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COVER ARTICLE
Raines *et al.*
Mechanistic insights on the conversion of sugars into 5-hydroxymethylfurfural

PERSPECTIVE
Artero *et al.*
Water electrolysis and photoelectrolysis on electrodes engineered using biological and bio-inspired molecular systems

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Mechanistic insights on the conversion of sugars into 5-hydroxymethylfurfural

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A sustainable bio-economy requires the efficient utilization of all of the components of biomass. After glucose, mannose and galactose are the most abundant 6-carbon sugars in plant hemicellulose; lactose is a common dairy byproduct. Here, we demonstrate the conversion of these sugars into 5-hydroxymethylfurfural (HMF), a key intermediate for renewable fuels and chemicals. Chromium salts enable the efficient conversion of mannose into HMF but are less effective for galactose, lactose, and the related hexulose, tagatose. Isotopic labeling studies and the reactivity of psicose and sorbose indicate that the key aldose-to-ketose conversion occurs *via* a 1,2-hydride shift, which is followed by dehydration of the furanose tautomer. These data valorize mannose, galatactose, and lactose as sources of HMF, and inform the design of new catalysts for the conversion of aldoses to ketoses.

Introduction

Readily available fossil energy has fueled the dramatic growth of human society in the recent past. In 1850, when the world population was just over 1 billion, global energy production was about 2×10^{19} J, primarily from biomass such as wood.[1] Since then, exponential growth of fossil fuel use has mirrored expanding population and industry, and today global energy production is roughly 5×10^{20} J, with 85% from fossil fuels and <10% from biomass.[2] As a result, civilization could face a major challenge in a few decades from declining petroleum supplies, inaccessible natural gas resources, and carbon-constrained coal usage. Advanced technology for chemical and biological biomass conversion could enable biomass to return to an important role in energy production and provide a replacement for diminishing fossil resources.

The hexose dehydration product, 5-hydroxymethylfurfural (HMF), is an important intermediate in the chemical transformation of biomass.[3] This bifunctional, six-carbon molecule can be easily converted into a variety of useful derivatives,[4] incorporated into a variety of polymers,[5] or upgraded into fuels.[6] Although HMF has long been synthesized in high yield from fructose,[4] we and others demonstrated only recently that HMF can be produced in high yield from glucose and in moderate yield from cellulose and lignocellulosic biomass using chromium salts in the presence of halide ions (Fig. 1).[7–9] High concentrations of chloride ions in solvents such as the ionic liquid 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl)[10] or *N*,*N*-dimethylacetamide–lithium chloride (DMA–LiCl)[11] dissolve cellulose, and chromium ions likely catalyze the isomerization of glucose into fructose for rapid HMF formation.[7] Together, these features enable remarkably high yields of HMF from glucan in heterogeneous and recalcitrant lignocellulosic biomass.

Despite these advances in the synthesis of HMF from glucose and glucose polysaccharides, the conversion of other hexoses into HMF has not been studied extensively. Because of our interest in the conversion of lignocellulosic biomass into HMF, we chose to study the transformation of D-mannose and D-galactose (Fig. 2) into HMF. Mannose-containing polymers can account for 10% of the dry weight of pine wood, while galactose can be as much as 2% of the carbohydrate in corn stover.[12,13] Lactose, because of its poor digestibility, is an underutilized product of the dairy industry that has potential as a chemical or energy feedstock.[14]

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Broader context

In 1850, global energy was produced primarily from biomass, such as wood. Since then, exponential growth of fossil fuel use has mirrored expanding population and industry. Today, 85% of global energy is produced from fossil fuels, and <10% from biomass. Re-establishing a sustainable bio-economy requires the efficient utilization of all components of biomass. We report on the high-yielding conversion of the monosaccharides galactose and mannose (which are prevalent in hemicellulose) and the disaccharide lactose (which is a major byproduct of the dairy industry) into 5-hydroxymethylfurfural (HMF), a key intermediate for renewable fuels and chemicals. We also integrate the differential reactivity of these sugars and related ones with the results of deuterium-labeling studies to provide mechanistic insight on the conversion process. These findings will be of interest to bioorganic and carbohydrate chemists, and inform the field of sustainable chemistry.

