrate conversion. In particular, we were interested in determining the strength of the interaction between carboxyl phenylboronic acids and hexose sugars, and if the isomeric structures of the hexose sugars influenced their level of conversion to HMF. We also sought to establish the ability of our system to convert other common saccharide materials. Finally, we hypothesized that additional substitution of the boronic acids' aryl ring beyond the carboxyl group would influence the yields of HMF obtained from our conversion technology.

4.4 Results and Discussion

The binding affinity of various phenylboronic acids has been determined previously under aqueous conditions.[145,153] In this environment, the carboxyl phenylboronic acids are reported to have weak affinity for fructose and glucose.[145,153] Nevertheless, as our system uses organic solvents and ionic liquids as the reaction medium, the reported affinities might not be relevant. For example, high-affinity boronic acids such as 2-hydroxymethylphenylboronic acid do not facilitate sugar conversion to HMF or sugar retention in our system.[157] Hence, we performed a ^{1}H NMR study in deuterated dimethylsulfoxide (DMSO-d_6) to elucidate if the phenylboronic acids coordinate to fructose formed in the course of glucose conversion to HMF (Figures 4.2, 4.3, and 4.4).

In organic solvents, phenylboronic acids are observed to form anhydride structures (Figures 4.2A, 4.3A), which can be broken up with the addition of water (Figures 4.2B, 4.3B). When fructose and glucose were added, we observed formation of a complex between 2-carboxyphenylboronic acid with both fructose and glucose (Figure 4.2C–F). A similar observation was seen with phenylboronic acid (Figure 4.3C–F). Furthermore, addition of $MgCl_2 \cdot 6H_2O$ to mimic our reaction conditions did not result in observable peak deviations (Figure 4.4). Unfortunately, the chemical shifts of the aromatic peaks of the free boronic acid and boronic acid–fructose complex changed according to quantity of sugar present, precluding a conclusive peak assignment. This in turn prevented the determination of the specific association constant values of 2-carboxyphenylboronic acid with fructose and glucose. Nonetheless, the formation of a boronate–sugar complex suggests that the boronic acids assist in isomerizing glucose to fructose and facilitate the dehydration of fructose to HMF.

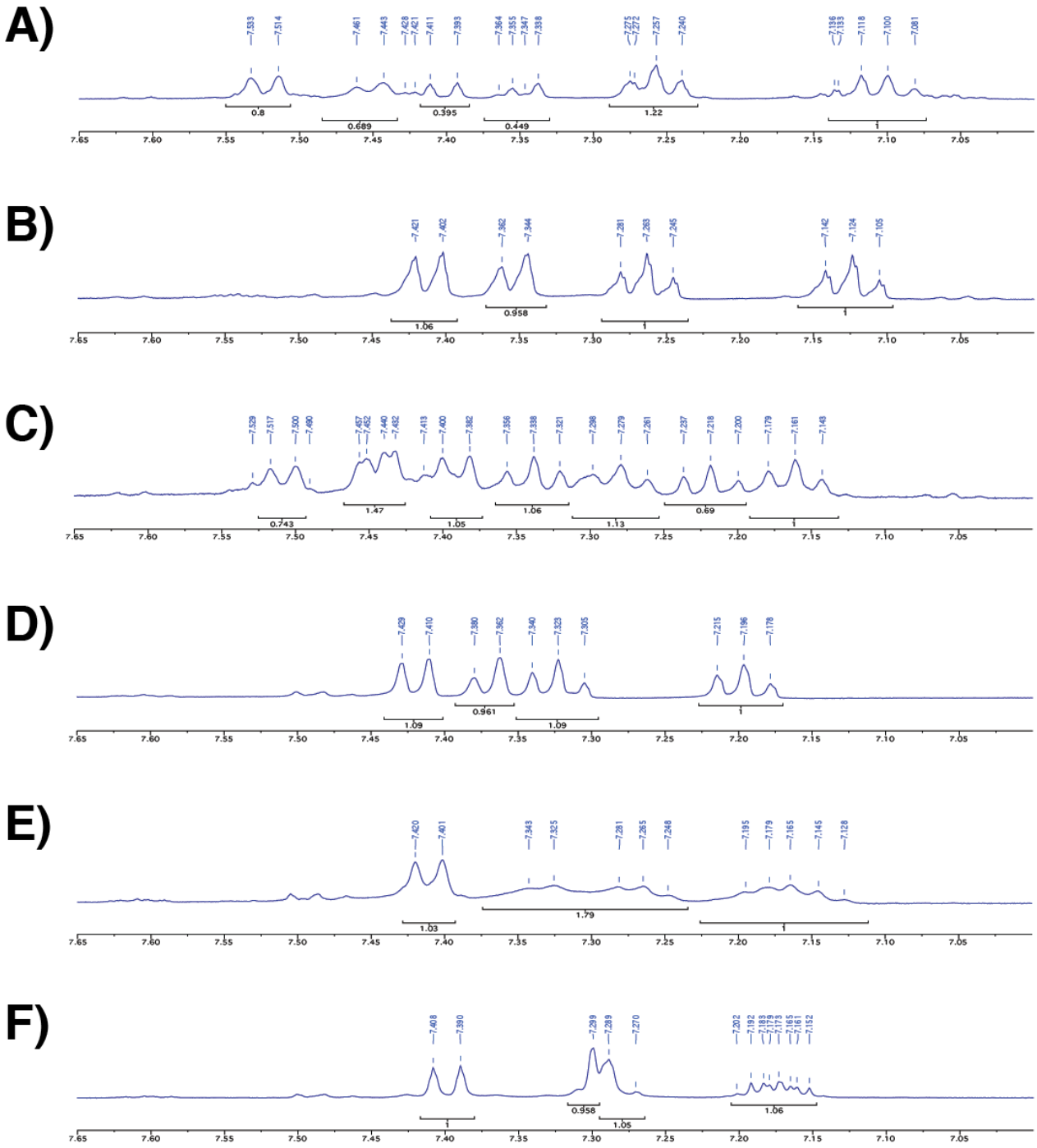

Figure 4.2 ^{1}H NMR characterization of 2-carboxyphenylboronic acid interactions with fructose and glucose in DMSO-d_6. (A) In the absence of ligands, 2-carboxyphenylboronic acid (10 mg, 60 µmol) forms anhydrides in DMSO-d_6. (B) Upon addition of H_2O (100 µL, 6 mmol), the boronic anhydrides break up and allow for proper resolution of the aromatic protons. (C) 2-Carboxyphenylboronic acid (10 mg, 60 µmoles) in the presence of 0.3 equivalents of D-fructose (3 mg, 18 µmol) demonstrates aryl peaks that are indicative of a boronic acid–fructose complex

due to the complex splitting. (D) 2-Carboxyphenylboronic acid (10 mg, 60 μmol) in the presence of 5 equivalents of D-fructose (54 mg, 300 μmol) demonstrates aryl peaks indicating complete binding of the boronic acid to fructose. (E) 2-Carboxyphenylboronic acid (10 mg, 60 μmol) in the presence of 0.3 equivalents of D-glucose (3 mg, 18 μmol) demonstrates significant broadening of the aryl peaks, which is consistent with boronic acid interactions with pyranose sugars. (F) 2-Carboxyphenylboronic acid (10 mg, 60 μmol) in the presence of 5 equivalents of D-glucose (54 mg, 300 μmol) demonstrates aryl peaks indicating complete binding of the boronic acid to glucose.

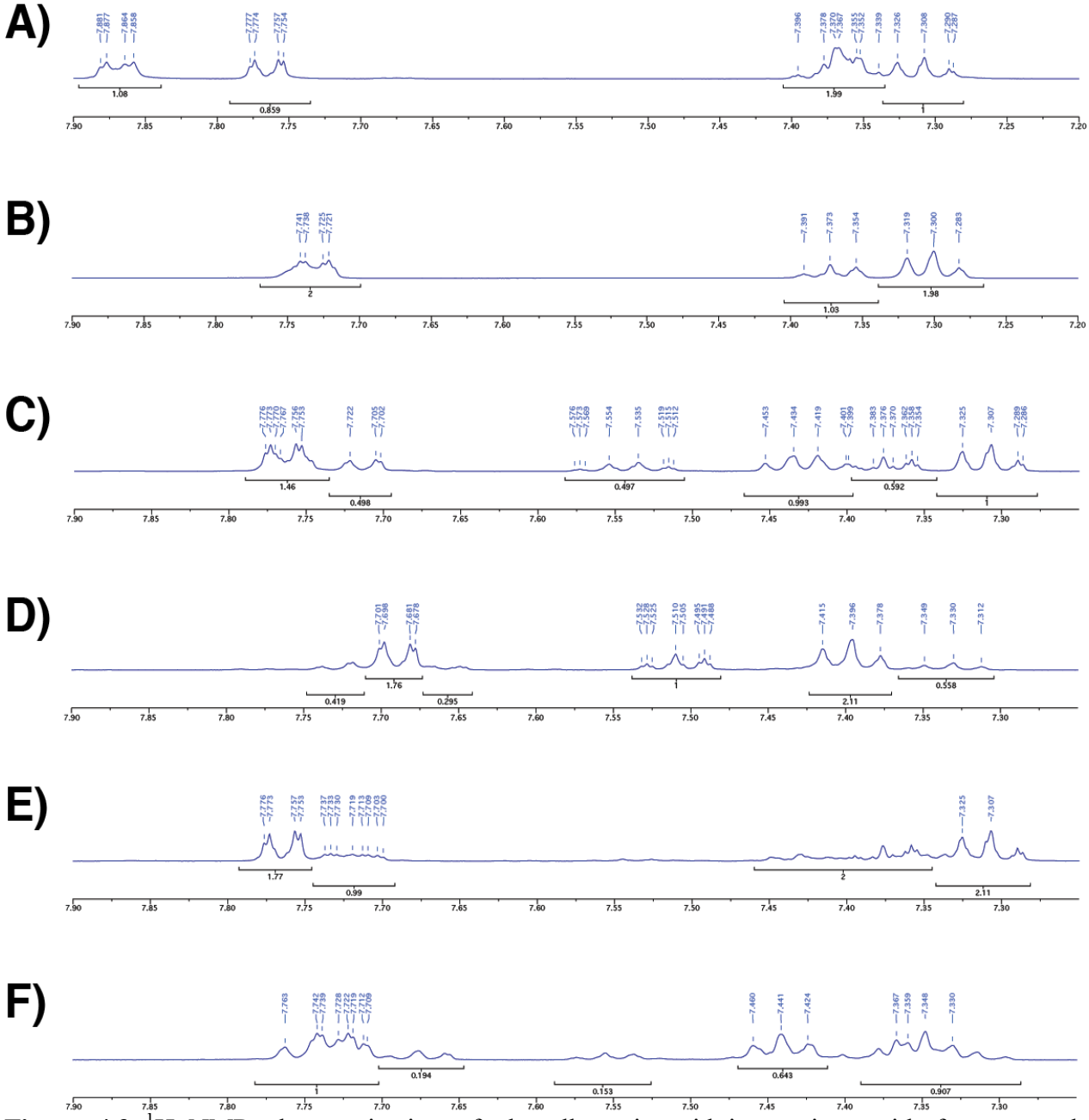

Figure 4.3 ^{1}H NMR characterization of phenylboronic acid interactions with fructose and glucose in DMSO-d_6. (A) In the absence of ligands, phenylboronic acid (7 mg, 60 µmol) forms anhydrides in DMSO-d_6. (B) Upon addition of H_2O (100 µL, 6 mmol), the boronic anhydrides break up and allow for proper resolution of the aromatic protons. (C) Phenylboronic acid (7 mg, 60 µmoles) in the presence of 0.3 equivalents of D-fructose (3 mg, 18 µmol) demonstrates aryl peaks that are indicative of a boronic acid–fructose complex. (D) Phenylboronic acid (7 mg, 60 µmol) in the presence of 5 equivalents of D-fructose (54 mg, 300 µmol) demonstrates aryl peaks indicating complete binding of the boronic acid to fructose. (E) Phenylboronic acid (7 mg, 60 µmol) in the presence of 0.3 equivalents of D-glucose (3 mg, 18 µmol) demonstrates significant broadening of the aryl peaks, which is consistent with boronic acid interactions with pyranose

sugars. (F) Phenylboronic acid (7 mg, 60 µmol) in the presence of 5 equivalents of D-glucose (54 mg, 300 µmol) demonstrates aryl peaks indicating complete binding of the boronic acid to glucose.

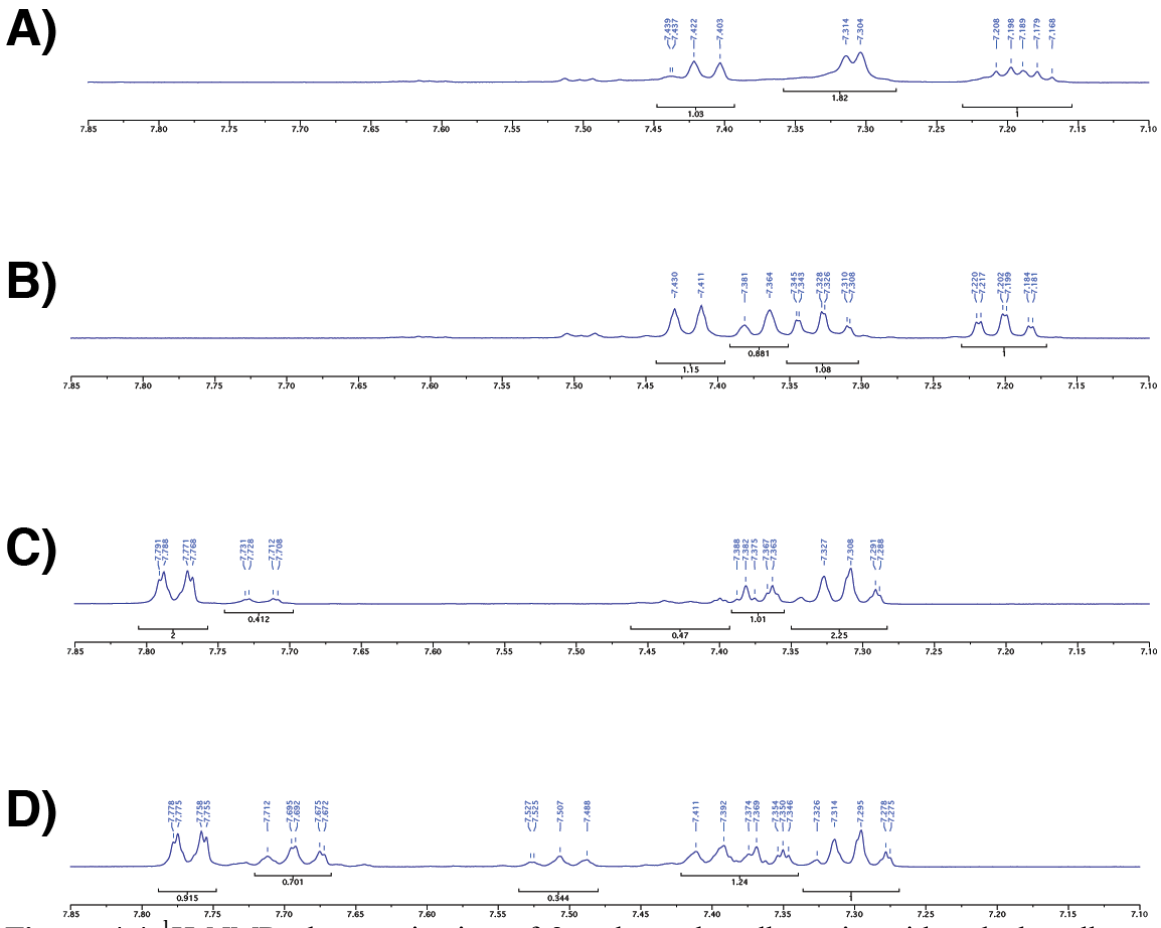

Figure 4.4 ^{1}H NMR characterization of 2-carboxyphenylboronic acid and phenylboronic acid interactions under mimicked reactions conditions in DMSO-d_6. No significant deviations of peak shifts or splitting were detected, indicating our complexation studies in Figures 4.2 and 4.3 correlate to the reaction conditions. (A) 2-Carboxyphenylboronic acid (10 mg, 60 µmol) in the presence of 0.9 equivalents of D-fructose (10 mg, 56 µmol) and 1.8 equivalents of $MgCl_2 \cdot 6H_2O$ (22 mg, 108 µmol). (B) 2-Carboxyphenylboronic acid (10 mg, 60 µmol) in the presence of 0.9 equivalents of D-glucose (10 mg, 56 µmol) and 1.8 equivalents of $MgCl_2 \cdot 6H_2O$ (22 mg, 108 µmol). (C) Phenylboronic acid (7 mg, 60 µmol) in the presence of 0.9 equivalents of D-fructose (10 mg, 56 µmol) and 1.8 equivalents of $MgCl_2 \cdot 6H_2O$ (22 mg, 108 µmol). (D) Phenylboronic acid (7 mg, 60 µmol) in the presence of 0.9 equivalents of D-glucose (10 mg, 56 µmol) and 1.8 equivalents of $MgCl_2 \cdot 6H_2O$ (22 mg, 108 µmol).

Previously, we determined that fructose is able to be transformed into HMF using solely the carboxyl phenylboronic acids.[157] We were interested in determining if this capacity for dehydration was limited to only fructose. Hence, we used the boronic acids with and without $MgCl_2 \cdot 6H_2O$ to transform the other D-ketohexoses: psicose, sorbose, and tagatose (Table 4.1).

Table 4.1 Ketohexose conversion using *ortho*-carboxyl phenylboronic acids

ketohexose	solvent	phenylboronic acid	metal chloride	*T* (˚C)	time (h)	HMF molar yield (%)
psicose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	4	39
psicose	DMA	2-methoxycarbonyl		105	4	51
psicose	**DMA**	**2-ethoxycarbonyl**		**105**	**4**	**62**
fructose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	4	53*
fructose	DMA	2-methoxycarbonyl	$MgCl_2 \cdot 6H_2O$	105	4	52*
fructose	**DMA**	**2-ethoxycarbonyl**		**105**	**3**	**84***
sorbose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	4	57
sorbose	DMA	2-methoxycarbonyl	$MgCl_2 \cdot 6H_2O$	105	4	52
sorbose	**DMA**	**2-ethoxycarbonyl**		**105**	**4**	**66**
tagatose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	4	32
tagatose	DMA	2-methoxycarbonyl		105	4	35
tagatose	DMA	2-ethoxycarbonyl		105	4	45

Boronic acids were used as 1 eq. and $MgCl_2 \cdot 6H_2O$ as 2.5 eq. relative to the sugar. Sugars were used as 10 wt% relative to the DMA. Molar yield is relative to the sugars. *Reported previously.

Interestingly, there appeared to be a disparity in the reactivity of the different boronic acids. 2-Carboxyphenylboronic acid attained its best HMF yields for all ketohexoses when it was used in conjunction with the magnesium salt. 2-Methoxycarbonylphenylboronic acid needed the salt for fructose and sorbose to achieve the best HMF yields, but did not for psicose and tagatose. Finally, 2-ethoxycarbonylphenylboronic acid accessed the highest HMF yields without the salt for all the ketohexoses. It also consistently had the highest HMF yields of the three boronic acids. Thus, it seems that the ethoxycarbonyl moiety conveys the highest level of reactivity to transform the ketohexoses to HMF.

The variance of the conditions required to achieve the best HMF yields suggests differing levels of dehydration activity for the three boronic acids. The 2-ethoxycarbonylphenylboronic acid has the highest dehydration capacity of the three, followed by 2-methoxycarbonylphenylboronic acid and then 2-carboxyphenylboronic acid. It is also of interest that the yields varied for the different ketohexoses, with fructose typically giving the highest HMF yields, followed by sorbose, psicose, and tagatose. It is possible that these differences are a result of the differing isomeric equilibria of the sugars. According to previous studies, fructose predominately exists in a furanose form in an organic medium, as does psicose.[77,158] Contrarily, sorbose primarily exists in a pyranose form and tagatose exists almost entirely in a pyranose form. As the dehydration of sugars easily proceeds through the furanose form of sugars,[8] those having greater isomeric furanose conformations should give higher HMF yields.

