University of Groningen

A Comparative Study on the Reactivity of Various Ketohexoses to Furanics in Methanol

van Putten, Robert-Jan; van der Waal, Jan C.; Harmse, Martin; van de Bovenkamp, Henk H.; de Jong, Ed; Heeres, Hero J.

Published in:
Chemsuschem

DOI:
[10.1002/cssc.201600252](https://doi.org/10.1002/cssc.201600252)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Putten, R.-J., van der Waal, J. C., Harmse, M., van de Bovenkamp, H. H., de Jong, E., & Heeres, H. J. (2016). A Comparative Study on the Reactivity of Various Ketohexoses to Furanics in Methanol. *Chemsuschem*, 9(14), 1827-1834. <https://doi.org/10.1002/cssc.201600252>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

A Comparative Study on the Reactivity of Various Ketohexoses to Furanics in Methanol

Robert-Jan van Putten,^{*,[a]} Jan C. van der Waal,^[a] Martin Harmse,^[a]
Henk H. van de Bovenkamp,^[b] Ed de Jong,^[a] and Hero J. Heeres^{*,[b]}

The acid-catalysed dehydration of the four 2-ketohexoses (fructose, sorbose, tagatose and psicose) to furanics was studied in methanol (65 g L⁻¹ substrate concentration, 17 and 34 mM sulfuric acid, 100 °C) with Avantium high-throughput technology. Significant differences in the reactivities of the hexoses and yields of 5-hydroxymethylfurfural (HMF) and its methyl ether (MMF) were observed. Psicose and tagatose were the most reactive, and psicose also afforded the highest combined yield of

MMF and HMF of approximately 55% at 96% sugar conversion. Hydroxyacetylfuran and its corresponding methyl ether were formed as byproducts, particularly for sorbose and tagatose, with a maximum combined yield of 8% for sorbose. The formation of hydroxyacetylfuran was studied through ¹³C NMR spectroscopy with labelled sorbose, which provided new insights into the reaction mechanism.

Introduction

The increasing demand for the sustainable production of energy and materials has resulted in a sharp increase in research into bio-based chemistry over the last decade. The dehydration of hexoses plays an important role in this field.

The dehydration of hexoses is well-known and initially leads to the formation of 5-hydroxymethylfurfural (HMF).^[1] This molecule is considered as a high-potential platform chemical and is listed in the US Department of Energy (DoE) top 12 bio-based chemicals.^[2] HMF can be converted into several interesting building blocks, such as 2,5-furandicarboxylic acid (FDCA, DoE top 12)^[1,2] and levulinic acid (LA, DoE top-12).^[2–5] Another interesting derivative is dimethylfuran, which has applications as a fuel additive, a solvent, and a precursor for green aromatics (*p*-xylene).^[6]

FDCA has been identified as a polymer precursor for polyethylene furanoate (PEF), which is a high-potential bio-based replacement for polyethylene terephthalate (PET) in which the terephthalic acid moiety is replaced by FDCA. Compared to PET production, PEF production results in significantly lower non-renewable energy use and greenhouse emissions.^[7] Additionally, PEF has superior physical properties to PET; therefore, it is very interesting for use in bottles, fibres and films.^[8,9]

In addition to HMF, another well-known platform chemical from hexoses is levulinic acid (LA), which may be converted to both bulk and fine chemicals.^[10] Examples are the multi-step conversion to δ -aminolevulinic acid, an active ingredient in a biodegradable herbicide,^[10] the oxidation to succinic acid, a DoE top 12 compound applicable as a monomer in polyesters,^[2,10] and reduction to γ -valerolactone, a precursor for methyltetrahydrofuran, which can be used as a solvent and a fuel additive.^[10]

Over the last decade, global research activities on the development of techno-economically viable HMF processes have increased dramatically. The main focuses have been on increasing yields through the development of selective catalysts and the use of solvents other than water.^[1] The maximum obtainable yield of HMF is limited by the instability of the molecule under reaction conditions.^[1] Under acidic conditions, HMF reacts with water to form levulinic and formic acids (Scheme 1).^[3–5] In addition, the formation of insoluble black-

Scheme 1. The dehydration of hexose in the absence and presence of alcohol to form RMF, followed by hydration to levulinates.

[a] Dr. R.-J. van Putten, Dr. J. C. van der Waal, M. Harmse, Dr. E. de Jong
Avantium Chemicals

Zekeringstraat 29, 1014 BV Amsterdam (The Netherlands)
E-mail: robert-jan.vanputten@avantium.com

[b] H. H. van de Bovenkamp, Prof. Dr. H. J. Heeres
Department of Chemical Engineering
University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
E-mail: h.j.heeres@rug.nl

Supporting Information and the ORCID identification number(s) for the author(s) of this article can be found under <http://dx.doi.org/10.1002/cssc.201600252>.