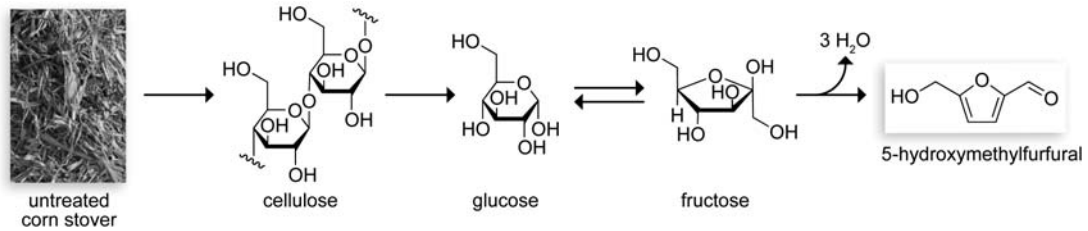

Fig. 1 Route for the synthesis of HMF from sugars and lignocellulosic biomass.[9]

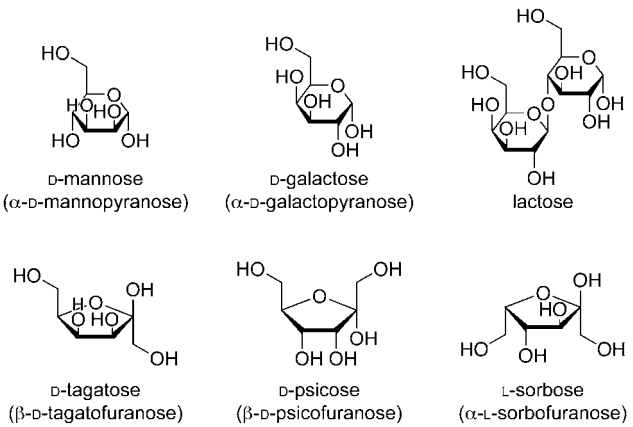

Fig. 2 Mono- and disaccharide precursors for HMF.

None of these common sugars had been converted into HMF in high yield. Ishida and co-workers studied lanthanide(III) ions as catalysts for HMF synthesis in both water and organic solvents, but achieved only a 6% yield from mannose and 7% yield from galactose, at most.[15] In other studies, HMF formation from these sugars has been examined primarily as a side reaction or intermediary process during pretreatment or pyrolysis.[13,16] Because chromium chlorides are efficient catalysts for the conversion of glucose into HMF,[7] we hypothesized that these catalysts would also provide high yields of HMF from other aldoses. To test this hypothesis, we studied HMF synthesis from not only mannose and galactose, but also lactose and related hexuloses, such as D-tagatose (Fig. 2). Our investigation revealed that some, but not all hexoses, can be transformed efficiently into HMF and provided mechanistic insights into the role of chromium and hexose structure in HMF formation.

Results and discussion

Mechanism of aldose-to-ketose conversion

Glucose, mannose and galactose are aldose sugars, and thus are likely to be converted into ketose sugars on the route to HMF (Fig. 1). Accordingly, we began by studying the mechanism of the aldose-to-ketose conversion. In the 1970s, Harris and Feather investigated the low yielding-conversion of glucose into fructose and HMF in acidic water.[17] They considered several mechanisms, though evidence from their isotopic labeling experiments supported a 1,2-hydride shift as a major contributor in the formation of fructose and HMF. In 2001, Nagorski and Richard likewise found that the zinc-catalyzed isomerization of the simplest aldose, glyceraldehyde, in acidic solution proceeds primarily *via* a 1,2-hydride shift.[18] In 2007, however, Zhao and co-workers proposed an enolization mechanism for the chromium-catalyzed synthesis of HMF from glucose.[7]