We continued our investigations with the D-aldohexoses to determine if the isomeric ratios influenced their conversion to HMF using the boronic acid and $MgCl_2 \cdot 6H_2O$ catalytic system (Table 4.2). Interestingly, only altrose, idose, and galactose gave higher yields of HMF using boronic acids alone. This selectivity could be due to their higher ratio of furanose isomeric conformations relative to the other aldohexoses.[158] The other aldohexoses all required the presence of $MgCl_2 \cdot 6H_2O$ to access higher HMF yields. This result suggests that the magnesium is involved in tautomerizing the pyranose conformations of sugars to their furanose forms. Once there, the boronic acids catalyze the dehydration to HMF. Sugars that are better able to access their furanose conformations appear to be converted to HMF in higher yields than those that exist primarily in their pyranose forms. It is possible that the α-anomer of the pyranose structure is the easiest path to isomerize to the furanose form because glucose and mannose have high ratios of the α-anomer and gave the highest HMF yields. Yet, gulose also gave high HMF yields

Table 4.2 Aldohexose conversion using *ortho*-carboxyl phenylboronic acids

aldohexose	solvent	phenylboronic acid	metal chloride	*T* (˚C)	time (h)	HMF molar yield (%)
allose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	8
allose	DMA	2-methoxycarbonyl	$MgCl_2•6H_2O$	105	4	26
allose	DMA	2-ethoxycarbonyl	$MgCl_2•6H_2O$	105	4	25
altrose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	28
altrose	**DMA**	**2-methoxycarbonyl**		**105**	**4**	**43**
altrose	**DMA**	**2-ethoxycarbonyl**		**105**	**4**	**49**
glucose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	46*
glucose	DMA	2-methoxycarbonyl	$MgCl_2•6H_2O$	105	4	61*
glucose	DMA	2-ethoxycarbonyl	$MgCl_2•6H_2O$	105	4	56*
mannose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	53
mannose	DMA	2-methoxycarbonyl	$MgCl_2•6H_2O$	105	3	51
mannose	DMA	2-ethoxycarbonyl	$MgCl_2•6H_2O$	105	4	54
gulose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	55
gulose	DMA	2-methoxycarbonyl	$MgCl_2•6H_2O$	105	4	56
gulose	DMA	2-ethoxycarbonyl	$MgCl_2•6H_2O$	105	4	49
idose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	48
idose	DMA	2-methoxycarbonyl	$MgCl_2•6H_2O$	105	4	51
idose	**DMA**	**2-ethoxycarbonyl**		**105**	**4**	**42**
galactose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	38
galactose	**DMA**	**2-methoxycarbonyl**		**105**	**4**	**50**
galactose	DMA	2-ethoxycarbonyl	$MgCl_2•6H_2O$	105	4	35
talose	DMA	2-carboxy	$MgCl_2•6H_2O$	105	4	21
talose	DMA	2-methoxycarbonyl	$MgCl_2•6H_2O$	105	4	30
talose	DMA	2-ethoxycarbonyl	$MgCl_2•6H_2O$	105	4	22

Boronic acids were used as 1 eq. and $MgCl_2•6H_2O$ as 2.5 eq. relative to the sugar. Sugars were used as 10 wt% relative to the DMA. Molar yield is relative to the sugars. *Reported previously.

and exists primarily in the β-anomer of its pyranose form, at least in DMSO.[158] The choice of organic solvent could alter the isomerization equilibria of the anomeric forms, as could the presence of a magnesium ion.[77,159]

Acid catalysis is often necessary to hydrolyze cellulosic materials to access the monomeric glucose before conversion to HMF can occur.[76,82-83,85] We were interested in determining if the boronic acids could bind to polymeric materials to facilitate conversion to HMF. Initially we focused on transformation of cellobiose, a β(1→4) dimer of glucose.

Surprisingly, we achieved higher yields of HMF using the 2-methoxycarbonyl- and 2-ethoxycarbonylphenylboronic acids alone than in tandem with $MgCl_2 \cdot 6H_2O$ (Table 4.3, Figure 4.5). Whereas the boronic acids were able to bind the cellobiose and facilitate hydrolysis and conversion to HMF, it seemed that coordination of the boronic acid makes the conversion facile for one monomer per saccharide, as the yields were always below 50%.

Table 4.3 Saccharide conversion using *ortho*-carboxyl phenylboronic acids

saccharide	solvent	phenylboronic acid	metal chloride	*T* (˚C)	time (h)	HMF molar yield (%)
cellobiose	DMA	2-carboxy		110	6	0
cellobiose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	110	6	10
cellobiose	**DMA**	**2-methoxycarbonyl**		**110**	**6**	**49**
cellobiose	DMA	2-methoxycarbonyl	$MgCl_2 \cdot 6H_2O$	110	5	37
cellobiose	**DMA**	**2-ethoxycarbonyl**		**110**	**6**	**44**
cellobiose	DMA	2-ethoxycarbonyl	$MgCl_2 \cdot 6H_2O$	110	5	27
cellotriose	**DMA**	**2-ethoxycarbonyl**		**105**	**4**	**21**
cellotetraose	**DMA**	**2-ethoxycarbonyl**		**120**	**4**	**38**
maltose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	4	4
maltose	DMA	2-methoxycarbonyl	$MgCl_2 \cdot 6H_2O$	105	4	7
maltose	DMA	2-ethoxycarbonyl	$MgCl_2 \cdot 6H_2O$	105	4	25
sucrose	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	4	46
sucrose	DMA	2-methoxycarbonyl	$MgCl_2 \cdot 6H_2O$	105	4	41
sucrose	DMA	2-ethoxycarbonyl		105	4	46
inulin	DMA	2-carboxy	$MgCl_2 \cdot 6H_2O$	105	1	29
inulin	DMA	2-methoxycarbonyl	$MgCl_2 \cdot 6H_2O$	105	1	29
inulin	DMA	2-ethoxycarbonyl		105	2	39

Boronic acids were used as 1 eq. and $MgCl_2 \cdot 6H_2O$ as 2.5 eq. relative to the sugar. Sugars were used as 10 wt% relative to the solvent. Molar yield is relative to the sugars.

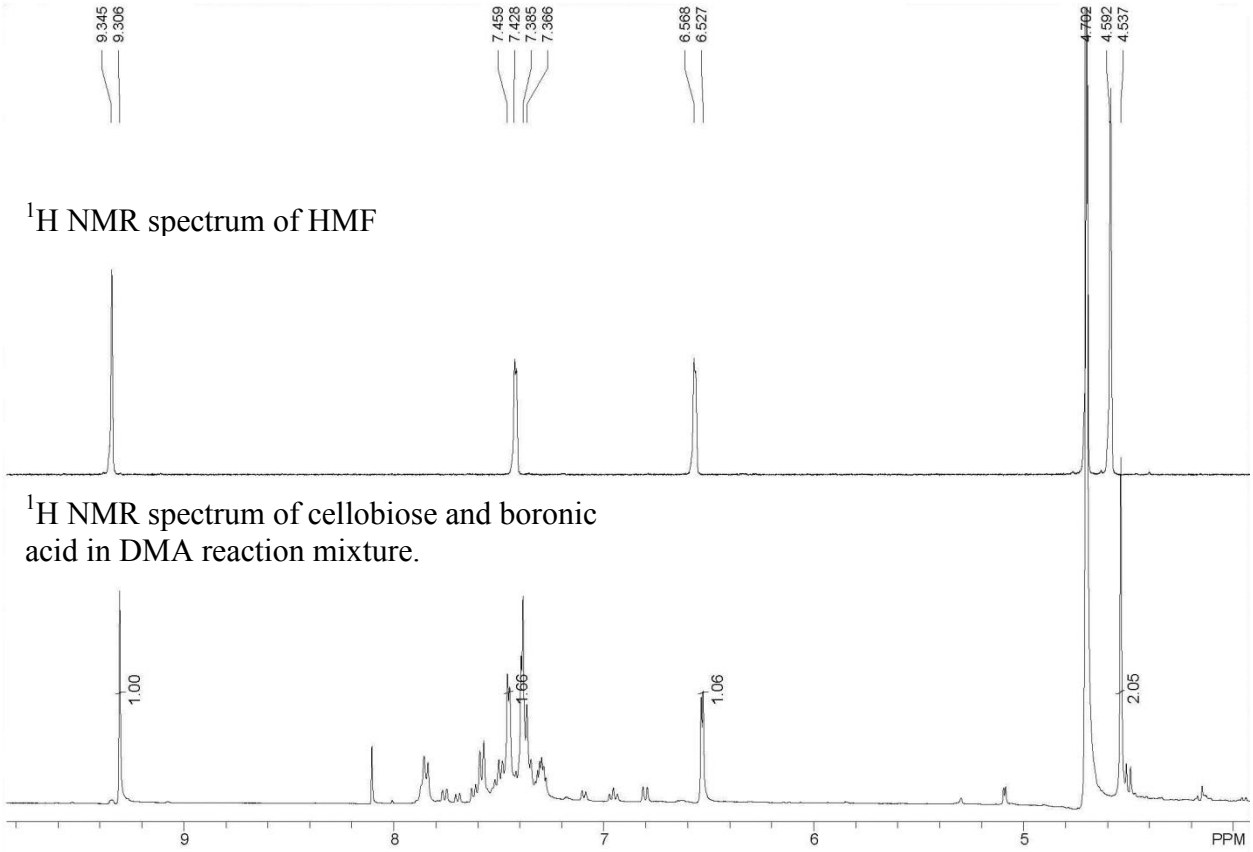

Figure 4.5 [1]H NMR spectra demonstrating HMF is formed from cellobiose using only boronic acids.

We explored this result further by transforming cellotriose and cellotetraose, the tri- and tetra-polymers of glucose, respectively. Both also were able to be converted to HMF using only a boronic acid, although it appeared again that only some of the monomers were able to be transformed. Additionally, the yields of HMF decreased with increased polymer length, and higher temperatures became necessary to achieve better HMF yields. A mechanism for a similar type of hydrolysis had been hypothesized previously to occur through a distortion of one of the glucose units to a half-chair, making its endocyclic oxygen lone pair synperiplanar to the other glucose unit.[160] The second glucose unit can then serve as a leaving group. In our system, the

boronic acid could distort a glucose unit to a half-chair to facilitate hydrolysis between two units, and then serve to dehydrate the distorted glucose unit to HMF.

The hydrolysis activity of the boronic acids was explored further with maltose, the α(1→4) dimer of glucose. Only small yields of HMF were attained, and those required the presence of $MgCl_2 \cdot 6H_2O$. Thus, it seems the ability of the boronic acids to mediate hydrolysis is limited by the anomeric form of the glycosidic bond between two glucose monomers. The hydrolysis of sucrose, a dimer of fructose and glucose, was achieved with comparable HMF yields to cellobiose. Finally, inulin, a polymer of fructose, was able to be converted to HMF, though the yields were decreased somewhat and $MgCl_2 \cdot 6H_2O$ was necessary for two of the boronic acids. This result is consistent with those observed for cellotriose and cellotetraose, as the increased chain length required higher temperatures to access higher yields. Whereas fructose is converted to HMF more easily than glucose, the length of the polymeric chain might hinder boronic acid activity.

Previously, we determined that the carboxyl moiety was essential for conversion of carbohydrates to HMF by phenylboronic acids.[157] Although 2-carboxy and 2-methoxycarbonyl groups accessed good HMF yields, 2-ethoxycarbonylphenylboronic acid typically had the highest activity in our carbohydrate conversion reactions. We were interested in determining if this activity could be enhanced by altering the structures and substitutions of the aryl ring (Figure 4.6). As activity had increased with increasing ester carbon side chains (**1**–**3**), we first sought to establish if there was a limit to the length of the side chain that would result in lower HMF yields. When we tested 2-isobutylcarboxyphenylboronic acid (**4**), we observed a significant decrease in HMF yields, suggesting that steric bulk within the ester side chain can hinder the conversion capability of the boronic acids (Table 4.4).

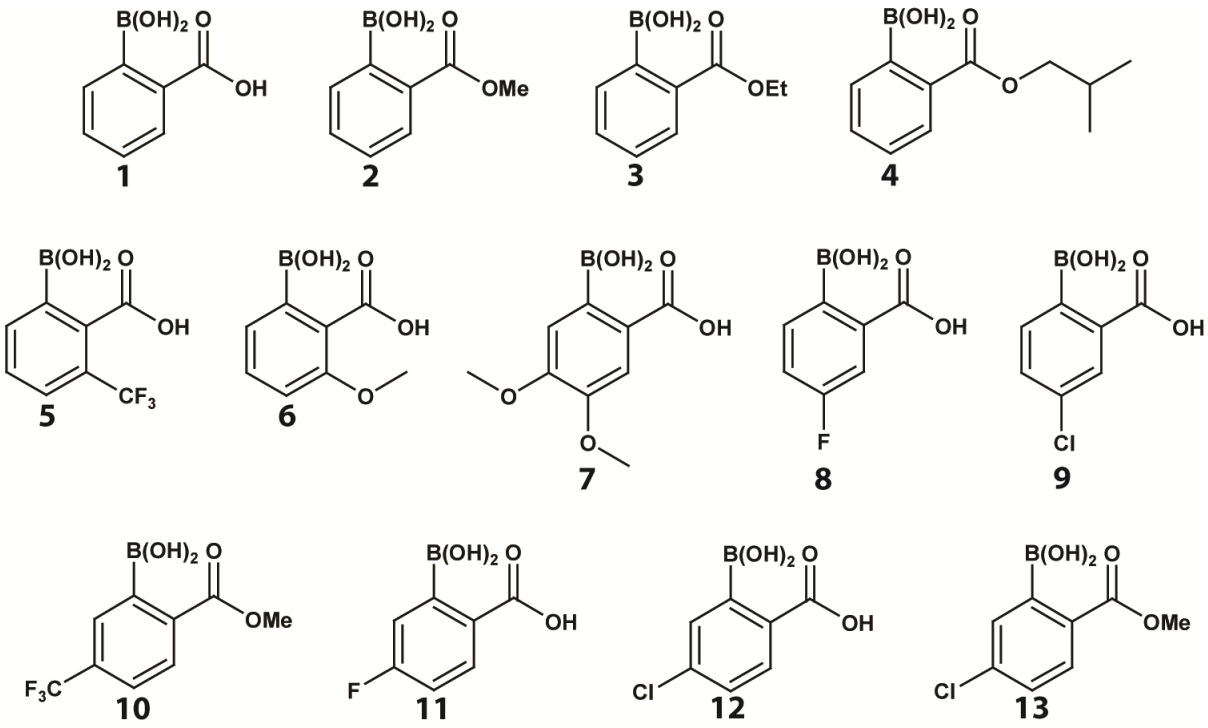

Figure 4.6 Structures of *ortho*-carboxyl phenylboronic acids.

Finally, we used carboxyl phenylboronic acids with an additional substitution to modify the electronics of the aryl ring and determine the influence on HMF yields. As compared to *ortho*-carboxyl phenylboronic acid (**1**) with $MgCl_2 \cdot 6H_2O$, additional substitutions such as a trifluoromethyl (**5**, **10**), methoxy (**6**, **7**), fluoro (**8**), and chloro (**9**, **12**–**13**) resulted in an increase in HMF yields (Table 4.4). The addition of a fluoro group at the 5-position (**11**) was, however, the only substitution tested that resulted in a drastic decrease in HMF yields, possibly due to high reactivity that caused degradation of the HMF product. Overall, the addition of inductively electron-withdrawing substituents appears to result in an enhancement in HMF yields. The increase in yields could result from an increased association of the boronic acids with the sugar due to a decrease in the electron density present at the boronic acid moiety.

Table 4.4 Saccharide conversion using substituted phenylboronic acids in DMA

saccharide	phenylboronic acid	metal chloride	*T* (˚C)	time (h)	HMF yield (%)
glucose	2-isobutylcarboxy	$MgCl_2•6H_2O$	105	4	22
glucose	**2-carboxy-3-trifluoromethyl**	**$MgCl_2•6H_2O$**	**105**	**1**	**68**
glucose	**2-carboxy-3-methoxy**	**$MgCl_2•6H_2O$**	**105**	**4**	**52**
glucose	**2-carboxy-4,5-dimethoxy**	**$MgCl_2•6H_2O$**	**105**	**3**	**63**
glucose	**2-carboxy-4-fluoro**	**$MgCl_2•6H_2O$**	**105**	**4**	**63**
glucose	**2-carboxy-4-chloro**	**$MgCl_2•6H_2O$**	**105**	**4**	**61**
glucose	**2-methoxycarbonyl-5-trifluoromethyl**	**$MgCl_2•6H_2O$**	**105**	**3**	**63**
glucose	2-carboxy-5-fluoro	$MgCl_2•6H_2O$	105	4	20
glucose	**2-carboxy-5-chloro**	**$MgCl_2•6H_2O$**	**105**	**1**	**70**
glucose	**2-methoxycarbonyl-5-chloro**	**$MgCl_2•6H_2O$**	**105**	**4**	**64**
cellobiose	2-carboxy-3-trifluoromethyl		105	4	64
cellobiose	2-carboxy-3-methoxy		105	3	43
cellobiose	2-carboxy-4,5-dimethoxy		105	3	38
cellobiose	2-methoxycarbonyl-5-trifluoromethyl		105	4	53
cellobiose	2-carboxy-5-chloro		105	4	66
cellobiose	2-methoxycarbonyl-5-chloro		105	4	48

Boronic acids were used as 1 eq. and $MgCl_2•6H_2O$ as 2.5 eq. relative to the sugar. Sugars were used as 10 wt% relative to the solvent. Molar yield is relative to the sugars.

4.5 Conclusions

Using ^{1}H NMR, we observed that the carboxyl phenylboronic acids are able to bind to both glucose and fructose *in situ*. The boronic acids readily dehydrate D-hexose sugars that exist predominantly in a furanose isomeric conformation to HMF. Still, the magnesium catalyst is necessary for conversion of pyranose sugars, isomerizing them to their furanose forms before dehydration. Interestingly, the boronic acids are also able to catalyze the hydrolysis of cellulosic disaccharide molecules before dehydration to HMF. Finally, we discovered that the HMF yields from reactions using boronic acids can be increased by decreasing the overall electron density of the aryl ring through the addition of electron-withdrawing substituents. These substituents could encourage tighter association of the boronic acids with the sugars. We anticipate that these

insights will allow for the design of optimal phenylboronic acids for an optimal organocatalytic conversion of cellulosic materials without a co-catalyst.

4.6 Acknowledgments

This work was funded by the DOE Great Lakes Bioenergy Research Center (DOE BER Office of Science DE-FC02-07ER64494). M.J.P. was supported by pre-doctoral fellowship 09PRE2260125 (American Heart Association). We are grateful to Dr. N.A. McGrath for contributive discussions. This study made use of the National Magnetic Resonance Facility at Madison, which is supported by NIH grants P41RR02301 (BRTP/ NCRR) and P41GM66326 (NIGMS). Additional equipment was purchased with funds from the University of Wisconsin, the NIH (RR02781, RR08438), the NSF (DMB-8415048, OIA-9977486, BIR-9214394), and the USDA.

4.7 Materials and Methods

4.7.1 Materials

Commercial chemicals were of reagent grade or better and were used without further purification. 1-Ethyl-3-methylimidazolium chloride (99.5%, [EMIM]Cl) was from Solvent-Innovation (Cologne, Germany). Glucose was from J. T. Baker (Phillipsburg, NJ). Cellulose (medium cotton linters, C6288), fructose, *N,N*-dimethylacetamide (DMA), and metal chlorides were from Sigma (St. Louis, MO). Magnesium chloride hexahydrate was from Fisher Scientific (Pittsburgh, PA). Boronic acids were from either Synthonix (Doylestown, PA) or Combi-Blocks, Inc. (San Diego, CA). All reactions were performed in 4-mL glass vials heated in a temperature-controlled VWR Mini Shaker at 600 rpm. The term “high vacuum” refers to vacuum (<0.1 torr)

achieved by a Welch mechanical belt-drive oil pump. NMR spectra were acquired with a Bruker DMX-400 Avance spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) at the National Magnetic Resonance Facility at Madison (NMRFAM). NMR spectra were obtained at ambient temperature unless indicated otherwise. Coupling constants *J* are given in Hertz.

4.7.2 Analytical Methods

Reaction products were analyzed by HPLC and quantified using calibration curves generated from commercially available standards. Product concentrations were calculated from HPLC-peak integrations, which were then used to calculate molar yields. During a reaction, an aliquot of the reaction mixture was taken, diluted with a known mass of deionized water, cooled to 4 ˚C, centrifuged at 12,000 rpm for 5 min to sediment insoluble products, and analyzed. HPLC was performed using an Agilent 1200 system equipped with refractive index and photodiode array detectors. HMF, ketohexoses, and aldohexoses were analyzed by ion-exclusion chromatography with a Bio-Rad Aminex HPX-87H column (300 x 7.8 mm) using a 5 mM H_2SO_4 mobile phase at a flow rate of 0.6 mL/min at 65 °C.

4.7.3 Representative Procedure for Synthesis of HMF from Saccharides

Glucose (51.6 mg, 286 μmol), 2-carboxyphenylboronic acid (47.3 mg, 285 μmol), and $MgCl_2$•$6H_2O$ (145.5 mg, 716 μmol) were mixed in DMA (500 mg). The reaction mixture was heated at 105 ˚C for 4 h. At 1 h intervals, aliquots of the reaction mixture were removed for HPLC analysis. For reactions using [EMIM]Cl, approximately 500 mg of the ionic liquid was added to the vial in place of DMA. 2-Methoxycarbonylphenylboronic acid and 2-ethoxycarbonylphenylboronic acid were also used at equimolar concentrations relative to the saccharide. Reactions involving other cellobiose, cellotriose, and cellotetraose were performed in

a similar manner, although they were added so their molar amounts of glucose would be equivalent to the boronic acids' and $MgCl_2 \cdot H_2O$ was not always used for their conversion.

4.7.4 ^{1}H NMR Experiments

The boronic acids and sugars were dissolved in DMSO-d_6, which served as a deuterated organic solvent substitute for DMA. As is commonly observed for organic solvents, the boronic acid was seen to form an anhydride species with itself (Figure S2A), which was hydrolyzed upon the addition of water (Figure S2B). We next analyzed the addition of fructose to the boronic acid. Typically, the aryl hydrogens of the boronic acid demonstrate a distinct shift in their chemical shifts upon complexation to a sugar.[145,153] We observed quantitative binding of fructose to 2-carboxyphenylboronic acid as demonstrated by two distinct sets of peaks corresponding to the free boronic acid and the boronic acid–fructose complex (Figure S2C,D). As a control, we observed the complexation of fructose and phenylboronic acid, which is known to occur in aqueous solvents (Figure S3C,D).[145-146,153,161] We also analyzed the addition of glucose to the boronic acid, and noted changes in the peak splitting as well (Figure S2E,F). Additionally, we performed a positive control using phenylboronic acid (Figure S3), which is reported to have a higher binding affinity toward fructose than glucose. We detected distinct shifts in the NMR peaks as expected, although the peaks did not demonstrate a consistency in their shifts as opposed to what is seen in an aqueous environment.[145,153] Nonetheless, these data indicate that fructose and glucose do break up the boronic acid anhydride, and that the affinity of the boronic acids for sugars is altered in organic solvents relative to aqueous solvents. Finally, we added $MgCl_2 \cdot 6H_2O$ and reexamined the spectra of the boronic acids in the presence of fructose and glucose to mimic our reaction conditions. While some peak broadening was observed, we did not

detect any significant changes to the overall spectra, indicating that the $MgCl_2 \cdot 6H_2O$ does not appear to affect the boronic acid–sugar binding.

CHAPTER FIVE*

SEPARABLE FLUOROUS IONIC LIQUIDS FOR THE DISSOLUTION AND SACCHARIFICATION OF CELLULOSE

5.1 Abstract

Ionic liquids are an attractive class of solvents for biomass conversion processes. The same properties that make them advantageous—high polarity, water solubility, and negligible vapor pressure—hinder their recovery from carbohydrates. We report on the synthesis of seven fluorous imidazolium chloride ionic liquids and on their ability to dissolve cellulose. One of these ionic liquids, 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride, dissolves cellulose. We found this fluorous ionic liquid to be suitable for use in cellulose hydrolysis reactions, and we achieved its recovery from glucose.

5.2 Author Contributions

J.B.B. proposed using fluorous labeling to facilitate isolation and recovery of ionic liquids. B.R.C. and J.B.B. designed the fluorous labeled ionic liquids. B.R.C., J.B.B., and J.J.B. performed the research. B.R.C. drafted the manuscript. B.R.C., J.B.B., and R.T.R. designed experiments, analyzed the data, and edited the manuscript and figures.

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5.3 Introduction

The implementation of a viable fuel and energy alternative to sources such as coal, natural gas, and petroleum is rapidly becoming critical for a sustainable future. Lignocellulosic biomass, both abundant and renewable, is one such alternative resource. Its primary component, cellulose, can be hydrolyzed to glucose, then transformed into the platform chemical 5-(hydroxymethyl)furfural (HMF)[13-14,31] or used as a feedstock for the growth of engineered microbes. Unfortunately, the polymeric, crystalline nature of cellulose makes it highly recalcitrant to dissolution, and few organic solvents accomplish this feat.[33] The desire to utilize environmentally benign solvents for cellulose dissolution aggravates the problem further.

Ionic liquids are an attractive class of solvents, as they are polar, water-soluble molten salts with negligible vapor pressures.[36,162-164] Importantly, ionic liquids can accomplish cellulose dissolution. The crystallinity of cellulose results from a complex network of intrastrand and interstrand hydrogen bonds.[33] To dissolve cellulose, a solvent must compete for these intermolecular hydrogen bonds. Ionic liquids accomplish dissolution because their charged species disrupt the hydrogen-bonding network by forming electron donor–electron acceptor complexes with the hydroxyl groups.[36,165] This results in separation of the polymer chains, allowing for dissolution. Dialkylimidazolium chlorides, in particular, demonstrate the capacity to dissolve high concentrations of cellulose,[38-40] and have been used in cellulose conversion processes.[20,61,63,76,105] For example, we accessed HMF in one step from lignocellulosic biomass using a chromium catalyst in 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl),[76] and fermentable sugars from lignocellulosic biomass by hydrolysis in an [EMIM]Cl/HCl/H_2O system.[63] Schüth and coworkers utilized solid acid catalysts in 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) for the depolymerization of cellulose to cello-oligomers.[105] Amarasekara

and Owereh accomplished cellulose hydrolysis to glucose and other reducing sugars in the Brønsted acidic ionic liquids 1-(1-propylsulfonic)-3-methylimidazolium chloride and 1-(1-butylsulfonic)-3-methylimidazolium chloride.[61] We realized that the physical properties that make ionic liquids ideal as a reaction medium for these biomass conversion processes hinder their separation and recovery from the desired carbohydrate products. Yet, as ionic liquids are more expensive than traditional organic solvents, it is imperative that they be recovered if they are to serve as a reaction medium in an economical process.

Fluorous tags are being employed increasingly to facilitate the separation of products and catalysts in organic synthesis.[166-173] They have a high affinity for a fluorous phase, which is distinct from polar/nonpolar and hydrophilic/hydrophobic phases.[167] Heavy fluorous tags containing >60% fluorine enable the extraction of a tagged compound.[171] Light fluorous tags (typically, C_3F_7 to $C_{10}F_{21}$) are suited for solid-phase extraction with a C_8F_{17}-bonded phase (as in fluorous silica gel) or isolation by fluorous HPLC.[171] We envisioned that these same separation strategies could be used with fluorous ionic liquids.

Fluorous ionic liquids are not available from commercial vendors. A variety, however, have been synthesized, not only to avail potential fluorine–fluorine interactions, but also to modulate the physical properties of the ionic liquids.[174-180] Modification of the fluorine-containing portion of the cation can have a substantial impact on melting point, viscosity, density, conductivity, solubility, and thermostability.[179] Additionally, the identity of the anion can be modified to alter the properties of an ionic liquid. The versatility is great, and a number of imidazolium fluorous ionic liquids, in particular, have been synthesized and tested as surfactants, in gas separations, and in metal-ion extraction.[174-178,180-181] Nonetheless, fluorous ionic liquids have not been employed in biomass- or bioproduct-conversion processes, and no fluorous ionic

liquids have been synthesized with the chloride counterion necessary for cellulose dissolution. Herein, we report on the synthesis of seven fluorous imidazolium chloride ionic liquids (**1**–**7**) and on their capabilities as biomass solvents. To our knowledge, ionic liquid **3** is novel. The other six fluorous imidazolium groups have been described previously (though not as a chloride salt),[174,181-183] but have not been used in a bioprocessing application.

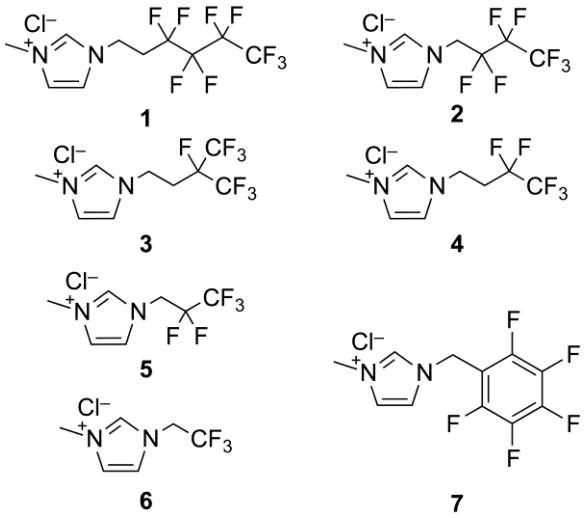
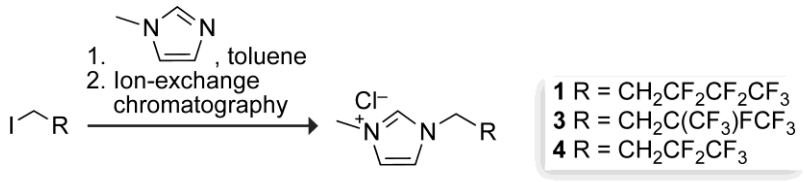


Figure 5.1 Synthesized fluorous ionic liquids.

5.4 Results and Discussion

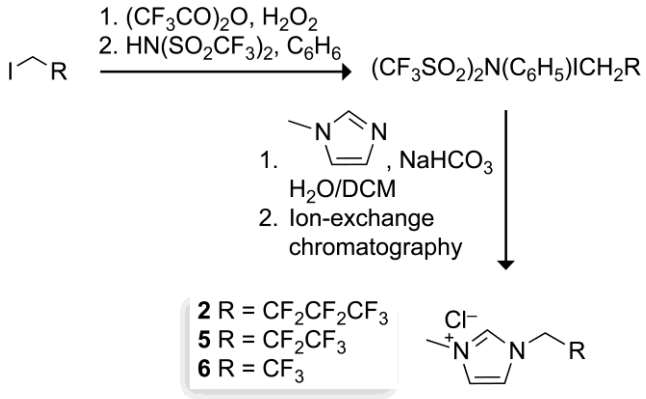
As its separation from non-fluorous molecules would be enhanced by a high fluorine-content,[172] we initially targeted an ionic liquid with nine fluoro groups, 3-methyl-1-(3′,3′,4′,4′,5′,5′,6′,6′,6′-nonafluorohexyl)-imidazolium chloride (**1**). Following the procedure of Noble and coworkers (Scheme 5.1),[174] ionic liquid **1** was synthesized by the reaction of a fluoroalkyl iodide precursor with 1-methylimidazole. Ion-exchange chromatography yielded ionic liquid **1** as a highly viscous oil. This ionic liquid was soluble in polar solvents such as

water, methanol, and acetonitrile, but demonstrated limited solubility in toluene. We found cellulose to be insoluble in ionic liquid **1**, even with heating.



Scheme 5.1 Synthesis of ionic liquids **1** and **3–4**.

Next, we synthesized 1-(2′,2′,3′,3′,4′,4′,4′-heptafluorobutyl)-3-methylimidazolium chloride (**2**), a fluorous ionic liquid containing a smaller fluorous tag. The steric bulk of the proximal fluoroalkyl group made the 1-position of heptafluorobutyl iodide especially resistant to nucleophilic attack. Hence, a hypervalent iodonium alkylating agent invented by DesMarteau and coworkers was employed as an intermediate (Scheme 5.2).[181-182] We again found the ionic liquid to be soluble in polar solvents, but unable to dissolve cellulose.



Scheme 5.2 Synthesis of ionic liquids **2** and **5–6**.

Then, we sought to consolidate the fluoro groups so as to minimize alteration to the dialkylimidazolium core structure. Hence, we synthesized 3-methyl-1-(3′,4′,4′,4′-tetrafluoro-3′-

trifluoromethyl-butyl)-imidazolium chloride (**3**) as a viscous oil following the procedure of Noble and coworkers.[174] Once again, while the ionic liquid was soluble in polar solvents, it was unable to dissolve cellulose.

The behavior of ionic liquids **1**–**3** was unexpected, as ionic liquids containing a chloride anion are typically able to dissolve at least low concentrations of cellulose. We reasoned that the size of the perfluorinated alkyl side chain on ionic liquids **1**–**3** could be hindering cellulose dissolution. A steric effect had been observed previously, as imidazolium ionic liquids with *N*-alkyl groups containing >8 carbons demonstrate a marked decrease in cellulose solubility.[39-40] Perfluorinated alkyl groups are significantly more bulky than the corresponding alkyl groups, which would explain why our fluorous ionic liquids were unable to dissolve cellulose, unlike their corresponding alkyl ionic liquids. For example, *A*-values indicate that a trifluoromethyl group is at least as large as a isopropyl group; Taft-type steric parameters indicate it to be as large as an isobutyl group.[184] Therefore, we sought to synthesize fluorous ionic liquids with smaller fluorous side chains (Table 5.1).

Table 5.1 Imidazolium volumes of fluorous ionic liquids **1–7**

Fluorous ionic liquid	Number of fluoro groups	Imidazolium volume [a] ($bohr^3$/mol)
1	9	1835
2	7	1669
3	7	1352
4	5	1303
5	5	1213
6	3	1089
7	5	1652

[a]Calculated with Gaussian ’03.

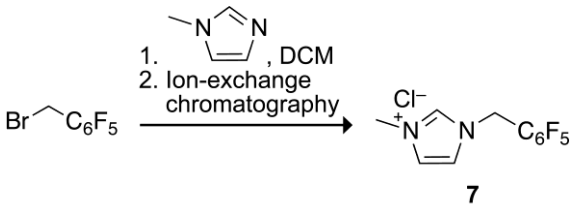
To access an ionic liquid with a smaller fluorous tag, we synthesized 3-methyl-1-(3′,3′,4′,4′,4′-pentafluorobutyl)-imidazolium chloride (**4**) as a viscous oil following the procedure of Noble and coworkers.[174] This ionic liquid was unable to dissolve cellulose, despite its solubility in polar solvents. Seeking to truncate further the side chain of the cation, we synthesized 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (**5**) following the procedure of DesMarteau and coworkers.[181-182] This ionic liquid was obtained as a crystalline solid at room temperature but melts at moderate temperatures and is a viscous liquid at 100 °C. Importantly, upon heating to 140 °C, ionic liquid **5** demonstrated dissolution of cellulose to ≥2 wt%, forming a viscous solution similar to that observed with typical dialkylimidazolium ionic liquids. Remarkably, this difference in cellulose solubility was accomplished upon deletion of a single methylene unit. This result demonstrates the profound influence of imidazolium size on solubilizing cellulose. Further, as dialkylimidazolium acetates are also known to dissolve cellulose,[5b,5c] we transformed **5** into its acetate counterpart. Again, a viscous solution formed upon heating, and cellulose dissolution was observed to ≥2 wt%.

Encouraged by this success, we sought to decrease further the size of the fluoroalkyl side chain. Hence, we again followed the procedure of DesMarteau and coworkers[181-182] to synthesize 3-methyl-1-(2′,2′,2′-trifluoroethyl)-imidazolium chloride (**6**) as a viscous oil. Cellulose was soluble in this ionic liquid, but

somewhat less so than in 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (**5**). Apparently, imidazolium structure has subtle and (now) inexplicable influences on interactions with cellulose.

As a final possibility, we were interested in testing a perfluorinated aryl–alkyl imidazolium ionic liquid as a solvent for cellulose. Aryl–alkyl ionic liquids allow for the

potential to modulate the physiochemical properties of an ionic liquid *via* σ- and π-based electronic effects.[185] To this end, we synthesized 3-methyl-1-pentafluorophenylmethylimidazolium chloride (**7**) as a white solid following the procedure of McGrangle and Saunders (Scheme 5.3).[183] Ionic liquid **7** demonstrated solubility in polar solvents, but was insoluble in toluene and had a melting point of 150 °C. Due to its high melting point, we attempted cellulose dissolution utilizing varying concentrations of the ionic liquid in *N,N*-dimethylacetamide–LiCl.[76] Yet, even when heated to 140 °C, no cellulose dissolution was observed in these solutions.



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Scheme 5.3 Synthesis of ionic liquid **7**.

Given the demonstrated ability of ionic liquid **5** to dissolve cellulose, we next sought a method for its extraction. Ionic liquid **5** is highly soluble in water, and we did not recover an appreciable quantity in an organic phase (*e.g.*, ethyl acetate). Nonetheless, we investigated whether a fluorous solvent (*e.g.*, perfluorinated hexane) could extract ionic liquid **5**. As typical fluorous tags used in this way contain >20 fluoro groups, we did not expect our ionic liquids to separate into the fluorous phase. Indeed, when tested for separation in water and perfluorinated hexane, no ionic liquid **5** was detected in the fluorous solvent. Next, we turned to fluorous solid-phase extraction (SPE) to remove our lightly fluorinated ionic liquid from water. Following a procedure from Fluorous Technologies (Pittsburgh, PA),[186] we used water as our fluorophobic

phase and methanol as our fluorophilic phase on a FluoroFlash® SPE cartridge. Although the majority of ionic liquid **5** was retained on the cartridge after water elution, we could detect the ionic liquid in the water eluant. A methanol elution recovered the remaining ionic liquid. These results suggested that the fluorous ionic liquid with only five fluoro groups is too polar and insufficiently fluorous for standard fluorous separation techniques. Fluorous SPE typically requires molecules to contain at least seven fluoro groups,[171] whereas our ionic liquid contained only five.

The moderate retention of the fluorous ionic liquid on the fluorous SPE cartridge led us to hypothesize that a chromatographic separation could be possible. To this end, we prepared a column using FluoroFlash® silica gel, as in the SPE cartridge. Using this column, we were able to separate ionic liquid **5** from glucose using water as the eluent (Figure 5.1). To conclude that the fluorous tag was responsible for the separation of the ionic liquid from the sugar, we performed a similar experiment using the pentafluorobutyl ionic liquid (**4**) and its non-fluorous counterpart, 1-butyl-3-methylimidazolium chloride. The fluorous ionic liquid again demonstrated a clean separation from glucose, while the non-fluorous ionic liquid was not cleanly separated from the glucose. This result is consistent with the fluorous tag enabling the separation of the ionic liquid from glucose.

With the successful separation of the fluorous ionic liquids from glucose, we sought to determine if ionic liquid **5** could be used in a cellulose hydrolysis reaction. Following a modified procedure that we employed previously,[76] we dissolved cellulose at 2 wt% in ionic liquid **5** and assessed the reaction mixture at known time points. After 2 h, we detected the presence of both fructose and glucose in the reaction mixture at 27 and 11 mol%, respectively. After 4 h, we detected traces of HMF. Finally, we achieved separation of ionic liquid **5** from the reaction

products by chromatography using FluoroFlash® silica gel (Figure 5.1), recovering >95% of **5**. This result suggests that 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (**5**) can indeed be used in cellulose conversion.

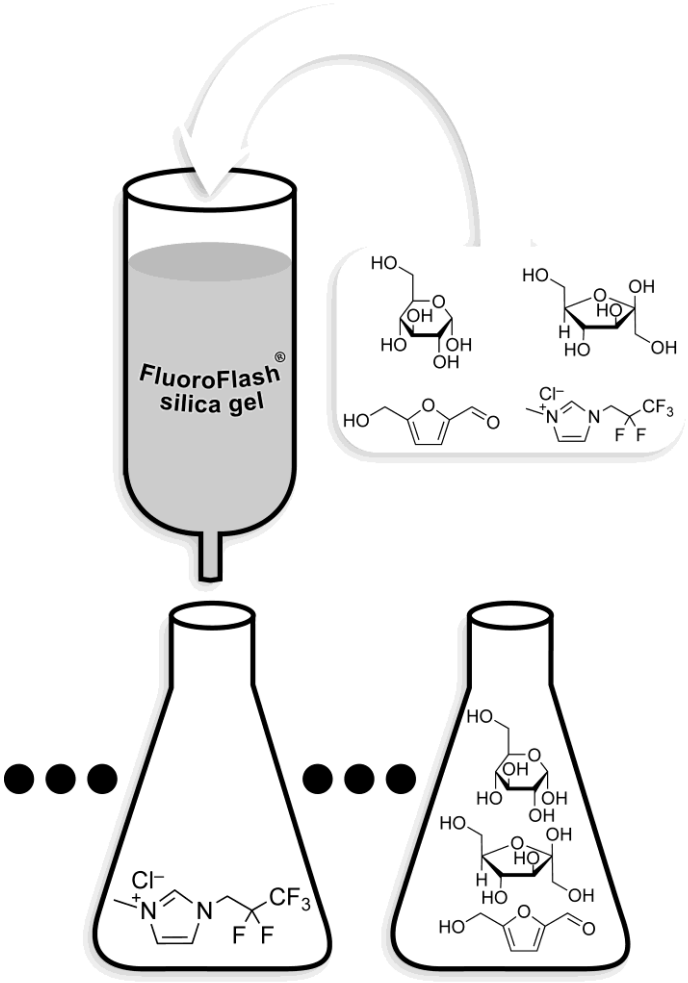


Figure 5.2 Schematic of the isolation of ionic liquid 5 from sugars and furanics by chromatography using FluoroFlash® silica gel. The eluent is water.