Accordingly, we considered two general mechanisms for the chromium-catalyzed formation of HMF from aldoses (Fig. 3). One possibility is that the aldose forms an enediol(ate) intermediate that is protonated at C-1 to yield a ketose, as proposed by Zhao and co-workers ("enolization" pathway).[7] This ketose then dehydrates into HMF, likely *via* a furanosyl oxocarbenium ion.[9,19] Another possibility is that chromium assists in a 1,2-hydride shift to form the ketose from the aldose in a single step ("hydride shift" pathway). Interestingly, known enzymic catalysts of hexose isomerization use each pathway.[20] The enolization mechanism is used by phosphoglucose isomerase,[21] which does not employ a metal cofactor. In contrast, the hydride shift mechanism is used by xylose isomerase,[22] the manganese-dependent enzyme used for the commercial isomerization of glucose into fructose.[23]

We tested these alternative mechanisms by using deuterium labels. In our first experiment, we converted glucose into HMF

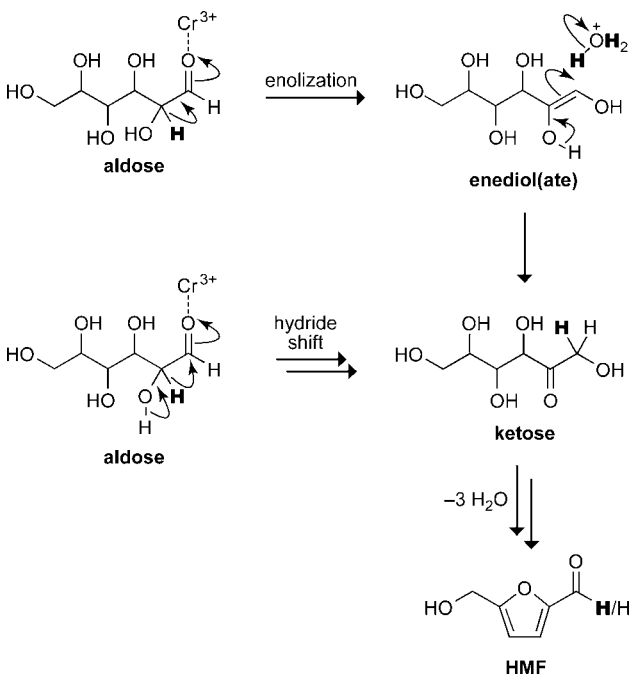

Fig. 3 Putative mechanisms for the chromium(III)-catalyzed conversion of an aldose into HMF. Hydrogens replaced with deuteriums in isotopic labeling studies are depicted in boldface type.

under the low-water conditions described previously[9] but with D_2O (100 wt% relative to glucose) as a deuteron source. We anticipated that if the enolization pathway were operative, some deuterium would be incorporated at C-1 of the resulting fructose and would be observable in the HMF product. On the contrary, ^1H NMR analysis of the products revealed <5% deuterium incorporation. Next, we converted glucose-2-*d* into HMF in the presence of H_2O (100 wt% relative to glucose) as a proton source. ^1H NMR analysis indicated ~33% deuterium incorporation at C-1 of HMF, corroborated by the appearance of a signal corresponding to the aldehydic deuteron in the ^2H NMR spectrum. These results, like those for aqueous aldose reactions,[17,18] are consistent with ketose formation occuring *via* a 1,2-hydride shift, as in the catalytic mechanism of xylose isomerase.[22,23]

HMF from mannose

Next, we characterized the reactivity of mannose, which is a C-2 epimer of glucose. We found its reactivity in DMA–LiCl and [EMIM]Cl to be similar to that of glucose (Table 1). In the absence of chromium(II) or chromium(III), little HMF was formed and nearly all mannose was recovered unchanged at 100 °C. On the other hand, the addition of catalytic chromium enabled HMF yields of 43–54% in DMA–LiCl at 100–120 °C. Higher HMF yields were obtained in either DMA–LiBr or [EMIM]Cl, with a maximum yield of 69% achieved at 100 °C. These trends are comparable to those with glucose, suggesting that these two epimeric aldoses form HMF through a similar mechanism. In D_2O, the conversion of mannose into HMF again led to <5% deuterium incorporation, supporting the 1,2-hydride shift mechanism.