5.5 Conclusions

We synthesized seven fluorous imidazolium chloride ionic liquids and assessed their ability to dissolve cellulose. We discovered that the ability of a fluorous ionic liquid to dissolve

cellulose is highly sensitive to the structure of the imidazolium cation, as only by decreasing the fluorous tag to a pentafluoropropyl group was cellulose dissolution possible. An even smaller tag, trifluoroethyl, also allowed some cellulose dissolution to occur. Although the content of fluorine in these fluorous tags is too small to allow for typical fluorous SPE methods, we accomplished separation of cellulose hydrolysis products from our optimal fluorous ionic liquid by utilizing chromatography with FluoroFlash® silica gel. Finally, we tested the pentafluoropropyl ionic liquid (**5**) in a cellulose hydrolysis reaction and discovered its support of monomeric sugar production. These results encourage the further development of fluorous imidazolium chloride ionic liquids for biomass conversion processes.

5.6 Acknowledgments

This work was supported by the Great Lakes Bioenergy Research Center, a DOE Bioenergy Research Center. We are grateful to A. Choudhary for his assistance with Gaussian calculations, and R.L. Kubiak for her assistance with cellulose dissolution studies. This study made use of the National Magnetic Resonance Facility at Madison, which is supported by NIH grants P41RR02301 (BRTP/NCRR) and P41GM66326 (NIGMS). Additional equipment was purchased with funds from the University of Wisconsin, the NIH (RR02781, RR08438), the NSF (DMB-8415048, OIA-9977486, BIR-9214394), and the USDA.

5.7 Materials and Methods

5.7.1 Materials

Cellulose (medium cotton linters, C6288) was from Sigma Chemical (St. Louis, MO). Other commercial chemicals were of reagent grade or better and were used without further purification. FluoroFlash® fluorous silica gel was from Aldrich Chemical (Milwaukee, WI).

The term "concentrated under reduced pressure" refers to the removal of solvents and other volatile materials using a rotary evaporator at water aspirator pressure (<20 torr) while maintaining the water-bath temperature below 50 °C unless noted otherwise. The term "high vacuum" refers to vacuum (<0.1 torr) achieved by a mechanical belt-drive oil pump.

5.7.2 Analytical Methods

Reaction products were analyzed by HPLC and quantified using calibration curves generated from commercially available standards. Reaction mixtures were diluted with a known mass of deionized water, subjected to centrifugation at 12,000 rpm for 5 min to sediment insoluble products, and analyzed. Product concentrations were calculated from HPLC-peak integrations, which were then used to calculate yields. HPLC was performed using an Agilent 1200 system equipped with refractive index and photodiode array detectors. Sugars were analyzed by ion-exclusion chromatography with a Bio-Rad Aminex HPX-87H column (300 × 7.8 mm) using a 5 mM H_2SO_4 mobile phase at a flow rate of 0.6 mL/min at 65 °C.

NMR spectra were acquired with a Bruker DMX-400 Avance spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) at the National Magnetic Resonance Facility at Madison (NMRFAM). NMR spectra were acquired at ambient temperature unless indicated otherwise. Mass spectrometry was performed with a Micromass LCT (electrospray ionization, ESI) in the

Mass Spectrometry Facility in the Department of Chemistry at the University of Wisconsin–Madison.

5.7.3 3-Methyl-1-(3',3',4',4',5',5',6',6',6'-nonafluorohexyl)-imidazolium chloride (1)

Under Ar(g), toluene (15 mL) and 1,1,1,2,2,3,3,4,4-nonafluorohexyl iodide (5.0 g, 13.4 mmol) were combined in a round-bottom flask. The resulting solution was cooled to 0 °C, and 1-methylimidazole was added dropwise. The solution was stirred for 19 d, and separated into an orange lower layer and a colorless upper layer. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel, 5:95–15:85 methanol/dichloromethane). Fractions containing the iodide salt were concentrated under reduced pressure.

Dowex 1-X8 resin (chloride form, 100–200 mesh) was mixed with 1:1 methanol/H_2O and poured into a glass column to create a resin bed (17 cm long, 20 mL volume, 24 meq). The resin bed was flushed extensively with 1:1 methanol/H_2O to remove contaminants. The iodide salt was dissolved in methanol (5 mL) and water (5 mL), and loaded onto the column. The column was eluted with 1:1 methanol/H_2O, and fractions were collected. The fractions containing ionic liquid were concentrated under reduced pressure to yield an orange oil contaminated with white solids. The oil and solids were dissolved in boiling methanol, and the solution was concentrated under reduced pressure until the white solids precipitated. The solids were removed by filtration and washed with tetrahydrofuran. Concentration of the filtrate under reduced pressure afforded **1** (0.7 g, 1.9 mmol, 14% yield) as an orange oil. ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 7.87 (s, 1H), 7.71 (s, 1H), 4.72 (t, J = 7.3 Hz, 2H), 4.02 (s, 3H), 3.03 (m, 2H).

5.7.4 1-(2',2',3',3',4',4',4'-Heptafluorobutyl)-3-methylimidazolium chloride (2)

A round-bottom flask was placed under Ar(g) to which trifluoroacetic anhydride (30.2 g, 143.9 mmol) was added. The flask was then cooled to –15 °C using a benzyl alcohol/dry ice bath before adding 50% v/v H_2O_2 (2.1 mL, 43.1 mmol) dropwise. 2,2,3,3,4,4,4-Heptafluoro-1-iodobutane (5.4 g, 17.4 mmol) was added to the round-bottom flask, which was protected from light with aluminum foil and allowed to warm to room temperature. The reaction mixture was stirred for 3 d. The reaction mixture was then concentrated under reduced pressure and left under high vacuum overnight to yield a white solid (5.3 g, 9.8 mmol). This solid was dissolved with trifluoroacetic anhydride (10 mL) in a round-bottom flask under Ar(g). Trifluoromethanesulfonimide (4.5 g, 15.9 mmol) was placed in another round-bottom flask under Ar(g), and the trifluoroacetic anhydride solution was transferred *via* cannula. The resulting solution was cooled to 0 °C in an ice-water bath and protected from light with aluminum foil. After stirring for 15 min, benzene (2.0 mL) was added. The reaction was allowed to warm to room temperature after 3 h and continued for another 15 h. A second portion of benzene (0.7 mL) was then added with stirring continued for an additional 5 h. The reaction mixture was then concentrated under reduced pressure and placed under high vacuum overnight to yield a brown oil (7.9 g). 1-Methylimidazole (0.7 mL, 9.1 mmol) and $NaHCO_3$ (0.9 g, 10.9 mmol) were dissolved in double deionized water (50 mL) in a round-bottom flask. The brown oil was then dissolved in dichloromethane (50 mL) and added to the aqueous mixture in one portion to give two layers. The mixture was stirred at room temperature for 4 h. The bottom, brown layer was then separated, concentrated under reduced pressure at 65 °C, and placed under high vacuum overnight to yield a brown oil (5.9 g). Purification was performed with flash chromatography (silica gel, 0:100–20:80 methanol/dichloromethane). Silica present in the residue was removed

by dissolution in dichloromethane and filtration through a Millipore GVHP 0.22-μm membrane to yield an orange oil (1.5 g, 2.8 mmol).

Dowex 1-X8 resin (chloride form, 200–400 mesh) was mixed with 1:1 methanol/H_2O and poured into a glass column to create a resin bed (3 cm long, 37 mL volume, 16 meq). The resin bed was flushed extensively with methanol/H_2O to remove contaminants. The salt was dissolved in methanol (7.5 mL) and water (2.5 mL) and loaded on the column. The column was eluted with H_2O, 1:1 methanol/H_2O, and methanol, and fractions were collected. Fractions containing ionic liquid were concentrated under reduced pressure to yield **2** (0.90 g, 3.1 mmol, 34% yield) as an orange oil. ^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 5.24 (t, J = 15.7 Hz, 2H), 3.92 (s, 3H). HRMS (ESI) m/z 265.0573 [calculated for $C_8H_8N_2F_7$ $(M - Cl)^+$ 265.0571].

5.7.5 3-Methyl-1-(3',4',4',4'-tetrafluoro-3'-trifluoromethyl-butyl)-imidazolium chloride (3)

Under Ar(g), anhydrous toluene (75 mL) and 1-methylimidazole (3.0 mL, 37.8 mmol) were added to a round-bottom flask equipped with a reflux condenser. 4-Iodo-2-(trifluoromethyl)-1,1,1,2-tetrafluorobutane (8.2 g, 25.2 mmol) was then added, and the reaction mixture was stirred at reflux for 16 h. The mixture was then allowed to cool to room temperature before the toluene was decanted to leave a brown oil. This oil was concentrated under reduced pressure before being placed under high vacuum overnight. Purification was attempted by flash chromatography (silica gel, 0:100–30:70 methanol/dichloromethane), but failed to yield the pure iodide salt. Hence, the compound was passed through a fluorous SPE cartridge according to the procedure by Fluorous Technologies, Inc.[186] to yield the pure iodide salt as an orange oil.

Dowex 1-X8 resin (chloride form, 200–400 mesh) was mixed with 1:1 methanol/H_2O and poured into a glass column to create a resin bed (4 cm long, 20 mL volume, 8 meq). The resin bed was flushed extensively with methanol/H_2O to remove contaminants. The salt was dissolved in methanol (7.5 mL) and water (2.5 mL), and loaded onto the column. The column was eluted with H_2O, 1:1 methanol/H_2O, and methanol, and fractions were collected. Fractions containing ionic liquid were concentrated under reduced pressure to yield **3** (1.2 g, 3.7 mmol, 15% yield) as an orange oil. ^{1}H NMR (400 MHz, CD_3OD) δ 9.08 (s, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 4.56 (t, J = 7.8 Hz, 2H), 3.92 (s, 3H), 2.93 (m, 2H). HRMS (ESI) m/z 279.0742 [calculated for $C_9H_{10}N_2F_7$ $(M - Cl)^+$ 279.0727].

5.7.6 3-Methyl-1-(3',3',4',4',4'-pentafluorobutyl)-imidazolium chloride (4)

In a round-bottom flask equipped with a magnetic stirbar and a reflux condenser were placed 3,3,4,4,4-pentafluorobutyl iodide (5.7 g, 20.8 mmol), 1-methylimidazole (2.5 mL, 31.2 mmol), and toluene (50 mL). The resulting solution was stirred and maintained at 75 °C for 15 h. Then, the temperature was increased to 100 °C. After 8 h, a red layer had appeared beneath the upper toluene layer. The reaction mixture was then concentrated under reduced pressure to a red-orange residue.

Dowex 1-X8 resin (chloride form, 100-200 mesh) was mixed with water and poured into a glass column to create a resin bed (17 cm long, 20 mL volume, 24 meq). The resin bed was flushed extensively with water to remove contaminants. The red-orange residue was dissolved in water and loaded on the column. The column was eluted with water, and fractions were collected. Fractions containing ionic liquid were concentrated under high vacuum, yielding an orange oil. The major impurity was 1-methylimidazole. The residue was purified by flash

chromatography (silica gel, 15:85–30:70 methanol/dichloromethane), and the fractions containing the chloride salt were concentrated under reduced pressure. To remove silica, the residue was dissolved partially in dichloromethane, and filtered through a Millipore GVHP 0.22-μm membrane. The filtrate was concentrated under high vacuum, yielding **4** (1.69 g, 6.39 mmol, 30.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.69 (s, 1H), 7.55 (s, 1H), 4.55 (t, J = 7.2 Hz, 2H), 3.88 (s, 3H), 2.84 (m, 2H). HRMS (ESI) m/z 229.0768 [calculated for $C_8H_{10}N_2F_5$ $(M - Cl)^+$ 229.0759].

5.7.7 3-Methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5)

A round-bottom flask was placed under Ar(g) to which trifluoroacetic anhydride (30.2 g, 143.9 mmol) was added. The flask was then cooled to –15 °C using a benzyl alcohol/dry ice bath before adding 50% H_2O_2 (2.1 mL, 43.1 mmol) dropwise. 1,1,1,2,2-Pentafluoro-3-iodopropane (5.1 g, 19.4 mmol) was then added to the round-bottom flask, which was protected from light with aluminum foil and allowed to warm to room temperature. The reaction mixture was stirred for 3 d. The reaction mixture was then concentrated under reduced pressure and left under high vacuum overnight to yield a brown oil (7.9 g). This oil was dissolved in trifluoroacetic anhydride (10 mL) in a round-bottom flask under Ar(g). Trifluoromethanesulfonimide (4.8 g, 17.1 mmol) was placed in a separate round-bottom flask under Ar(g), and the trifluoroacetic anhydride solution was transferred *via* cannula. The resulting solution was cooled to 0 °C in an ice-water bath and protected from light with aluminum foil. After stirring for 15 min, benzene (2.0 mL) was added. The reaction mixture was allowed to warm to room temperature after 3 h and continued for another 15 h. A second portion of benzene (0.7 mL) was then added with stirring continued for an additional 5 h. The reaction mixture was then concentrated under reduced

pressure and placed under high vacuum overnight to yield a brown oil (8.5 g). 1-Methylimidazole (0.9 mL, 11.3 mmol) and $NaHCO_3$ (1.2 g, 13.6 mmol) were dissolved in double deionized water (50 mL) in a round-bottom flask. The brown oil was then dissolved in dichloromethane (50 mL) and added to the aqueous mixture in one portion to give two layers. The mixture was stirred at room temperature for 4 h. The bottom, brown layer was then separated, concentrated under reduced pressure at 70 °C, and placed under high vacuum overnight to yield a brown oil (5.6 g). Purification was performed with flash chromatography (silica gel, 0:100–20:80 methanol/dichloromethane). Silica present in the residue was removed by dissolution in dichloromethane and filtration through a Millipore GVHP 0.22-μm membrane to yield an orange oil, which formed a crystalline solid at room temperature (3.8 g, 7.8 mmol).

Dowex 1-X8 resin (chloride form, 200–400 mesh) was mixed with 1:1 methanol/H_2O and poured into a glass column to create a resin bed (4 cm long, 52 mL volume, 8 meq). The resin bed was flushed extensively with 1:1 methanol/H_2O to remove contaminants. The salt was dissolved in methanol (7.5 mL) and water (2.5 mL) and loaded on the column. The column was eluted with H_2O, 1:1 methanol/H_2O, and methanol, and fractions were collected. Fractions containg ionic liquid were concentrated under reduced pressure to yield **5** (1.6 g, 6.4 mmol, 33% yield) as an orange oil. ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 5.27 (t, J = 15.5 Hz, 2H), 3.94 (s, 3H). HRMS (ESI) m/z 215.0600 [calculated for $C_7H_8N_2F_5$ (M – Cl)$^+$ 215.0603].

5.7.8 3-Methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium acetate

Lead(II) acetate trihydrate (1.5 g, 3.9 mmol) and 3-Methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (0.7 g, 2.6 mmol) were dissolved together in water (10

mL). Upon standing, a brown precipitate formed, which was filtered off. The filtrate was concentrated under reduced pressure, resulting in a mixture of ionic liquid and unreacted lead(II) acetate. This mixture was treated with acetone, precipitating white $Pb(OAc)_2$, which was filtered off. The filtrate was concentrated under reduced pressure. This process of treating the residue with acetone, filtering off lead(II) acetate, and concentrating the filtrate was repeated three more times, yielding 3-Methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium acetate (432 mg, 1.6 mmol, 60% yield) as an orange oil. ^{1}H NMR (400 MHz, CD_3OD): δ 9.22 (s, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 5.31 (t, J = 15.5 Hz, 3H), 3.98 (s, 3H), 1.87 (s, 3H).

5.7.9 3-Methyl-1-(2',2',2'-trifluoroethyl)-imidazolium chloride (6)

A round-bottom flask was placed under Ar(g) to which trifluoroacetic anhydride (30.2 g, 143.9 mmol) was added. The flask was then cooled to –15 °C using a benzyl alcohol/dry ice bath before adding 50% H_2O_2 (2.1 mL, 43.1 mmol) dropwise. 2,2,2-Trifluoroiodoethane (5.7 g, 27.2 mmol) was then added to the round-bottom flask, which was protected from light with aluminum foil and allowed to warm to room temperature. The reaction mixture was stirred for 3 d. The reaction mixture was then concentrated under reduced pressure and left under high vacuum overnight to yield a brown oil (9.2 g). This oil was dissolved with trifluoroacetic anhydride (10 mL) in a round-bottom flask under Ar(g). Trifluoromethanesulfonimide (5.3 g, 18.9 mmol) was placed in a separate round-bottom flask under Ar(g), and the trifluoroacetic anhydride solution was tranferred *via* cannula. The resulting solution was cooled to 0 °C in an ice-water bath and protected from light with aluminum foil. After stirring for 15 min, benzene (2.0 mL) was added. The reaction was allowed to warm to room temperature after 3 h and continued for another 15 h. A second portion of benzene (0.7 mL) was then added with stirring continued for an additional 5

h. The reaction mixture was then concentrated under reduced pressure and placed under high vacuum overnight to yield a brown oil (7.0 g). 1-Methylimidazole (0.7 mL, 8.8 mmol) and $NaHCO_3$ (1.0 g, 12.0 mmol) were dissolved in double-deionized water (50 mL) in a round-bottom flask. The brown oil was then dissolved in dichloromethane (50 mL) and added to the aqueous mixture in one portion to give two layers. The mixture was stirred at room temperature for 4 h. The bottom, brown layer was then separated, concentrated under reduced pressure at 70 °C, and placed under high vacuum overnight to yield a brown oil (4.6 g, 10.4 mmol). Purification was performed with flash chromatography (silica gel, 0:100–20:80 methanol/dichloromethane). Silica present in the residue was removed by dissolution in dichloromethane and filtration through a Millipore GVHP 0.22-μm membrane to yield an orange oil (1.5 g, 3.4 mmol).

Dowex 1-X8 resin (chloride form, 200–400 mesh) was mixed with 1:1 methanol/H_2O and poured into a glass column to create a resin bed (3 cm long, 22 mL volume, 16 meq). The resin bed was flushed extensively with methanol/H_2O to remove contaminants. The salt was dissolved in methanol (7.5 mL) and water (2.5 mL) and loaded on the column. The column was eluted with H_2O, 1:1 methanol/H_2O, and methanol, and fractions were collected. Fractions containing ionic liquid were concentrated under reduced pressure to yield **6** (0.80 g, 4.0 mmol, 15% yield) as an orange oil. ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 5.14 (q, J = 8.6 Hz, 2H), 3.90 (s, 3H). HRMS (ESI) *m/z* 165.0644 [calculated for $C_6H_8N_2F_3$ $(M - Cl)^+$ 165.0635].

5.7.10 3-Methyl-1-pentafluorophenylmethylimidazolium chloride (7)

To a round-bottom flask containing dichloromethane (125 mL) was added 1-methylimidazole (1.5 mL, 18.8 mmol) and 2,3,4,5,6-pentafluorobenzyl bromide (4.9 g, 18.8

mmol). The solution was stirred at room temperature for 20 h. The reaction mixture was then concentrated under reduced pressure and placed under high vacuum to afford a colorless oil (6.17 g). Purification was performed by flash chromatography (silica gel, 0:100–30:70 methane/dichloromethane). Silica present in the residue was removed by dissolution in dichloromethane and filtration through a Millipore GVHP 0.22-μm membrane to yield a colorless solid (3.5 g, 10.2 mmol).

Dowex 1-X8 resin (chloride form, 200–400 mesh) was mixed with 1:1 methanol/H_2O and poured into a glass column to create a resin bed (5 cm long, 70 mL volume, 8 meq). The resin bed was flushed extensively with methanol/H_2O to remove contaminants. The salt was dissolved in methanol (7.5 mL) and water (2.5 mL) and loaded on the column. The column was eluted with H_2O, 1:1 methanol/H_2O, and methanol, and fractions were collected. Fractions containing ionic liquid were concentrated under reduced pressure to yield **7** (2.6 g, 8.7 mmol, 46% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (s, 1H), 7.60 (s, 1H), 7.54 (s, 1H), 5.55 (s, 2H), 3.84 (s, 3H). HRMS (ESI) *m*/*z* 263.0594 [calculated for $C_{11}H_8N_2F_5$ $(M - Cl)^+$ 263.0603].

5.7.11 Cellulose solubility in 3-methyl-1-(3',3',4',4',5',5',6',6',6'-nonafluorohexyl)-imidazolium chloride (1)

Cellulose (3.5 mg, 0.5 wt % relative to ionic liquid) was added to the fluorous ionic liquid (0.7 g) at 100 °C with stirring. After heating and stirring overnight, cellulose fibers remained visible in the ionic liquid. The temperature of the ionic liquid was raised to 140 °C. After 1 h, insoluble cellulose fibers were visible.

5.7.12 Cellulose solubility in 1-(2',2',3',3',4',4',4'-heptafluorobutyl)-3-methylimidazolium chloride (2)

Cellulose (1.4 mg, 1.0 wt % relative to ionic liquid) was added to the fluorous ionic liquid (145.6 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, an aliquot was taken and examined under a light microscope to reveal cellulose fibers.

5.7.13 Cellulose solubility in 3-methyl-1-(3',4',4',4'-tetrafluoro-3'-trifluoromethyl-butyl)-imidazolium chloride (3)

Cellulose (1.7 mg, 3.0 wt % relative to ionic liquid) was added to the fluorous ionic liquid (56.2 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, an aliquot was taken and examined under a light microscope to reveal cellulose fibers.

5.7.14 Cellulose solubility in 3-methyl-1-(3',3',4',4',4'-pentafluorobutyl)-imidazolium chloride (4)

Cellulose (2.6 mg, 1.1 wt % relative to ionic liquid) was added to the fluorous ionic liquid (228.0 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, an aliquot was taken and examined under a light microscope to reveal cellulose fibers.

5.7.15 Cellulose solubility in 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5)

Cellulose (1.1 mg, 0.6 wt % relative to ionic liquid) was added to the fluorous ionic liquid (187.8 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, an aliquot was taken of the viscous solution and examined under a light microscope. No cellulose fibers were visible.

5.7.16 Cellulose solubility in 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium acetate

Cellulose (2.0 mg, 0.9 wt % relative to ionic liquid) was added to the fluorous ionic liquid (216.1 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, an aliquot was taken of the viscous solution and examined under a light microscope. No cellulose fibers were visible.

5.7.17 Cellulose solubility in 3-methyl-1-(2',2',2'-trifluoroethyl)-imidazolium chloride (6)

Cellulose (1.3 mg, 1.2 wt % relative to ionic liquid) was added to the fluorous ionic liquid (105.6 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, an aliquot was taken of the viscous solution and examined under a light microscope to reveal slight traces of cellulose fibers.

5.7.18 Cellulose solubility in 3-methyl-1-pentafluorophenylmethylimidazolium chloride (7)

Cellulose (1.4 mg, 1.4 wt % relative to ionic liquid) was added to the fluorous ionic liquid (97.6 mg), and the resulting mixture was heated at 140 °C with stirring. After 1 h, the ionic liquid had not melted, so the temperature was increased to 160 °C. After a 1 h, the ionic liquid had turned black due to decomposition. It was then tested using DMA–LiCl (10 wt%) as a co-solvent to solubilize the ionic liquid. Four concentrations of ionic liquid were tested: 1.0 mg cellulose (1.0 wt%), 79.7 mg ionic liquid, 20.3 mg DMA–LiCl; 1.2 mg cellulose (1.1 wt %), 65.9 mg ionic liquid, 45.2 mg DMA–LiCl; 1.4 mg cellulose (1.4 wt%), 35.3 mg ionic liquid, 65.4 mg DMA–LiCl; and 1.4 mg cellulose (1.3 wt%), 22.5 mg ionic liquid, 86.3 mg DMA–LiCl. An aliquot of each was taken and examined under a light microscope to reveal all contained visible cellulose fibers.

5.7.19 Attempted separation of 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5) from glucose with FluoroFlash SPE cartridge

The cartridge was washed with *N,N*-dimethylformamide (5 mL) and conditioned with 4:1 methanol/H_2O (30 mL) followed by H_2O (30 mL). Glucose (27.4 mg) and 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (24.1 mg) were dissolved in water (600 mg). This mixture was then loaded and eluted with ice-cold H_2O (40 mL), followed by methanol (40 mL). Fractions were collected for each elution, concentrated under reduced pressure, and analyzed by ^{1}H NMR spectroscopy. Glucose eluted in the third and fourth fractions of the H_2O wash, and the ionic liquid eluted in the third, fourth, and fifth fractions. The majority of the ionic liquid eluted in the second and third fractions of the methanol wash. The breakthrough of the fluorous ionic liquid in the water wash revealed that the SPE cartridge did not obtain a clean separation.

5.7.20 Separation of 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5) from glucose in water

Glucose (25 mg) and 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (24 mg) were dissolved in water (511 mg). A slurry of FluoroFlash silica (10 g) in water and methanol was poured into a flash chromatography column (20 cm length × 1 cm diameter), and the silica was washed extensively with water. The ionic liquid solution was loaded onto the column and eluted with water while fractions were collected. Fractions were concentrated under reduced pressure and analyzed by ^{1}H NMR spectroscopy. Glucose eluted in the fourth fraction, fractions five and six had no solute, and fraction seven contained the ionic liquid, demonstrating

a clean separation. 3-Methyl-1-(3′,3′,4′,4′,4′-pentafluorobutyl)-imidazolium chloride (**4**) was also separated from glucose in a similar manner.

5.7.21 Attempted separation of 1-butyl-3-methylimidazolium chloride from glucose in water

Glucose (25 mg) and 3-methyl-1-butylimidazolium chloride (25 mg) were dissolved in water (500 mg). A slurry of FluoroFlash silica (10 g) in water and methanol was poured into a flash chromatography column (20 cm length × 1 cm diameter), and the silica was washed extensively with water. The ionic liquid solution was loaded on the column and eluted with water while fractions were collected. Fractions were concentrated under reduced pressure and analyzed by ^{1}H NMR spectroscopy. Glucose eluted in the third, fourth, and fifth fractions, while the ionic liquid began to elute in the fourth and fifth fractions, demonstrating that a clean separation of glucose and the ionic liquid was not possible under these conditions.

5.7.22 Procedure for cellulose hydrolysis in 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5)

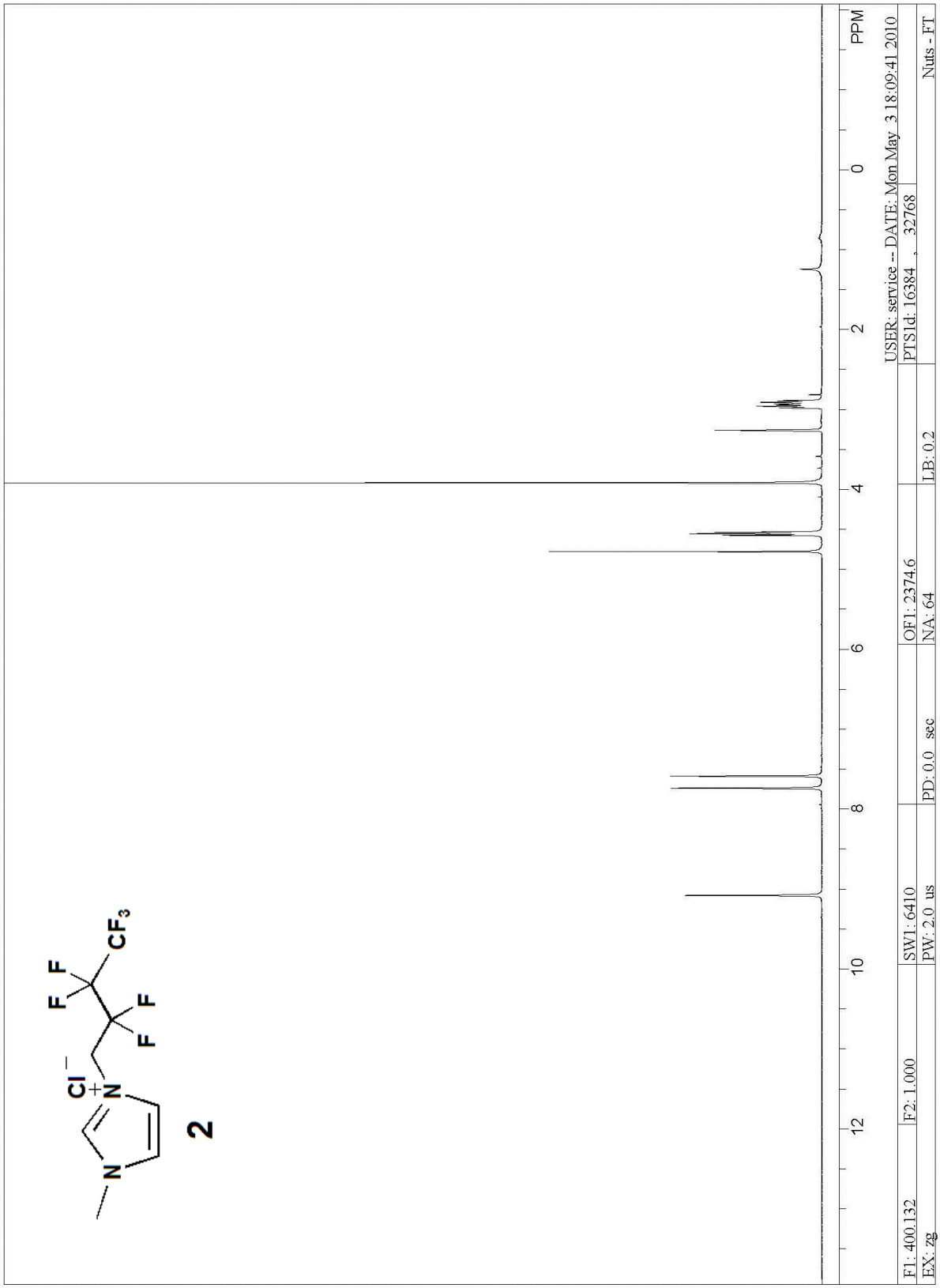
The reaction was performed in a 4-mL glass vial heated in a temperature-controlled VWR Mini Shaker at 600 rpm. Cellulose (5.0 mg, mmol) was dissolved in 3-methyl-1-(2′,2′,3′,3′,3′-pentafluoropropyl)-imidazolium chloride (254.2 mg) by stirring at 90 °C for 3 h. Hydrochloric acid (2.36 mg, 0.065 mmol) and $CrCl_2$ (2.2 mg, 0.018 mmol) were added, the vial was capped, and the mixture was heated at 105 °C for 4 h. At 1-h intervals, an aliquot of the reaction mixture was removed, quenched with deionized water, subjected to centrifugation to sediment insolubles, and analyzed by HPLC.

5.7.23 Separation of 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5) from cellulose hydrolysis products

The cellulose hydrolysis reaction mixture (120.1 mg) was dissolved in 1 mL of water. This solution was then loaded on the FluoroFlash silica (10 g) column used previously. Fractions were concentrated under reduced pressure and analyzed by ^{1}H NMR spectroscopy. The cellulose hydrolysis products were detected in the first fraction, and fluorous ionic liquid **5** was recovered in the third, fourth, and fifth fractions. The column was then eluted with methanol to recover additional amounts of **5**. The fluorous ionic liquid containing fractions were combined to recover 115 mg of **5**, resulting in a >95% recovery.

5.7.24 Computational methodology

Hybrid density functional theory as implemented in Gaussian '03[187] was employed to determine the conformational preferences of compounds **1**–**7**. Gas-phase full-geometry optimizations and frequency calculations were performed at the B3LYP/6-311+G (2d,p) level of theory[188,189] employing Berny algorithm and a tight SCF convergence criteria.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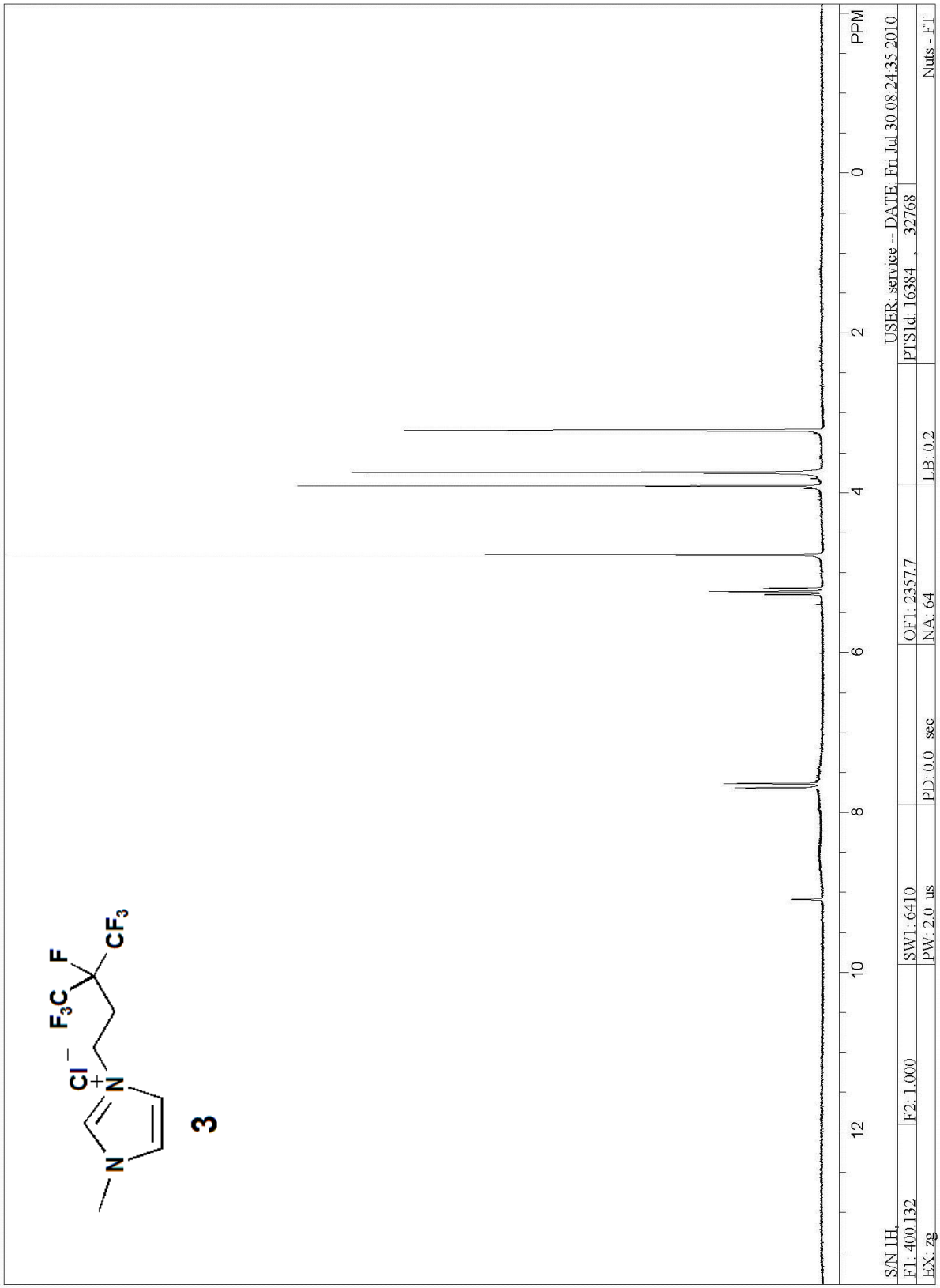
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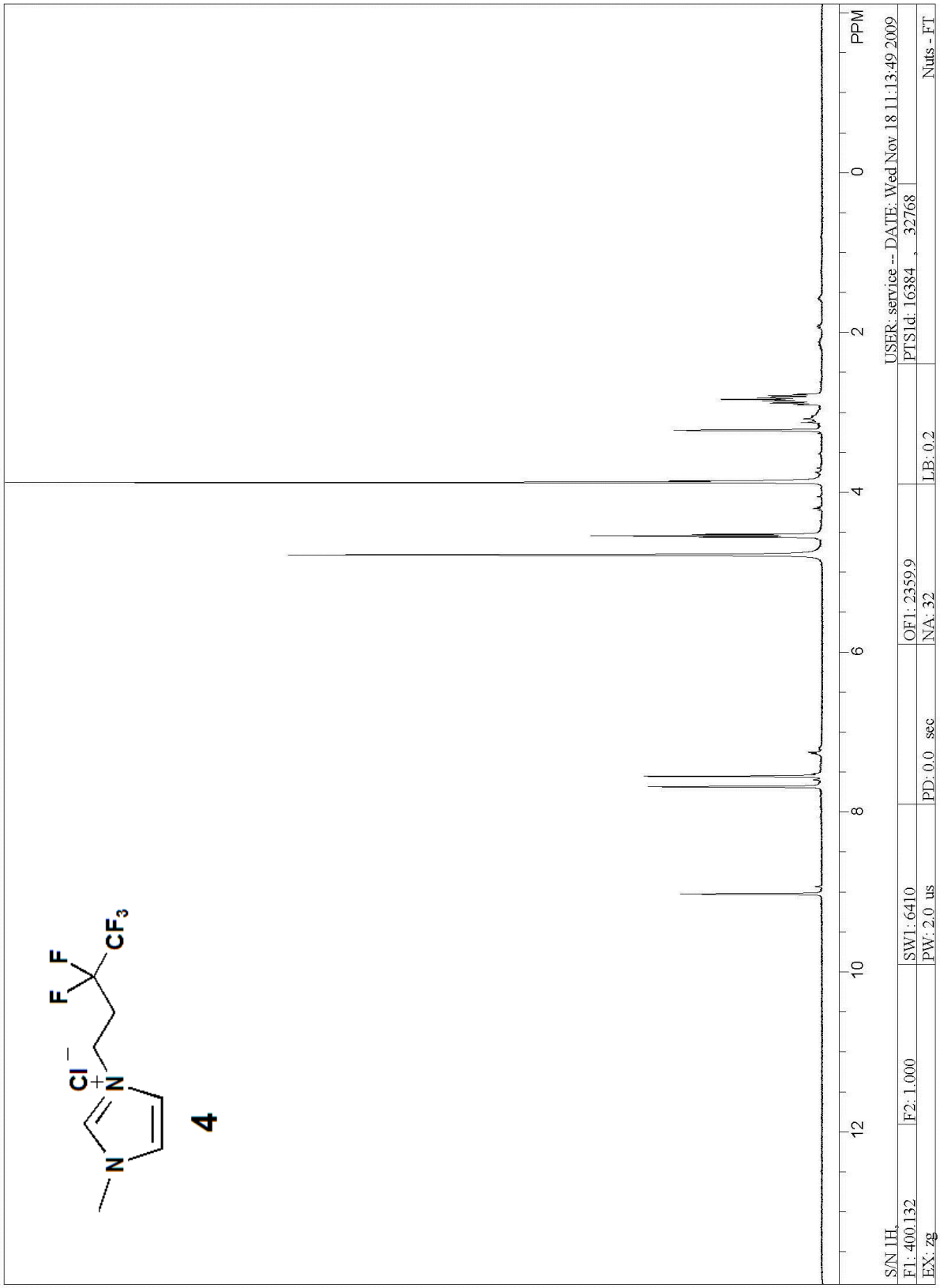
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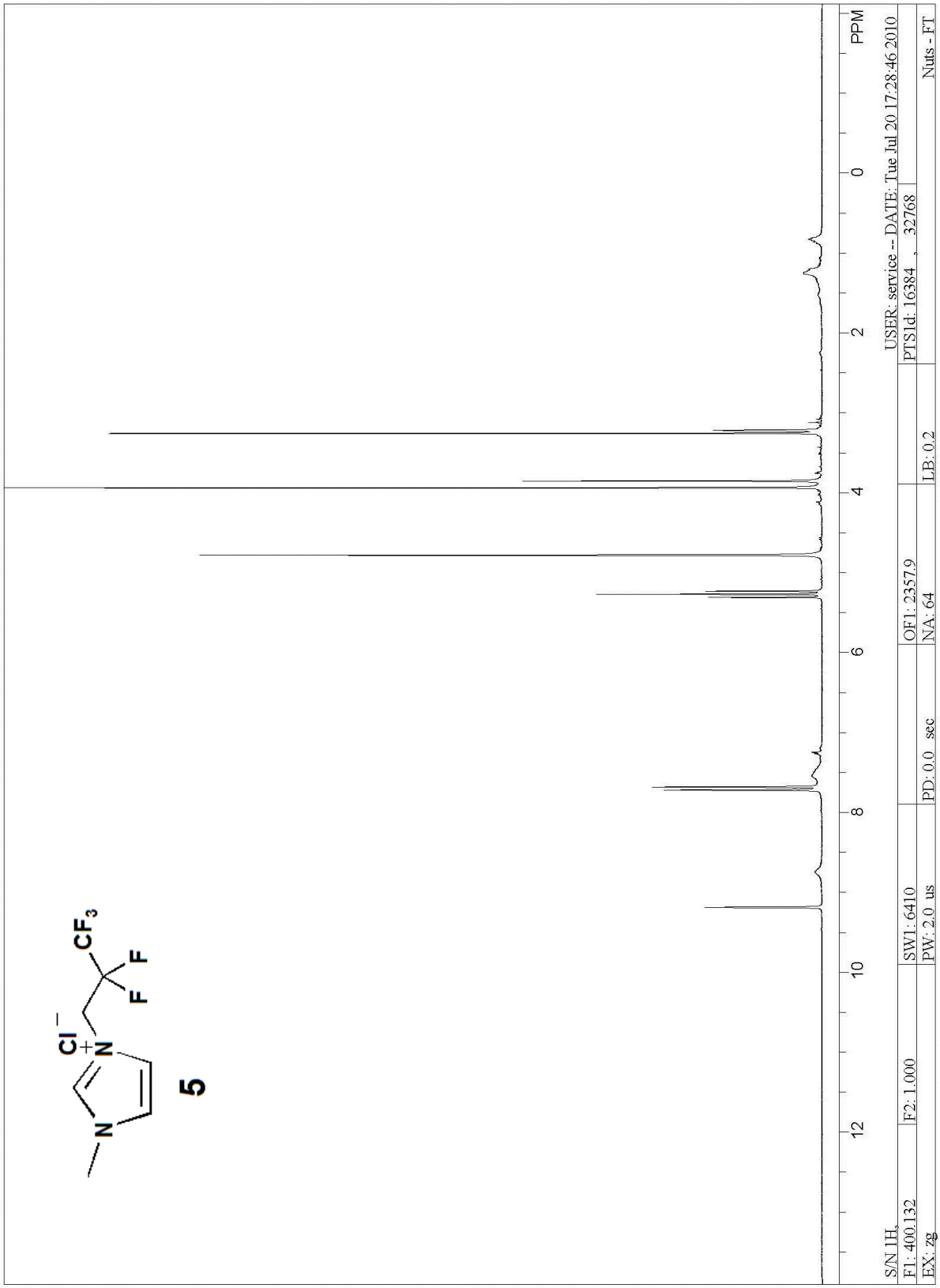
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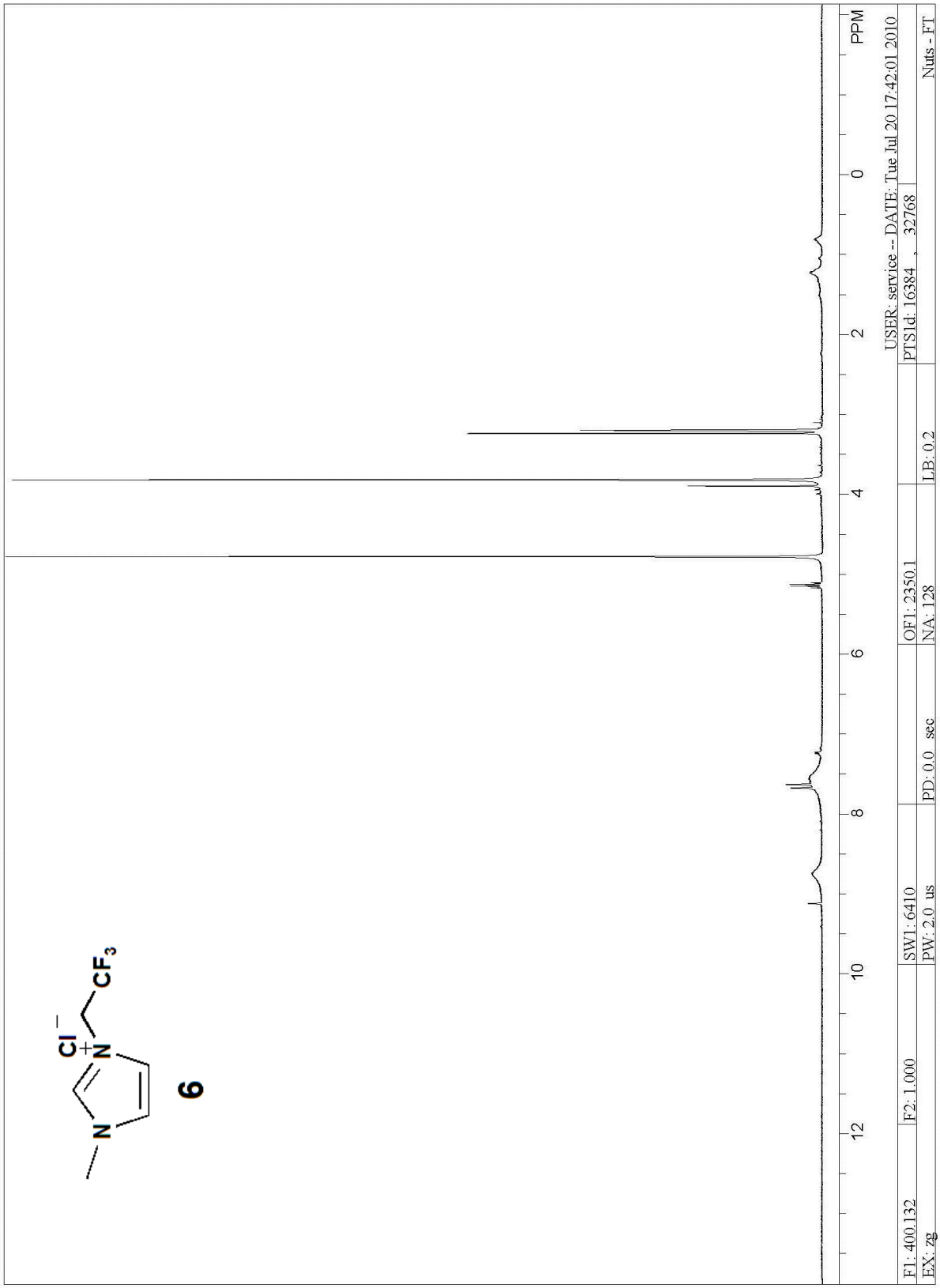
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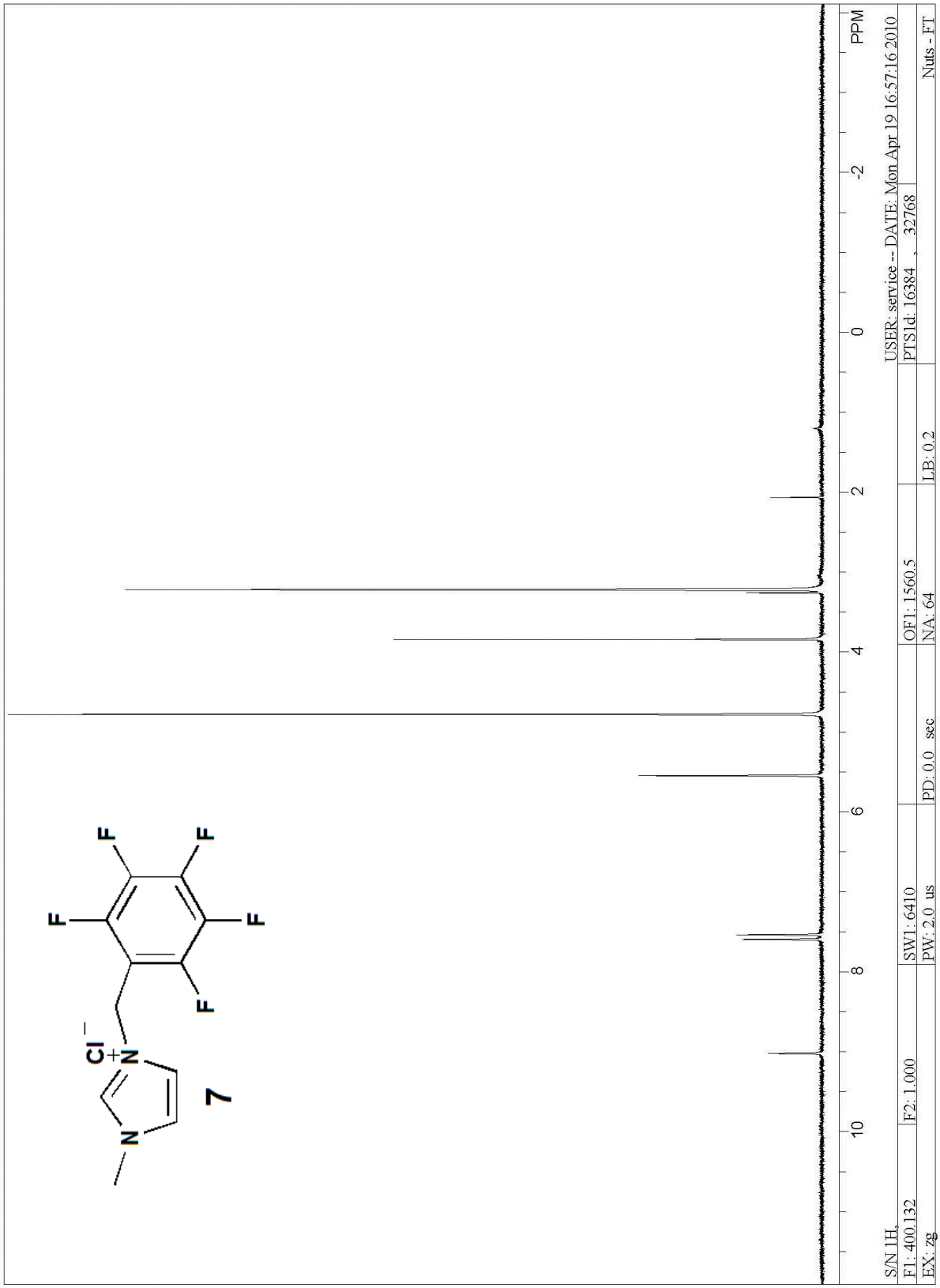
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CHAPTER SIX*