HMF from lactose

We found the transformation of the disaccharide lactose into HMF to be challenging (Table 2). Use of chloride-containing solvents resulted in yields of about 20%, which is far lower than achieved with most other sugars. Slightly higher yields were obtained in DMA without LiCl, and DMA containing bromide salts such as $CrBr_3$ enabled the highest yields. HMF yields from lactose parallel roughly the average of the yields from glucose and galactose under the same conditions.

The likely route to HMF from lactose provides a possible rationale for these results. Lactose can be cleaved into glucose and galactose units through acid catalysis, and H_2SO_4 probably aids in this process. We know that the resulting glucose is converted efficiently into HMF through chromium catalysis. Perhaps the galactose unit forms HMF less readily.

HMF from galactose

High yields of HMF from galactose were indeed elusive under a range of reaction conditions (Table 3). As anticipated, no HMF was produced from galactose in the absence of chromium salts. With $CrCl_2$ or $CrCl_3$ in DMA–LiCl at 120 °C, HMF was produced in only 10% yield, far lower than that observed with glucose and mannose. Adding H_2SO_4 as a co-catalyst resulted in still lower yields, and using [EMIM]Cl as the solvent in place of DMA did not greatly improve the results. On the other hand, switching to non-chloride solvents increased HMF yields. Substituting LiBr for LiCl raised the HMF yield to 18%, and using $CrBr_3$ without a halide additive allowed a yield of 33%. Still, these yields are far lower than those observed for other aldoses, and reveal an unexpected deleterious effect from halide additives. Regardless, the differential reactivity of glucose and galactose does foretell the low yields of HMF from lactose.

The stereochemical configuration of glucose and galactose provides a possible explanation for the difficulty of galactose conversion to HMF. Whereas glucose and mannose share fructose as a common intermediate on the pathway to HMF *via* the hydride shift mechanism (Fig. 3), the isomerization of galactose into a ketose results in tagatose, the C-4 epimer of fructose (Fig. 2). Thus, inefficient dehydration of tagatose into HMF could prevent high HMF yields from galactose.

Additional experiments substantiated our hypothesis about poor tagatose reactivity. In chloride-containing solvents with chromium or H_2SO_4 catalyst, yields of HMF from tagatose were typically <20% (Table 4). Just as was observed with galactose,

Table 1 Synthesis of HMF from mannose[a]

Sugar	Solvent	Catalyst (mol%)	Additive (wt%)	*T*/°C	*t*/h	Yield (%)
Mannose	DMA		LiCl, 10	120	2	2
Mannose	[EMIM]Cl			120	2	1
Mannose	DMA	$CrCl_2$, 6	LiCl, 10	120	2	54
Mannose	DMA	$CrCl_3$, 6	LiCl, 10	120	2	43
Mannose	DMA	$CrCl_2$, 6	LiBr, 10	120	2	51
Mannose	DMA	$CrCl_3$, 6	LiBr, 10	120	2	64
Mannose	[EMIM]Cl	$CrCl_2$, 6		120	2	57
Mannose	[EMIM]Cl	$CrCl_3$, 6		120	2	56
Mannose	DMA	$CrCl_2$, 6	LiCl, 10	100	2	54
Mannose	DMA	$CrCl_3$, 6	LiCl, 10	100	2	47
Mannose	DMA	$CrCl_2$, 6	LiBr, 10	100	2	69
Mannose	DMA	$CrCl_3$, 6	LiBr, 10	100	2	60
Mannose	[EMIM]Cl	$CrCl_2$, 6		100	2	68
Mannose	[EMIM]Cl	$CrCl_3$, 6		100	2	52
Glucose	DMA	$CrCl_2$, 6	LiCl, 10	120	3	53[b]
Glucose	DMA	$CrCl_2$, 6	LiBr, 10	100	4	79[b]

[a] Mannose and glucose were reacted at a concentration of 10 wt% relative to the total mass of the reaction mixture. Additive concentrations are relative to the total mass of the reaction mixture. Catalyst loading is relative to sugar. Yields are based on HPLC analysis. [b] From ref. 9.