SEPARATION AND RECOVERY OF SUGARS AND IONIC LIQUID FROM BIOMASS HYDROLYSATE WITH SIMULATED MOVING BED CHROMATOGRAPHY

6.1 Abstract

Lignocellulosic biomass could serve as a renewable source of fuels and chemicals. Ionic liquids are ideal solvents for overcoming the recalcitrance of biomass for dissolution, although their expense hinders large-scale implementation. There is an urgent need for technologies to transform biomass into useful intermediates, and to recover the ionic liquid. Simulated moving bed (SMB) chromatography achieves continuous separation of a multi-component mixture and can be used for large scale separations. Here, we report on the chemical hydrolysis of biomass to monosaccharaides yielding >90% glucose and xylose in the ionic liquid 1-butyl-3-methylimidazolium chloride ([BMIM]Cl). Using SMB chromatography, we separate the sugars from the ionic liquid and recovered the ionic liquid quantitatively. This process illustrates the potential viability of using chemical hydrolysis and SMB chromatography to access sugars from biomass in an industrial biorefinery.

6.2 Author Contributions

B.R.C., T.R.V.O., F.L., and S.L. performed the research. B.R.C. drafted the manuscript. B.R.C., J.R., and R.T.R. designed experiments, analyzed the data, and edited the manuscript and figures.

*This chapter will be published, in part, under the same title. Reference: Caes, B.R.; Van Oosbree, T.R.; Lu, F.; Liu, S.; Ralph, J.; Raines, R.T. *In preparation*.

6.3 Introduction

Since the dawn of recorded history, fossil fuels have served as an energy source for humankind. Today, they supply the vast majority of the world's energy and chemicals.[1] Nonetheless, global and socioeconomic concerns mandate a reduction in our dependence on these reserves.[2,4,119] Cellulose, the most abundant organic molecule in the world, is the primary component of lignocellulosic biomass and could serve as a renewable and sustainable energy resource. Cellulose is, however, recalcitrant, having a highly crystalline structure and being intermingled with hemicelluloses and lignin in biomass materials.[33] A transition from fossil fuels to cellulose as an energy resource requires accessing and transforming the cellulose in biomass.

Monosaccharides result from the hydrolysis of cellulose and hemicellulose polymers present in biomass (Figure 6.1). From here, chemical and biological methods can be employed to access a variety of useful compounds.[13,74,76,190-192] Acid hydrolysis is a common method for depolymerization, although enzymatic methods are used as well.[13,76,105,107,193-194] Unfortunately,

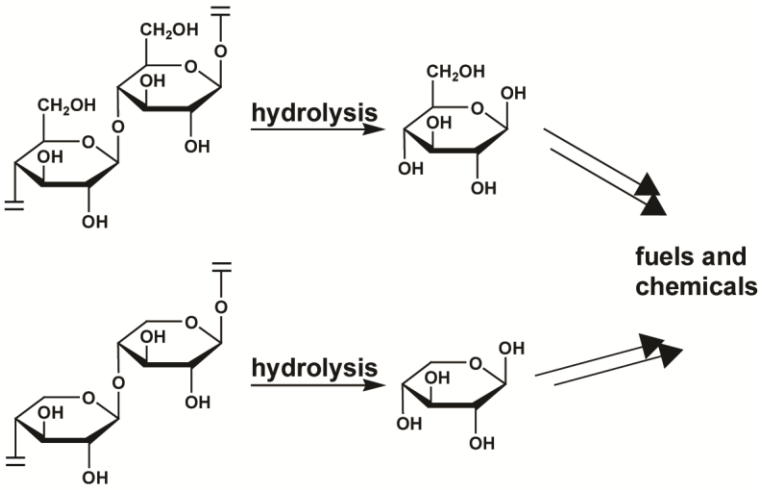

Figure 6.1 Hydrolysis of cellulose and the hemicellulose xylan to glucose and xylose. Biological and chemical methods can transform these monosaccharides to fuels and chemicals.

the surrounding lignin in biomass often limits the effectiveness of these methods.[195] Hence, pretreatment techniques are often needed to disrupt the structure of lignocellulosic biomass, separating the components and providing greater access to cellulose and hemicelluloses. However, by using specific chemical techniques, sugar intermediates such as glucose and xylose can be accessed directly from cellulose and hemicelluloses in raw biomass materials.

Room temperature ionic liquids—salts that melt near ambient temperature—are useful in solvating cellulosic material.[36-40] Specifically, ionic liquids containing chloride and other simple anions disrupt the network of inter- and intra-polymer hydrogen bonds that endow cellulose with its high crystallinity. In this manner, ionic liquids themselves serve as a form of pretreatment, disrupting the structure of biomass by dissolving the polysaccharides and removing them from the lignin cage. Hydrolysis after this pretreatment can then provide monosaccharides for enzymatic and chemical use.[196-197]

Recently, we demonstrated that high yields of sugars could be obtained from raw biomass using acid hydrolysis with water dilution.[63] By using the ionic liquid 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) for biomass dissolution, high yields of glucose (70%) and xylose (79%) were obtained after two hydrolysis reactions on raw corn stover biomass. Separation of the [EMIM]Cl from the sugars was accomplished using ion-exclusion chromatography, resulting in >95% recovery of the ionic liquid, and 94% and 88% recovery of glucose and xylose respectively. Nonetheless, large-scale implementation remained elusive due to the high costs associated with separating ionic liquids from biomass products.

Simulating moving bed (SMB) chromatography is a continuous separation method that is currently used for large-scale separations in the petrochemical, food, mining, and pharmaceutical industries.[198-202] Additionally, in recent years there has been an increase in using SMB

chromatography for the separation of biomass components.[203-206] SMB chromatography emulates counter-current separation wherein the mobile phase flows in the opposite direction of the solid phase (Figure 6.2). The solid phase is represented by the individual columns connected in series; the mobile phase is represented by inlet streams of feed and eluent, and outlet streams of raffinate and extract. Valves between the columns are switched open or closed at timed intervals to introduce the inlet streams and withdraw the outlet streams between the separation zones, simulating counter clockwise rotation of the columns. Under appropriate conditions, continuous separation of sample components can be achieved with extremely high purity and recovery. Furthermore, selective optimization of flow rates and column switch times allows a higher level of separation to occur with less solvent consumption, making SMB chromatography a powerful tool for separating binary mixtures. Here, we report the high yielding recovery (>99%) of pure ionic liquid and sugars using optimized SMB chromatography to purify a multi-gram scale hydrolysis of raw biomass.

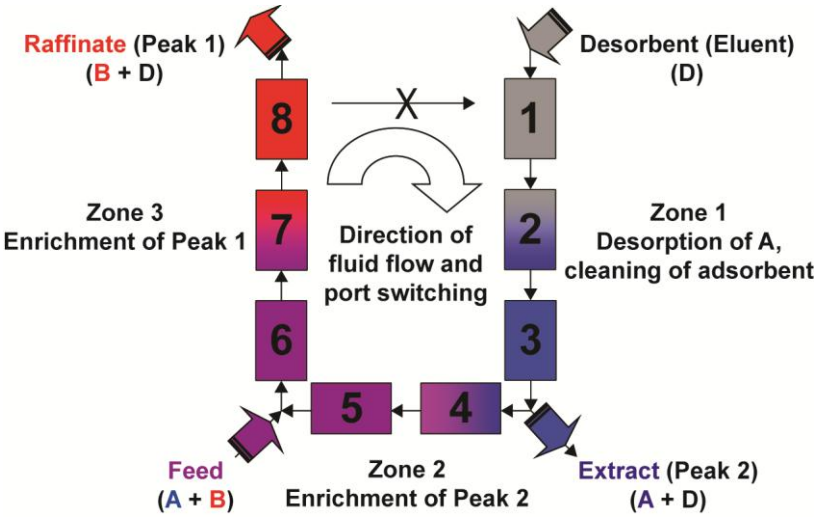

Figure 6.2 Schematic of 3 zone (3-2-3) simulated moving bed chromatography.

6.4 Results and Discussion

We sought to develop a method to enable a multi-gram-scale hydrolysis of biomass materials. 1-Butyl-3-methyl-imidazolium chloride ([BMIM]Cl) is reported to have a higher capacity to dissolve cellulose than [EMIM]Cl,[40] allowing less ionic liquid to be used and thus lessening cost.[207] We quickly discovered, however, that using the optimized hydrolysis conditions determined previously for our hydrolysis in [EMIM]Cl provided drastically lower yields in [BMIM]Cl (<20% glucose and xylose). These low yields necessitated a re-optimization of the hydrolysis reaction conditions.

Our re-optimization began by using pure cellulose in [BMIM]Cl. As acid catalyzed hydrolysis of cellulose can often lead to undesirable byproducts such as 5-hydroxymethylfurfural and humins,[28] it is important to have fine control of water addition to stop the reaction after hydrolysis. Hypothesizing that our low glucose and xylose yields were a result of the sugars being transformed into these byproducts, we varied the amounts and times of water addition. Still, we were unable to achieve comparable yields to the process developed in [EMIM]Cl. Next, we tested the hypothesis that the cellulose does not have enough time to hydrolyze; but upon extending the reaction time, the yields demonstrated no improvement. Then, we attempted the hydrolysis using an increased concentration of acid from that used in the process using [EMIM]Cl. A screening of different concentrations of HCl did result in increased glucose yields, and we found that a 6 M HCl solution was optimal, giving a glucose yield of 69% (Table 6.1).

Having determined a reaction system to use for hydrolysis in [BMIM]Cl, we next optimized a separation strategy using SMB chromatography to separate [BMIM]Cl from glucose and xylose. The first step was to determine their retention times on the adsorbent beds with single column experiments. We exchanged an ion-exclusion column with [BMIM]Cl in water,

Table 6.1 Acid hydrolysis of cellulose in [BMIM]Cl

molarity of HCl solution (M)	glucose molar yield (%)
2	9
4	31
6	**69**
8	56
10	50
12	50

and the approximate retention times were determined with single injections of [BMIM]Cl, glucose, and xylose. These experiments showed that [BMIM]Cl was least adsorbed, followed by glucose, and then xylose in accordance with data published by Nam *et al*.[203] A follow-up single column experiment was done with a mixture of [BMIM]Cl (3.637 min) and glucose (5.195 min), giving us the void fraction, fast peak time of retention, and slow peak time of retention (Figure 6.3 and 6.4). These values were entered into the SMB chromatography parameter calculator—based on the Triangle model[208-212]—for determining internal flow to achieve optimal separation

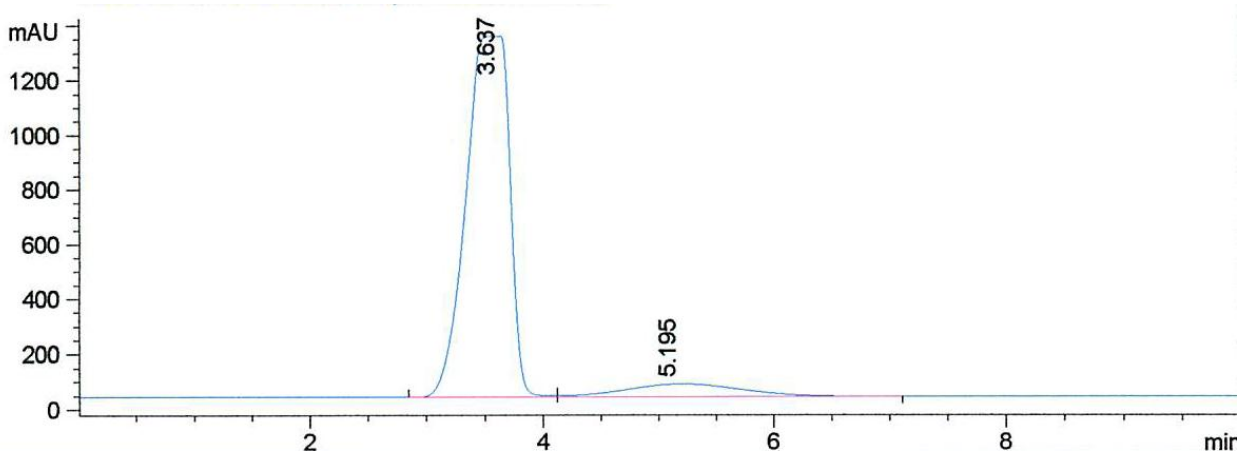

Figure 6.3 Single column separation of [BMIM]Cl and glucose. A mixture of [BMIM]Cl and glucose was injected onto a Dowex® 50WX4-400 ion exclusion column. The column was eluted with deionized water at 2 mL/min at ambient temperature.