Table 2 Synthesis of HMF from lactose[a]

Sugar	Solvent	Catalyst (mol%)	Additive (wt%)	*T*/°C	*t*/h	Yield (%)
Lactose	[EMIM]Cl			120	2	3
Lactose	[EMIM]Cl	H_2SO_4, 6		120	2	3
Lactose	DMA	$CrCl_2$, 6	LiCl, 10	120	2	23
Lactose	DMA	$CrCl_3$, 6	LiCl, 10	120	2	19
Lactose	DMA	$CrCl_2$, 6; H_2SO_4, 6	LiCl, 10	120	2	19
Lactose	DMA	$CrCl_3$, 6; H_2SO_4, 6	LiCl, 10	120	2	22
Lactose	[EMIM]Cl	$CrCl_2$, 6		120	2	17
Lactose	[EMIM]Cl	$CrCl_2$, 6; H_2SO_4, 6		120	2	21
Lactose	DMA	$CrCl_2$, 6		120	3	23
Lactose	DMSO	$CrCl_2$, 6		120	2	23
Lactose	DMA	$CrCl_2$, 6; H_2SO_4, 6		120	3	26
Lactose	DMSO	$CrCl_2$, 6; H_2SO_4, 6		120	3	11
Lactose	DMA	$CrCl_2$, 6	LiBr, 10	120	2	27
Lactose	DMA	$CrCl_3$, 6	LiBr, 10	120	2	29
Lactose	DMA	$CrCl_2$, 6; H_2SO_4, 6	LiBr, 10	120	2	39
Lactose	DMA	$CrCl_3$, 6; H_2SO_4, 6	LiBr, 10	120	2	35
Lactose	DMA	$Cr(NO_3)_3$, 6		120	3	4
Lactose	DMSO	$Cr(NO_3)_3$, 6		120	3	13
Lactose	DMA	$CrBr_3$, 6		120	3	41

[a] Lactose was reacted at a concentration of 10 wt% relative to the total mass of the reaction mixture. Additive concentrations are relative to the total mass of the reaction mixture. Catalyst loading is relative to the monosaccharide units contained in lactose. Yields are based on HPLC analysis.

the highest yields of HMF were achieved in the absence of chloride ions. Moreover, the maximal yield from tagatose was 61%, which is significantly lower than the 80–90% yields commonly achieved with fructose.[4,9,24] These data indicate that the transformation of tagatose (and thus galactose) into HMF is both more challenging than that of fructose and affected detrimentally by halide ions.

Role of ketose tautomers

The disparity in fructose and tagatose reactivity could result from their tautomeric composition. Dehydration of ketoses into HMF probably proceeds through the equilibrium protonation and dehydration of the furanose form of the sugar to form an oxocarbenium intermediate.[19] Increased concentrations of the furanose form would increase the rate of this reaction. As a result, fructose is poised for conversion into HMF in polar aprotic organic solvents because it exists primarily in furanose forms (48% β-furanose, 20% α-furanose, and 27% β-pyranose in DMSO at 27 °C).[25] Tagatose, on the other hand, preferentially forms pyranose tautomers in both water and organics (76% α-pyranose, 17% β-pyranose, 4% α-furanose and 3% β-furanose in DMSO at 27 °C).[25] As a result, tagatose is less likely to undergo dehydration to produce HMF and more likely to participate in deleterious side reactions.

For further evidence, we examined the reactivity of two other epimeric hexuloses: D-psicose and L-sorbose (Table 4). Psicose is the C-3 epimer of fructose and exists as 50% furanose tautomers in DMSO (15% β-furanose, 35% α-furanose, 24% α-pyranose and 26% β-pyranose at 27 °C).[25] In contrast, we found by using

Table 3 Synthesis of HMF from galactose[a]

Sugar	Solvent	Catalyst (mol%)	Additive (wt%)	*T*/°C	*t*/h	Yield (%)
Galactose	DMA		LiCl, 10	120	2	1
Galactose	[EMIM]Cl			120	2	1
Galactose	[EMIM]Cl	H_2SO_4, 6		120	2	1
Galactose	DMA	$CrCl_2$, 6	LiCl, 10	120	2	10
Galactose	DMA	$CrCl_3$, 6	LiCl, 10	120	2	10
Galactose	DMA	$CrCl_2$, 6; H_2SO_4, 6	LiCl, 10	120	2	9
Galactose	DMA	$CrCl_3$, 6; H_2SO_4, 6	LiCl, 10	120	2	7
Galactose	[EMIM]Cl	$CrCl_2$, 6		120	2	14
Galactose	[EMIM]Cl	$CrCl_3$, 6		120	2	4
Galactose	DMA	$CrCl_2$, 6	LiBr, 10	120	2	18
Galactose	DMA	$CrCl_3$, 6	LiBr, 10	120	2	17
Galactose	DMA	$CrCl_2$, 6; H_2SO_4, 6	LiBr, 10	120	2	9
Galactose	DMA	$CrCl_3$, 6; H_2SO_4, 6	LiBr, 10	120	2	9
Galactose	DMA	$CrCl_2$, 6		120	2	22
Galactose	DMSO	$CrCl_2$, 6		120	2	22
Galactose	DMA	$CrBr_3$, 6		120	3	33
Galactose	DMSO	$CrBr_3$, 6		120	3	24
Galactose	DMA	$Cr(NO_3)_3$, 6		120	3	9

[a] Galactose was reacted at a concentration of 10 wt% relative to the total mass of the reaction mixture. Additive concentrations are relative to the total mass of the reaction mixture. Catalyst loading is relative to galactose. Yields are based on HPLC analysis.

Table 4 Synthesis of HMF from tagatose, psicose and sorbose[a]

Sugar	Solvent	Catalyst (mol%)	Additive (wt%)	T/°C	t/h	Yield (%)
Tagatose	DMA			120	2	0
Tagatose	DMA		LiCl, 10	120	2	9
Tagatose	[EMIM]Cl			120	2	15
Tagatose	DMA	$CrCl_2$, 6	LiCl, 10	120	2	10
Tagatose	DMA	$CrCl_3$, 6	LiCl, 10	120	2	8
Tagatose	DMA	H_2SO_4, 6	LiCl, 10	120	2	7
Tagatose	DMA	$CrCl_2$, 6; H_2SO_4, 6	LiCl, 10	120	2	11
Tagatose	[EMIM]Cl	$CrCl_2$, 6		120	2	14
Tagatose	[EMIM]Cl	$CrCl_3$, 6		120	2	10
Tagatose	[EMIM]Cl	H_2SO_4, 6		120	2	12
Tagatose	[EMIM]Cl	$CrCl_2$, 6; H_2SO_4, 6		120	2	9
Tagatose	DMSO	$CrCl_2$, 6	LiCl, 10	120	2	20
Tagatose	DMSO	H_2SO_4, 6	LiCl, 10	120	2	13
Tagatose	DMSO		LiCl, 10	120	2	14
Tagatose	DMA	H_2SO_4, 6		120	2	45
Tagatose	DMSO			120	2	52
Tagatose	DMSO	Dowex		120	2	55
Tagatose	DMSO	H_2SO_4, 6		120	2	61
Tagatose	DMA	$CrCl_2$, 6		120	2	21
Tagatose	DMSO	$CrCl_2$, 6		120	2	27
Tagatose	DMA	$CrCl_2$, 6	LiBr, 10	120	2	13
Tagatose	DMA	$CrCl_3$, 6	LiBr, 10	120	2	12
Tagatose	DMA	H_2SO_4, 6	LiBr, 10	120	3	26
Psicose	DMA		LiCl, 10	120	3	35
Psicose	DMA	H_2SO_4, 6	LiCl, 10	120	3	33
Psicose	DMA	H_2SO_4, 6		120	3	30
Psicose	DMSO		LiCl, 10	120	3	39
Psicose	DMSO	H_2SO_4, 6	LiCl, 10	120	3	37
Psicose	DMSO	H_2SO_4, 6		120	3	82
Sorbose	DMA		LiCl, 10	120	3	39
Sorbose	DMA	H_2SO_4, 6	LiCl, 10	120	3	38
Sorbose	DMA	H_2SO_4, 6		120	3	37
Sorbose	DMSO		LiCl, 10	120	3	45
Sorbose	DMSO	H_2SO_4, 6	LiCl, 10	120	3	37
Sorbose	DMSO	H_2SO_4, 6		120	3	60