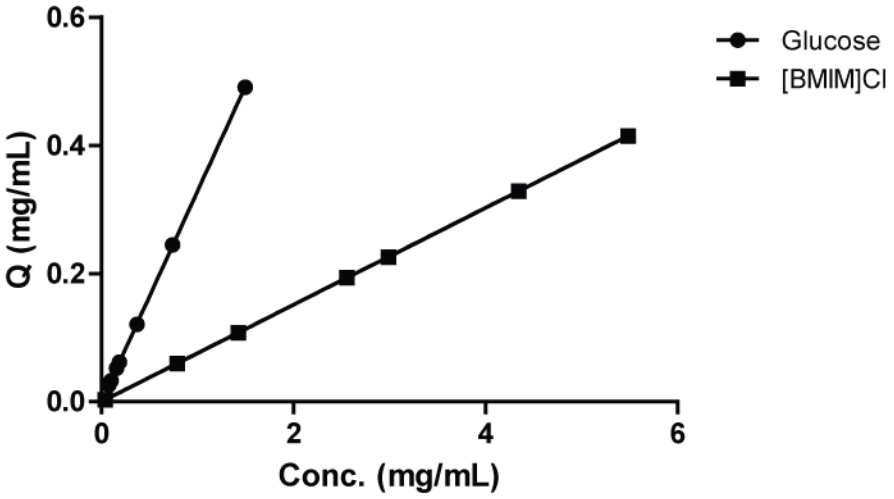

Figure 6.4 Adsorption isotherm of [BMIM]Cl and glucose.

of the ionic liquid and sugars. A representative example of the SMB chromatography parameter calculator worksheet for 3-zone separations is shown in Figure 6.5. When we applied these parameters to the separation of pure glucose and xylose from pure [BMIM]Cl, we found that the 3-zone separation gave us the best recovery and purification of the sugars and ionic liquid. Additionally, by varying both concentration (Table 6.2) and flow rates (Table 6.3), we were able to modulate the amount of [BMIM]Cl and sugars recovered in the raffinate and extract fractions, respectively.

Next, we attempted to utilize our conversion and separation strategies on biomass material in the form of raw corn stover. Our preliminary experiments used twenty parts [BMIM]Cl relative to the corn stover (5 wt% solution). As biomass is comprised of more than cellulose, we again screened varying acid concentrations to ensure that the requisite higher acid concentration would not result in a build-up of unwanted side products *via* breakdown of hemicelluloses and lignin and their subsequent polymerization to humins. Our results determined

that 8 M HCl was the optimal acid concentration for maximal yields of glucose (35%) and xylose (78%) in a single-stage hydrolysis reaction (Table 6.4). These results were consistent with those reported previously in [EMIM]Cl for glucose (42%) and xylose (71%).[63]

Development Column Volume:	19.63
Flow Rate for t_0 ml/min:	2
t_0 min:	3.1
Void Fraction of Adsorbent:	0.32
Fast Peak 1 T_r min:	3.64
Slow Peak 2 T_r min:	5.2
Henry Constant H_1:	0.08
Henry Constant H_2:	0.31
Selectivity (H_2/H_1):	3.89
SMBC Column Volume ml:	7.9
Extra Column Volume ml:	0.39

Scenario:	**1**	**2**	**3**	**4**
Switch Time, sec:	40	40	40	40
Q_{feed} ml/min:	0.25	0.25	0.25	0.25
$Q_{desorbent}$ ml/min:	4.5	4.5	4.5	4.5
$Q_{extract}$ ml/min:	1.3	1.4	1.5	1.6
$Q_{raffinate}$ ml/min:	3.45	3.35	3.25	3.15
$Q_{recycle}$ ml/min:	3.0	3.0	3.0	3.0
Q_1 ml/min:	7.50	7.50	7.50	7.50
Q_2 ml/min:	6.20	6.10	6.00	5.90
Q_3 ml/min:	6.45	6.35	6.25	6.15
Q_4 ml/min:	3.00	3.00	3.00	3.00
m_1:	**0.39**	**0.39**	**0.39**	**0.39**
m_2:	**0.23**	**0.22**	**0.21**	**0.19**
m_3:	**0.26**	**0.25**	**0.24**	**0.22**
m_4:	**0.26**	**–0.16**	**–0.16**	**–0.16**
Mass Balance, ml/min:	4.75	4.75	4.75	4.75

Figure 6.5 Representative example of a SMB chromatography parameter calculator worksheet for a 3 zone configuration.

Table 6.2 Dependence of [BMIM]Cl conc. on its recovery in the raffinate fraction

[BMIM]Cl feed concentration (mg/mL)	[BMIM]Cl recovery in raffinate (%)*
200	**97**
250	83
300	33
400	24

*Percent recovery was determined by amount recovered relative to amount loaded.

Table 6.3 Dependence of extract flow rates on fraction recovery

extract flow rate (mL/min)	Sample	recovered [BMIM]Cl (%)*	recovered glucose (%)*	recovered xylose (%)*
1.3	Raffinate	98	31	13
1.3	Extract	2	69	87
1.4	Raffinate	97	27	0
1.4	Extract	3	73	100
1.5	**Raffinate**	**89**	**0**	**0**
1.5	**Extract**	**11**	**100**	**100**
1.6	Raffinate	65	0	0
1.6	Extract	35	100	100

*Percent recovery was determined by amount recovered relative to amount loaded.

Table 6.4 Acid hydrolysis of biomass in [BMIM]Cl

molarity of HCl solution (M)	glucose molar yield (%)	xylose molar yield (%)*
2	4	43
4	20	79
6	24	83
8	**35**	**78**
10	32	79
12	38	62

*Yields were determined by HPLC and are relative to the glucose and xylose monomers in the stover.

Next, we sought to take advantage of the superior capacity of [BMIM]Cl to dissolve cellulose by decreasing the loading of the ionic liquid relative to the corn stover. We tested three

different concentrations using single-stage hydrolysis reactions. Interestingly, we found that our concentration could be increased from a 5 to 7.5 wt% solution of corn stover in [BMIM]Cl and still access comparable sugar yields (Table 6.5). A 10 wt% solution, however, began to show decreasing glucose yields. Hence, for higher productivity, we chose the 7.5 wt% solution for

Table 6.5 Optimization of biomass loading in [BMIM]Cl

biomass	conc. of corn stover in [BMIM]Cl (wt%)	glucose molar yield (%)	xylose molar yield (%)*
corn stover	**5.0**	**42**	**85**
corn stover	**7.5**	**39**	**83**
corn stover	10.0	33	82
AFEX treated corn stover	**5.0**	**47**	**88**
AFEX treated corn stover	7.5	32	85
AFEX treated corn stover	10.0	10	75

*Yields were determined by HPLC and are relative to the glucose and xylose monomers in the stover.

future experiments. We were also interested in applying our system to ammonia fiber expansion (AFEX) pre-treated corn stover, which uses liquid ammonia under high pressures and temperatures to decrystallize cellulose, depolymerize and remove lignin, and increase micropore size and number in cell walls, providing increased access to the sugars.[213] Interestingly, when we hydrolyzed the AFEX corn stover, we obtained comparable yields of glucose (47%) and xylose (88%) to those from un-treated corn stover (Table 6.5). This finding indicates that our hydrolysis system does not require any pretreatment of biomass material to access the sugars in high yields as we reported previously for hydrolysis in [EMIM]Cl.[63] Furthermore, when we subjected the corn stover and AFEX treated corn stover hydrolysates to purification from the [BMIM]Cl with SMB chromatography, we achieved >95% in the [BMIM]Cl raffinate for both hydrolysates.

These optimized conditions led us to test our system on a larger, multi-gram scale. To do so, we increased our loadings and were gratified to discover that by performing a two-stage hydrolysis reaction on corn stover, we were able to access high yields of glucose (92%) and xylose (95%). The two-stage hydrolysis effectively doubled our glucose yields due to the slower rate of hydrolysis of cellulose than hemicelluloses containing xylose. After purification using SMB chromatography, we again attained >95% ionic liquid in the raffinate. For this process to be industrially viable, it would need to recover the ionic liquid quantitatively.[214] Hence, we subjected our extract, which contained traces of ionic liquid, to SMB chromatography and were able to achieve an overall recovery of 99.5% of the [BMIM]Cl in the raffinate fractions. Thus, using a two-stage hydrolysis reaction followed by SMB chromatography, ionic liquids can be recovered in high yields that enable their use as a viable industrial solvent in a biomass conversion process.

After successfully purifying [BMIM]Cl in the raffinate fraction, we were interested in recycling it for use in subsequent reactions. Hence, we subjected the raffinate to lyophilzation to facilitate the removal of the aqueous eluent from the ionic liquid. When we performed a hydrolysis reaction using the recycled [BMIM]Cl and fresh corn stover, we found that our yields were reduced significantly compared to those using fresh [BMIM]Cl (Table 6.6). This decrease

Table 6.6 Results using recycled [BMIM]Cl in two-stage hydrolysis reactions of corn stover

stage	molarity of HCl solution (M)	glucose molar yield (%)*	xylose molar yield (%)*
1	8	18	66
2	8	3	5
1	12	12	40
2	12	8	12

*Yields were determined by HPLC and are relative to the monomers in the stover.

was most likely due to the hydroscopy of the ionic liquid, resulting in a retention of water in the [BMIM]Cl. This retention was evidenced by the appearance of the [BMIM]Cl, which is a white solid but appears as a yellow oil upon water absorption. We suspect that the retained water molecules hinder the dissolution of cellulose. In an effort to increase hydrolysis and offset the water retention, we employed a greater concentration of HCl, but were unsuccessful in obtaining increased yields. Hence, while >99% recovery of the [BMIM]Cl is possible, further purification to remove the majority of retained water would be necessary for its use in subsequent hydrolysis reactions.

We were also interested in testing the viability of our purified sugars for use as feedstocks for microbial growth. It is imperative that sugars be free of any contaminants that would hinder growth, necessitating their clean separation from the ionic liquid, which can be toxic.[197] We tested our sugars using *Escherichia coli* strain KO11, a microbe engineered to use hexose and pentose sugars as feedstocks for ethanol production.[215] By using the corn stover hydrolysate sugars as the carbon source, we were able to achieve aerobic growth of *E. coli* strain KO11 (Figure 6.6). Furthermore, the growth rate was comparable to that of *E. coli* strain KO11 using a control mixture of pure glucose and xylose. This demonstrates that the SMB chromatography process is able to recover contaminant-free sugars suitable for microbial consumption.

Finally, our hydrolysis strategy provides the opportunity to recover residual lignin. Many extant hydrolysis processes dismiss lignin as a commodity of little value and propose to simply burn or otherwise dispose of it. However, lignin is a potential source of aromatic chemicals, and efforts are being made to specifically access its aromatic constituents.[216-218] Hence, we evaluated the recovered lignin for any degradation resulting from the acid hydrolysis reaction. Using 2D-

NMR, we observed that our recovered lignin shows no signs of degradation and contains fewer polysaccharides than lignin samples recovered from cellulase saccharification processes (Figure 6.7).

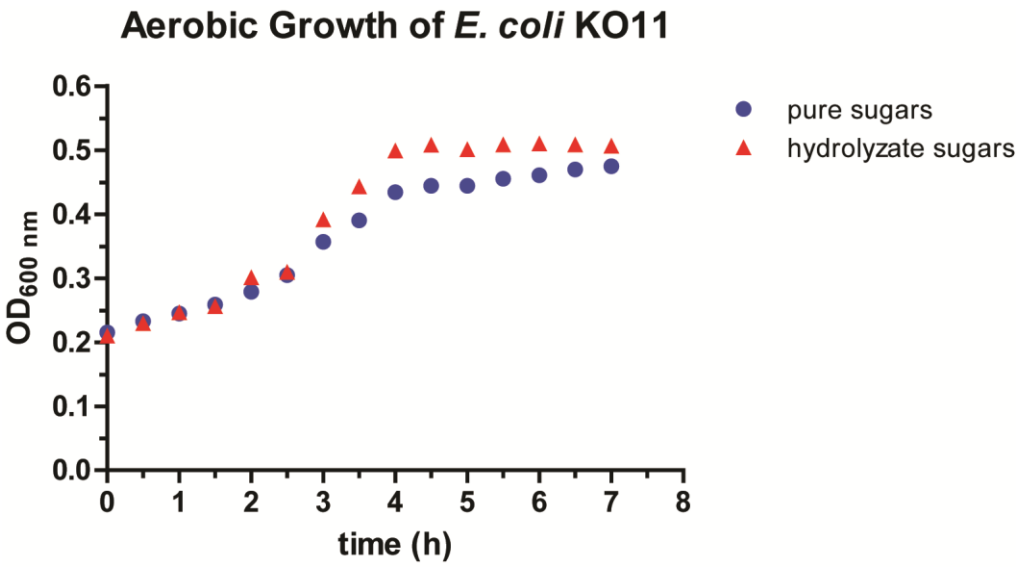

Figure 6.6 Comparison of aerobic growth rates of *E. coli* strain KO11 on pure glucose and xylose versus SMB chromatography recovered hydrolysate sugars.

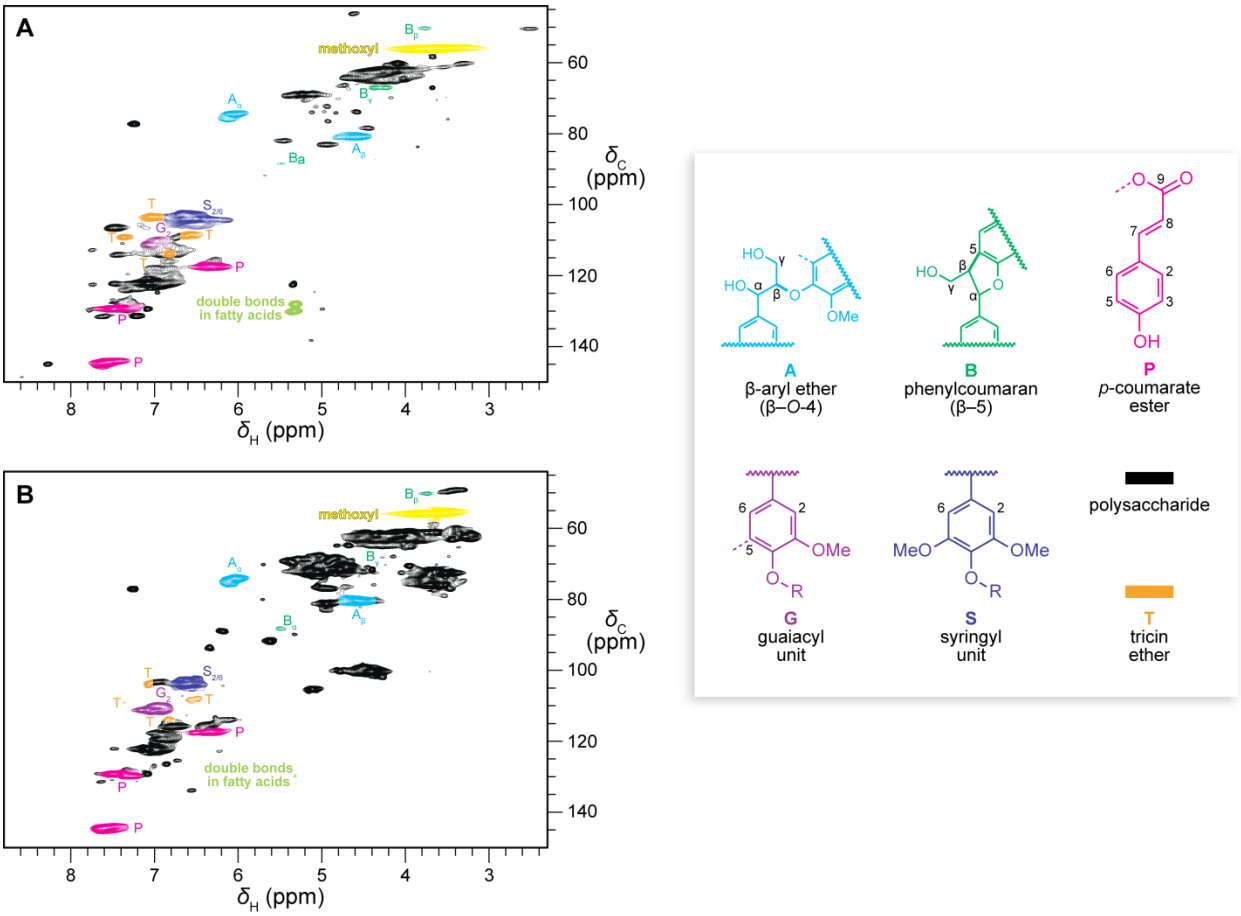

Figure 6.7 Side-chain (δ_C/δ_H 50−90/2.5−5.8) and aromatic/unsaturated (δ_C/δ_H 90−155/5.5−8.0) regions in the 2D HSQC NMR spectrum of corn stover after treatment with (**A**) H_2O (gradual addition) in [BMIM]Cl containing 8 M HCl, or (**B**) a typical cocktail of cellulases. The acid/IL-treated lignin in panel A appears to be largely intact—the labile β-aryl ethers (cyan, A) are prominent, as are the phenylcoumarans (green, B), both prominent inter-unit linkage types in lignin. Aromatic guaiacyl units (purple, G), syringyl units (blue, S), as well as newly identified tricin ethers (orange, T) and *p*-coumarate esters (magenta) are readily seen, although there is considerable overlap—signals are only colored/assigned when they are reasonably well resolved. Notably, the signals corresponding to polysaccharides (black) are much less prominent in panel A than in panel B, indicative of much more efficient saccharification in [BMIM]Cl than by the cellulases (data obtained by F. Lu, S. Liu, and J. Ralph).

6.5 Conclusions

We demonstrated the potential for the industrial application of both [BMIM]Cl as a solvent for biomass and SMB chromatography as a successful purification technique for the

recovery of both ionic liquid and sugar products from biomass hydrolysates. By using 8 M HCl in a two-stage hydrolysis reaction, we accessed both glucose and xylose sugars in high yields from raw corn stover biomass without adversely affecting the lignin. SMB chromatography was able to separate and recover the [BMIM]Cl and sugars at near quantitative levels. Although an additional step is required to dry the [BMIM]Cl for further use in hydrolysis reactions, its purity assures its continued viability for biomass dissolution. Furthermore, the recovered hydrolysate sugar products are able to be used as feedstocks for microbes, as we demonstrated using *E. coli* KO11 to produce ethanol. This technology could lend itself to application in an industrial biorefinery to convert tons of raw biomass to contaminant-free sugars whilst recycling ionic liquid solvents for continued use.

6.6 Acknowledgments

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6.7 Materials and Methods

6.7.1 Materials

Commercial chemicals were of reagent grade or better and were used without further purification from Sigma-Aldrich (Milwaukee, WI). 1-Butyl-3-methylimidazolium chloride (98%,

[BMIM]Cl) was a gift from Merck KGaA (Darmstadt, Germany). Cellulose (medium cotton linters, C6288, ~95% dry solids) was from Sigma (St. Louis, MO). Milled and sieved corn stover (2009, 35.0% glucan, 22.0% xylan) and AFEX pre-treated corn stover (batch #740-140, 35.7% glycan, 21.2 % xylan) were gifts from the GLBRC. Dowex® 50WX4-400 columns were purchased from Semba Biosciences (Madison, WI). Hydrolysis reactions were performed in 20 mL glass vials in a temperature-controlled VWR Mini Shaker at 600 rpm. The term "concentrated under reduced pressure" refers to the removal of solvents and other volatile materials using a rotary evaporator under reduced pressure provided by a Welch 2025 self-cleaning dry vacuum system while maintaining the water-bath temperature below 50 °C except where noted. The term "high vacuum" refers to vacuum (<0.1 torr) achieved by a Welch mechanical belt-drive oil pump.

6.7.2 Analytical Methods

Hydrolysis reaction products were analyzed by HPLC and quantified using calibration curves generated from commercially available standards. Product concentrations were calculated from HPLC-peak integrations, which were then used to calculate molar yields. During a reaction, an aliquot of the reaction mixture was taken, diluted with a known mass of deionized water, centrifuged at 12,000 rpm for 5 min to sediment insoluble products, and analyzed. HPLC was performed using an Agilent 1200 system equipped with refractive index and photodiode array detectors. Glucose, xylose, and [BMIM]Cl were analyzed by ion-exclusion chromatography with a Bio-Rad Aminex HPX-87H column (300 x 7.8 mm) using a 5 mM H_2SO_4 mobile phase at a flow rate of 0.6 mL/min at 65 °C.

6.7.3 Representative Procedure for Hydrolysis of Cellulose

[BMIM]Cl (6 vials of 4 g) was heated with mixing at 105 °C until melting of the [BMIM]Cl. Cellulose (250 mg with 1.39 mmol glucose units) was added to each of the six vials. The reaction mixtures were stirred vigorously at 105 °C for 6 h. To each mixture was added 0.20 mL of aqueous HCl (2, 4, 6, 8, 10 and 12 M). After 10 min, deionized water (0.80 mL) was added to each mixture with continued stirring, followed by additional aliquots of water at 20 min (0.40 mL), 30 min (0.60 mL), and 60 min (1.00 mL). After a total reaction time of 3 h, the solutions were diluted with water (6.00 mL) and cooled to ambient temperature. Insoluble materials were removed by centrifugation and an aliquot of the solution was used for HPLC analysis.

6.7.4 Representative Procedure for the Two-Step Hydrolysis of Corn Stover

[BMIM]Cl (6 vials of 5 g) was heated with mixing at 105 °C until melting of the [BMIM]Cl. Corn stover (6 vials of 0.375 g with 4.37 mmol glucose units and 2.88 mmol xylose units) was added and the reaction mixtures were stirred vigorously at 105 °C for 6 h to achieve complete dissolution. To each mixture was added 0.25 mL of aqueous 8 M HCl. After 10 minutes, 0.50 mL of deionized water was added to each mixture with continued stirring. Additional aliquots of water were added at 15 min (0.50 mL), 20 min (0.25 mL), 25 min (0.25 mL), 30 min (0.75 mL), 60 min (1.00 mL). After 2 h, the reactions were cooled to room temperature. Each reaction was brought to a total volume of 25 or 50 mL with deionized water and mixed to yield a [BMIM]Cl concentration of 200 or 100 mg/mL, respectively. Insoluble material was sedimented and removed with centrifugation, and aliquots of the supernatant were passed through a 0.45 μm filter and analyzed by HPLC.

The pellet from the first hydrolysis reaction was dried under high vacuum overnight. [BMIM]Cl (3 vials of 5 g) was heated with mixing to 105 °C until melting of the [BMIM]Cl. The brown solid pellet was split and added (3 vials of 0.600 g), and the reaction mixtures were stirred vigorously at 105 °C for 4 h to achieve complete dissolution. To each mixture was added 0.25 mL of aqueous 8 M HCl. After 10 min, 0.50 mL of deionized water was added to each mixture with continued stirring. Additional aliquots of water were added at 15 min (0.50 mL), 20 min (0.25 mL), 25 min (0.25 mL), 30 min (0.75 mL), 60 min (1.00 mL). After 2 h, the reactions were cooled to room temperature. Each reaction was brought to a total volume 25 or 50 mL with deionized water and mixed to yield a [BMIM]Cl concentration of 200 or 100 mg/mL, respectively. Insoluble material was sedimented and removed with centrifugation, and aliquots of the supernatant were passed through a 0.45 μm filter and and analyzed by HPLC.

6.7.5 Parameter Calculations for Simulated Moving Bed (SMB) Chromatography

Retention times and isotherm data were collected with single column experiments using a Dowex® 50WX4-400 ion exclusion column (1 cm x 25 cm). It was exchanged with [BMIM]Cl (22 g) dissolved in deionized water (125 mL). At the end of the exchange procedure, the column effluent was neutral, indicating an exchange of H^+ by $[BMIM]^+$. Approximate retention times were determined with single injections of [BMIM]Cl, glucose, and xylose. The mobile phase used for these experiments was deionized water at a flow rate of 2 mL/min with column temperatures at 22 °C, 50 °C, or 65 °C. Subsequent single column experiments were done with mixtures of [BMIM]Cl and glucose. Data obtained from these experiments were used to determine retention times and isotherms. SMB chromatography parameters such as switch times and flow rates were calculated and optimized with the SMBC Parameter Calculator worksheet

(available online at www.sembabio.com). Isotherm calculations were performed with ChromWorks™ software.

6.7.6 SMB Chromatography

SMB chromatography was performed with the Octave™ Chromatography System (Semba Biosciences, Inc.). Eight Dowex® 50WX4-400 columns (1 cm x 10 cm) were connected in series and fluid flow paths were controlled through a pneumatic valve system. The columns were exchanged with [BMIM]Cl as indicated above, and deionized water or 5 mM H_2SO_4 was used as the desorbent. Fluid flow was controlled with 4 independent pumps capable of flow rates from 0.05 to 10 mL/min and supplied with the Octave 10 System. Each column had 9 valve positions with inlet access to all 4 pumps, 4 outlet lines, and an inter-column shutoff valve that controlled the flow to the next column in series. Pump flow rates and valve operation to achieve SMB chromatography protocols were controlled by SembaPro™ software. All SMB experiments were performed at ambient temperature.

6.7.7 Bacterial Growth

E. coli strain KO11 was a gift from D.H. Keating (University of Wisconsin–Madison). An *E. coli* freezer stock was grown on a Luria–Bertani agar plate containing chloramphenicol (15 mg/L) for 12 h at 37 °C. single colony was picked and inoculated into Luria–Bertani medium (5 mL) containing xylose (20 g/L) in a culture tube at 37 °C and 250 rpm for 18 h. The cells were collected by centrifugation (4000 rpm for 5 min at 4 °C) and resuspended in M9 minimal medium (2 mL) containing M9 salts (1X), $MgSO_4$ (1 mM), $CaCl_2$ (0.1 mM), and thiamine (0.1 μg/mL).

In a polystyrene 96-well plate, 33 wells were filled with the M9 minimal medium (190 μL). Then a solution of pure sugars (8.6 mg/mL glucose, 10.0 mg/mL xylose) was added (10 μL)

to 11 wells. A solution of recovered hydrolysate sugars (8.5 mg/mL glucose, 9.8 mg/mL xylose) containing traces of [BMIM]Cl (50 mg/mL) was added (10 μL) to another 11 wells. Finally, more M9 minimal medium was added (10 μL) to the remaining 11 wells. The above cell suspension (10 μL) was used to inoculate 10 wells from each of the 3 sets, leaving 1 well without added bacteria as a negative control. The plate was capped with a low-evaporation lid and incubated with rapid agitation in a warm room at 37 °C. The $OD_{600\ nm}$ of each well was measured every 30 min for 7 h using a Tecan Infinite M1000 Absorbance Microplate Reader.

CHAPTER SEVEN

FUTURE DIRECTIONS

7.1 Abstract

Biomass resources will be important contributors in building a sustainable energy infrastructure. The research described in this dissertation contains numerous possibilities for continued development and application. The novelty of both phenylboronic acids as catalysts for carbohydrate conversions and fluorous ionic liquids for cellulose dissolution are totally unknown in biomass conversion processes. Hydrolysis reactions of cellulose provide a unique opportunity to recover unused biomass materials for other conversion processes. Research projects such as these will continue to bring us closer to a source of sustainable energy.

7.2 Develop Boronic Acids to Convert Lignocellulosic Biomass

The catalytic activity of the phenylboronic acids to transform carbohydrates to 5-(hydroxymethyl)furfural (HMF) is unprecedented. In Chapters Three and Four, I described how when used in conjunction with hydrated $MgCl_2$, *ortho*-carboxyl phenylboronic acids could convert cellulose and hexose sugars to HMF. The yields are comparable to those obtained using toxic chromium catalysts.[76,82] Whereas chromium is believed to catalyze a 1,2-hydride shift to isomerize glucose to fructose,[76-77] our studies suggest the boronic acids catalyze the isomerization through an enolization. Furthermore, chromium catalysts have been shown to be able to convert lignocellulosic biomass, but my preliminary work shows that boronic acids suffer in their ability to convert biomass materials. Nonetheless, the boronic acids are able to convert municipal cellulosic sources such as newspaper and cotton.

It is possible that the difference in boronic acids' inability to convert lignocellulosic biomass while being able to convert other cellulosic sources is due to the presence of lignin in biomass materials. Municipal cellulosic sources such as newspaper and cotton are processed before distribution and much of the lignin is removed. In order for phenylboronic acids to enolize glucose to fructose, it must bind to the hydroxyl groups of the sugar. In lignocellulosic biomass, the cellulose and hemicelluloses are encased by lignin. The lignin could distract boronic acids from binding to the sugars. Ammonia fiber expansion (AFEX) pre-treatment serves to expose cellulose from the lignin in biomass, and could be used to access better yields of HMF from biomass materials.[213]

7.3 Hydrolysis of Biomass in Fluorous Ionic Liquids

Ionic liquids are privileged solvents that enable the dissolution of cellulosic materials. Yet, their expense makes it essential that they be recovered and recycled if they are to be used for large scale biomass conversion processes. As they share a number of similar physical properties with carbohydrates (polarity, water solubility, and negligible vapor pressure), specific strategies are necessary to facilitate their recovery. In Chapter Five, I illustrated how fluorous labeling of ionic liquids enables their isolation from cellulose hydrolysate using fluorous solid-phase extraction (SPE). In Chapter Six, I described the use of simulated moving bed chromatography to isolate and recover biomass hydrolysate sugars from ionic liquids. Dissolution of biomass materials in the fluorous ionic liquid for hydrolysis as detailed in Chapter Six and subsequent fluorous SPE would allow for the rapid and facile isolation of pure sugars.

7.4 Recovery and Characterization of Lignin from Hydrolyzed Biomass

Efficient biomass conversion technologies for must allow for the use of all parts of the biomass materials. The research illustrated in this dissertation focused exclusively on transforming the cellulose and hemicellulose present in biomass, but the lignin must also be available for transformative processes. Lignin can serve as a source of aromatic chemicals, and efforts are being made to access its aromatic constituents.[216-218] The hydrolysis I described in Chapter Six allows for the facile recovery of intact lignin. Our initial characterization determined that lignin remains undamaged during the hydrolysis reaction, but further experiments are needed to access the individual aromatic compounds. Doing such would provide some of the first evidence demonstrating the full scope of biomass utilization.

7.5 Conclusions

The goal of shifting from a fossil-fuel based economy to a renewable resource based economy is one of the great challenges of this age. The projects discussed in this dissertation are small steps toward this goal. Biomass resources have great potential to serve as a sustainable, carbon-neutral energy source, and many opportunities exist for continued development in biomass transformations. Organic chemistry can play an important role in helping shape this field, particularly in catalytic biomass conversion processes. Still, much work remains to be done before our modern civilization can be sustained without a reliance on fossil fuels. I sincerely look forward to the day when fields will not only supply our food, but our fuel as well.

APPENDIX

STABILITY OF IONIC LIQUIDS UNDER HYDROLYSIS CONDITIONS

A.1 Abstract

The high cost of ionic liquids necessitates their recovery and recycling after a reaction. However, the conversion reactions discussed in Chapters 3, 4, 5, and 6 often employ acid catalysts, increasing water concentrations, and temperatures in excess of 100 °C for prolonged times. These types of conditions could lead to degradation of the ionic liquids, which would preclude them from being recycled for continued use. Hence, 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) and 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) were subjected to theses reaction conditions and characterized to determine if any degradation had occurred.

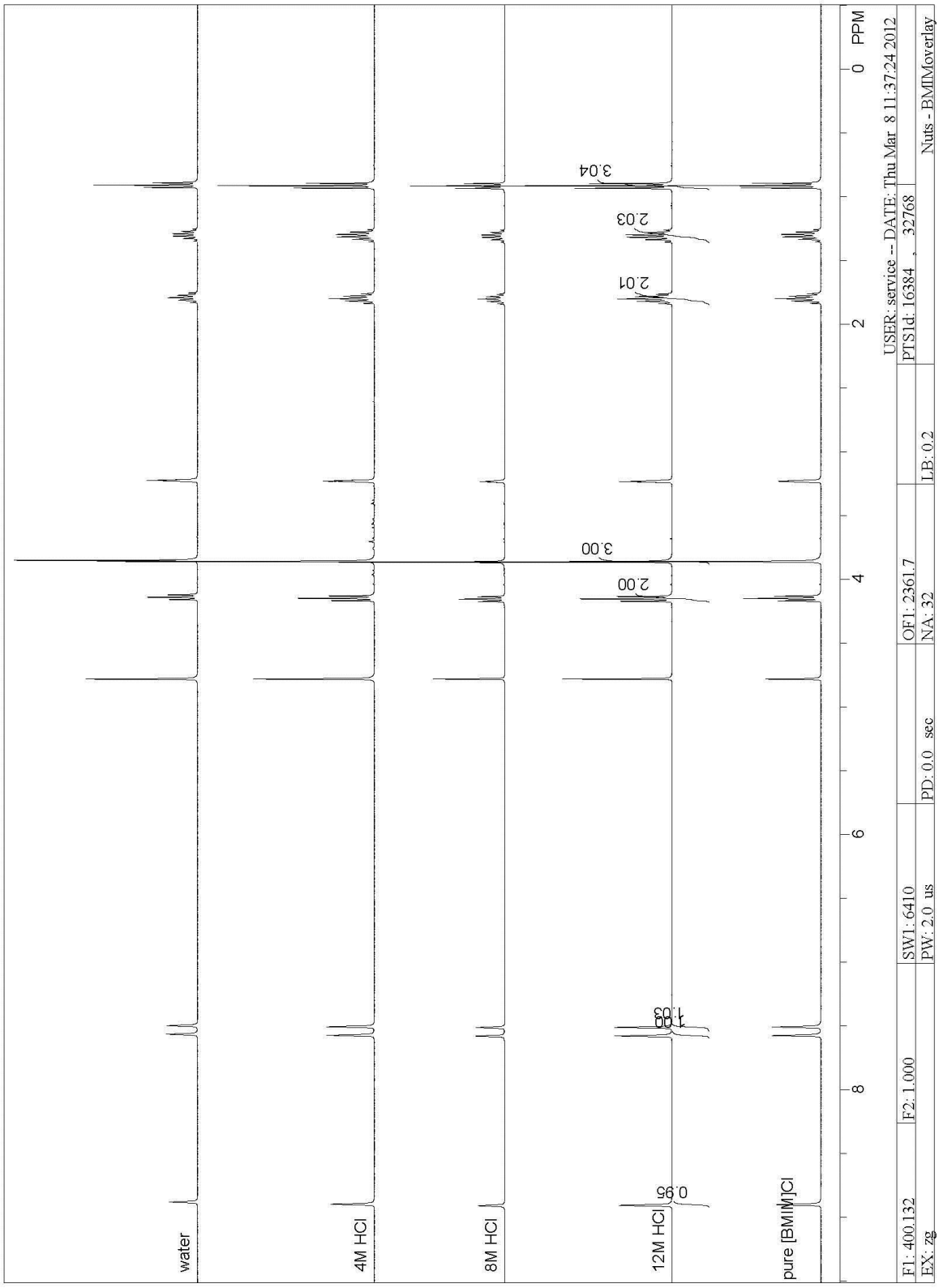

Figure A.1 Comparison of differing reaction conditions on [BMIM]Cl degradation.

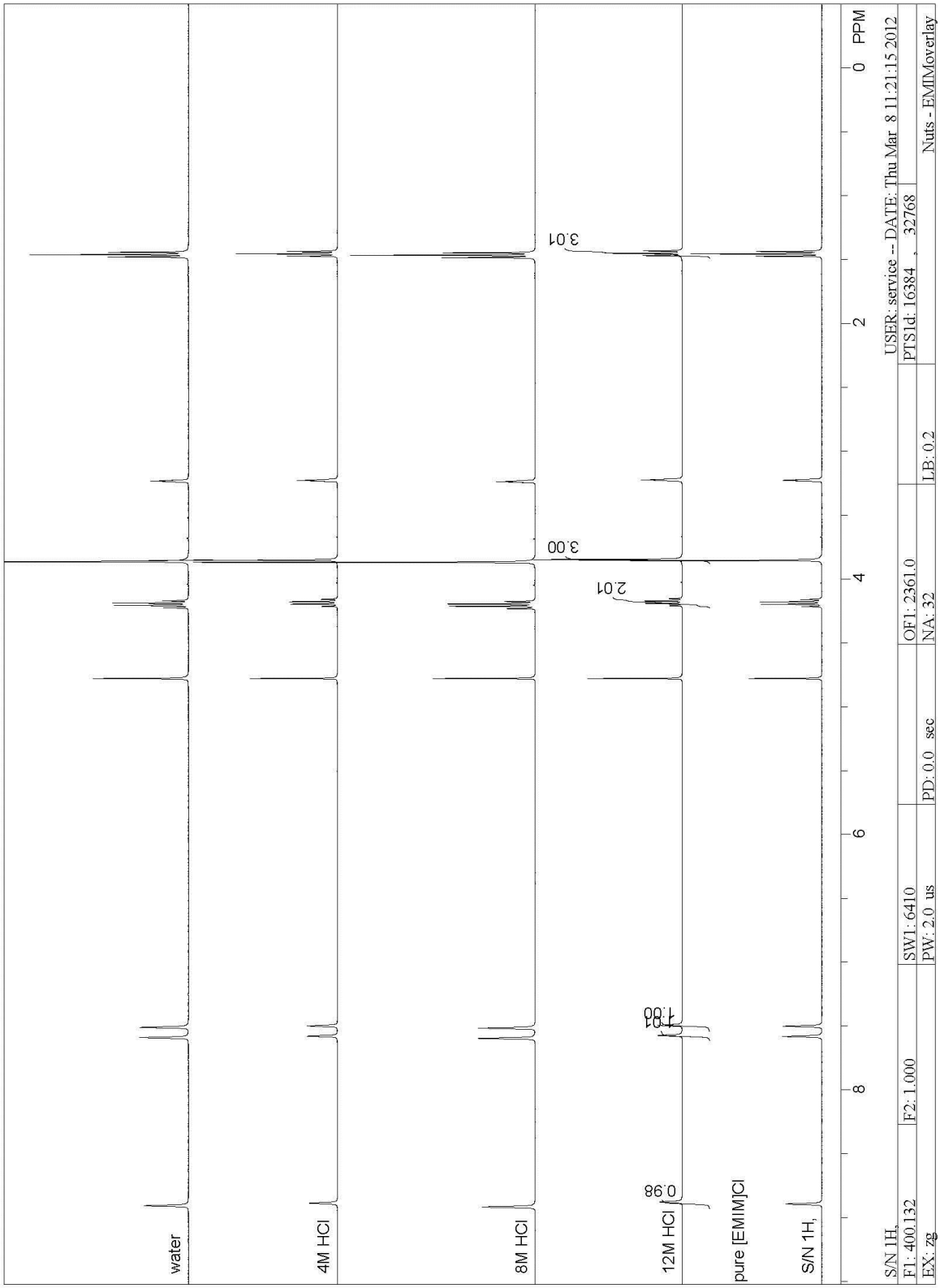

Figure A.2 Comparison of differing reaction conditions on [EMIM]Cl degradation.

A.2 Conclusions

Both [BMIM]Cl and [EMIM]Cl were combined with water, 4, 8, and 12 M HCl at amounts to simulate a hydrolysis reaction. These reaction combinations were then heated for 30 days at 105 °C. A ^{1}H NMR was taken of each condition and compared to a pure sample of the ionic liquids. In all cases for both ionic liquids, there was no observable difference in the ^{1}H NMR spectra as seen for [BMIM]Cl in Figure A.2 and [EMIM]Cl in Figure A.3. Thus, the ionic liquids remain viable without suffering from any degradation when subjected to hydrolysis reaction conditions.

A.3 Materials and Methods

A.3.1 Materials

Commercial chemicals were of reagent grade or better and were used without further purification. 1-Ethyl-3-methylimidazolium chloride (99.5%, [EMIM]Cl) was from Solvent-Innovation (Cologne, Germany). 1-Butyl-3-methylimidazolium chloride (98%, [BMIM]Cl) was a gift from Merck KGaA (Darmstadt, Germany). Reactions were performed in 4-mL glass vials heated in a temperature-controlled VWR Mini Shaker at 600 rpm.

A.3.2 Analytical Methods

NMR spectra were acquired with a Bruker DMX-400 Avance spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) at the National Magnetic Resonance Facility at Madison (NMRFAM). NMR spectra were obtained at ambient temperature unless indicated otherwise.

A.3.3 Representative Procedure

[BMIM]Cl (511.7 mg) was heated at 105 °C with stirring at 400 rpm to melt the ionic liquid. A solution of 12 M HCl was added at 1 wt% relative to the ionic liquid (4.2 μL). The

mixture was then heated at 105 °C with stirring at 400 rpm for 30 days. An aliquot was then removed for ^{1}H NMR analysis in CD_3OD.

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