[a] Sugars were reacted at a concentration of 10 wt% relative to the total mass of the reaction mixture. Additive concentrations are relative to the total mass of the reaction mixture. Catalyst loading is relative to sugar. Yields are based on HPLC analysis.

NMR spectroscopy that sorbose, which is the C-5 epimer of fructose, greatly prefers a pyranose tautomer (7% α-furanose and 93% α-pyranose in DMSO at 25 °C; Fig. 4). The yield of HMF from psicose with H_2SO_4 in DMSO was higher than that of either tagatose or sorbose, and similar to those obtained with fructose, which is consistent with the relatively high furanose preference of psicose. Under other conditions, however, yields of HMF from psicose and sorbose were similar. In DMA and in the presence of LiCl, both sugars formed HMF in 30–45% yields. Both sorbose and psicose delivered significantly higher yields than did tagatose in the presence of lithium chloride. Apparently, reaction conditions can modulate the relative reactivity of hexuloses, perhaps by altering their tautomeric equilibria.

Conclusions

Methods for converting sugars into chemicals and fuels are crucial for efficient utilization of biomass resources. We discovered that HMF can be produced efficiently from mannose. This result is consistent with a mechanism in which mannose and glucose share a common intermediate, fructose, and isotopic labeling studies support a pathway for fructose formation *via* a 1,2-hydride shift. Galactose, lactose, and tagatose, the hexulose expected from isomerization of galactose, were converted only poorly into HMF, providing further mechanistic insight. Among fructose and its three epimers, the highest HMF yields were obtained from fructose and psicose, the sugars with the highest furanose propensity, suggesting that tautomeric equilibria are responsible for the poor yield of HMF from tagatose. These findings offer not only new opportunities for the production of renewable chemicals and fuels, but also insight into the mechanism of HMF formation, informing future catalyst development.

Experimental

General considerations

Commercial chemicals were of reagent grade or better and were used without further purification. Reactions were performed in glass vessels heated in a temperature-controlled oil-bath with magnetic stirring.

1-Ethyl-3-methylimidazolium chloride (99.5%, [EMIM]Cl) was from Solvent-Innovation (Cologne, Germany). 5-Hydroxymethylfurfural, D-mannose, D-galactose, D-psicose, and Dowex® 50WX4 (200–400 mesh, H^+ form) were from Aldrich (Milwaukee, WI). D-Tagatose was from Acros (Geel, Belgium). L-Sorbose was a gift from H. A. Lardy (University of Wisconsin-Madison).

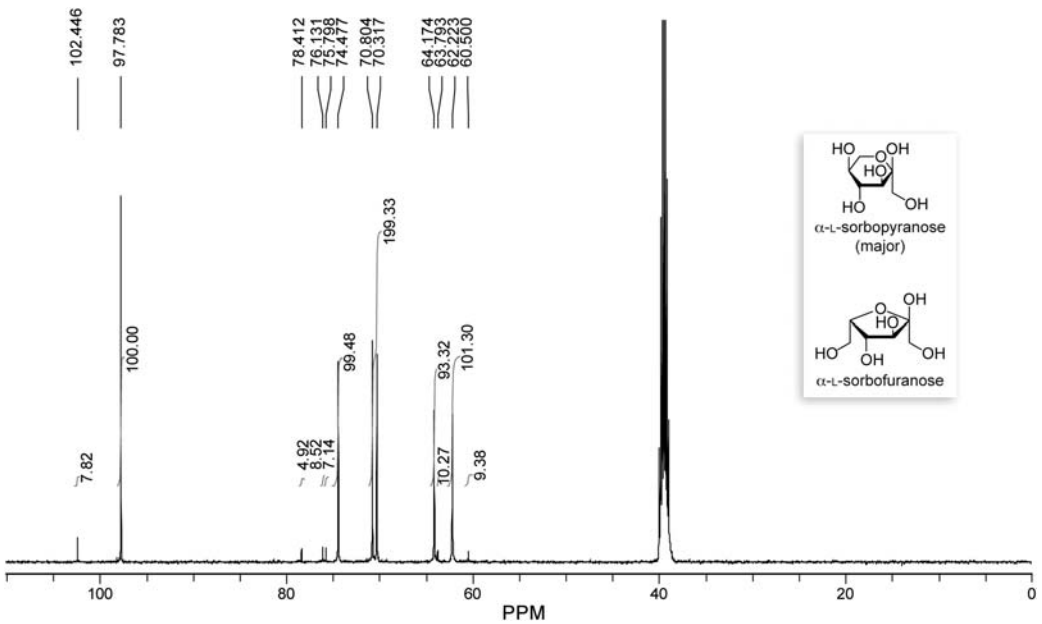

Fig. 4 $^{13}C\{^1H\}$ NMR spectrum of L-sorbose in DMSO-d_6 at 25 °C. Integrations of all six signals for each tautomer were used to calculate an α-pyranose : α-furanose ratio of 93 : 7.

Analytical methods

All reaction products were analyzed by HPLC and quantified using calibration curves generated with commercially-available standards. Following a typical reaction, the product mixture was diluted with a known mass of deionized water, centrifuged to sediment insoluble products, and analyzed. The concentrations of products were calculated from HPLC-peak integrations and used to calculate molar yields. HPLC was performed with either a Waters system equipped with two 515 pumps, a 717 Plus autosampler, and a 996 photodiode array detector, or an Agilent 1200 sytem equipped with refractive index and photodiode array detectors. HMF was analyzed either by reversed-phase chromatography using a Varian Microsorb™-MV 100-5 C18 column (250 × 4.6 mm; 93 : 7 water–acetonitrile, 1 mL min^{-1}, 35 °C) or by ion-exclusion chromatography using a Bio-Rad Aminex® HPX-87H column (300 × 7.8 mm; 5 mM H_2SO_4, 0.6 or 0.9 mL min^{-1}, 65 °C). NMR spectra were recorded at 25 °C using a Bruker DMX-400 Avance spectrometer (^1H, 400.1 MHz; ^2H, 76.7 MHz; ^{13}C, 125.7 MHz) at the National Magnetic Resonance Facility at Madison (NMRFAM).

Representative procedure for synthesis of HMF from sugars

Tagatose (18.2 mg, 101 μmol) and LiCl (16 mg) were dissolved in DMA (200 mg), and the reaction mixture was stirred at 120 °C for 2 h. Then, the solution was diluted with H_2O (300 mg) and analyzed by HPLC. Except where noted otherwise, reactions proceeding to high conversion and low yields indicate high byproduct formation. NMR analyses of products were performed on crude reaction mixtures diluted with D_2O for ^1H NMR and H_2O for ^2H NMR.

Determination of L-sorbose tautomeric equilibrium in DMSO

L-Sorbose (100 mg) was dissolved in DMSO-d_6 (1 mL) and equilibrated at ambient temperature for 8 d. A broadband ^1H-decoupled ^{13}C NMR spectrum was recorded at 25 °C using an inverse-gated pulse program with a relaxation delay of 10 s. The spectrum was referenced to the DMSO-d_6 signal at 39.52 ppm. Signals from the α-pyranose and α-furanose tautomers were identified by comparison with chemical shifts in D_2O.[26] Other tautomers were not observed. Integrations of all signals for each tautomer were averaged to calculate tautomeric ratios.

α-L-Sorbopyranose: δ_C (125.7 MHz; DMSO-d_6) 97.78, 74.48, 70.80, 70.32, 64.17, 62.22.

α-L-Sorbofuranose: δ_C (125.7 MHz, DMSO-d_6) 102.45, 78.41, 76.13, 75.80 63.79, 60.50.

Acknowledgements

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References and notes

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