brown byproducts, referred to as humins, reduces the yield and causes processing issues such as reactor fouling.^[11] The conversion of fructose to HMF under aqueous conditions has a maximum yield of approximately 50%.^[11] In ionic liquids and polar aprotic solvents such as DMSO, yields of over 90% have been reported.^[11] For glucose, an aldose, the reported yields are generally much lower (<10%) unless specific co-catalysts and advanced solvent systems are used.^[11] Avantium is developing a process in which hexoses are dehydrated in alcohols. This leads to the formation of HMF ethers as the predominant products (Scheme 1). Dehydration in alcohols has several advantages over HMF production in water, aprotic polar solvents and ionic liquids. The use of an organic solvent increases the attainable yield of furanics by suppressing the formation of levulinic acid. Additionally, the HMF will be converted mainly to its alkyl ether. For lower alcohols, these ethers have lower boiling points than that of HMF; thus, separation by distillation is simplified.^[12,13] It is generally very challenging to separate HMF from aprotic polar solvents or ionic liquids, as these solvents typically have very high affinities for HMF.^[11] On the contrary, lower alcohols can be removed readily by evaporation. The solubilities of several sugars, including fructose, in methanol have been studied previously, and fructose has a solubility of approximately 10 wt% in methanol at room temperature.^[14]

Despite the large volume of research on the formation of HMF from hexoses, the reaction mechanism is still under debate.^[11] A better understanding is of pivotal importance for the development of efficient catalytic systems for the production of HMF and derivatives. We have shown recently that aldose dehydrations follow a different reaction pathway than ketose dehydrations.^[15] This led to the conclusion that glucose and fructose require different catalyst systems for the dehydration to HMF. Furthermore, we reported that the relative positions of the hydroxy groups in the different ketoses (Scheme 2) resulted in different reactivities for the dehydration to HMF in water.^[15] Tagatose reacts significantly quicker than sorbose and fructose. These results essentially disprove a reaction mechanism with acyclic intermediates, and a reaction mechanism with cyclic intermediates is more likely.

Scheme 2. The α -furanose structures of the D-ketoses

In addition to the differences in reaction rates for the ketoses, the maximum obtainable HMF yield in water was significantly lower for sorbose than for fructose and tagatose.^[15]

The reactivities of four ketohexoses (fructose, sorbose, tagatose and psicose) in methanol with sulfuric acid as the catalyst were studied in detail to gain further insights into the sugar-furan yield relationships. For this purpose, the Avantium high-throughput platform was used. In addition, a ^{13}C NMR spectroscopy experiment with labelled sorbose was performed to

gain insights into the pathways for the formation of 2-hydroxyacetylfuran (HAF), a byproduct of sorbose dehydration.

Results and Discussion

The acid-catalysed dehydration of the ketoses fructose, tagatose, sorbose and psicose to furanics in methanol was studied with a high-throughput batch setup to enable a systematic comparison of the reactivities of the four ketohexoses under similar reaction conditions. Duplicates and triplicates of selected experiments were performed to enable the statistical analysis of the product yields and hexose conversions. The reactions were followed over time at a fixed temperature (100 °C) with two H_2SO_4 concentrations (17 and 34 mM) at a constant substrate concentration (65 g L^{-1}). In general, insoluble humins were not formed, though the reaction mixtures did show brown colouring, which increased with the severity of the reaction conditions. In the following, the concentration versus time profiles and yield-selectivity data will be provided and discussed in detail for the four ketohexoses used in this study.

High-throughput experiments

The conversion versus time profiles for experiments with all four ketohexoses are shown in Figure 1. The spread in the duplicates and triplicates does not exceed 3% (absolute); therefore, the experiments are highly reproducible. As can be seen clearly from a comparison of the conversion-time trends for

Figure 1. The conversions versus reaction time for fructose ($\blacktriangle$), sorbose ($\bullet$), tagatose ($\blacklozenge$) and psicose ($\blacktriangledown$) at 65 g L^{-1} substrate in methanol at 100 °C with (a) 17 and (b) 34 mM H_2SO_4 .

the different hexoses, tagatose and psicose show very similar reactivity. The trends for fructose and sorbose show a similar pattern, though both are less reactive than tagatose and psicose. A similar reactivity trend in water was observed previously, though a full comparison is impossible as psicose was not tested in that study.^[15]

The yields of HMF over time are shown in Figure 2. The HMF yield shows a clear optimum in all cases; for both acid concentrations, the HMF yield is the highest for psicose, followed by

Figure 2. The yields of HMF versus reaction time for fructose ($\blacktriangle$), sorbose ($\bullet$), tagatose ($\blacklozenge$) and psicose ($\blacktriangledown$) at 65 g L^{-1} substrate in methanol at $100\text{ }^{\circ}\text{C}$ with (a) 17 and (b) 34 mM H_2SO_4 .

tagatose, fructose and sorbose. In contrast to sugar dehydration in water,^[15] the HMF yield decreases over time at low conversions. This is mainly caused by the acid-catalysed methylation of HMF to methoxymethylfurfural (MMF)^[16] and, at this early stage of the reaction, not to the subsequent conversion to LA and ML. The MMF yield (Figure 3) is also consistently the highest for psicose, followed by tagatose and fructose with approximately equal values and then sorbose. The highest MMF yield was approximately 55% from psicose. For fructose and tagatose, the maximum MMF yield was approximately 43%, and that for sorbose was only approximately 25%.

Figure 3. The yields of MMF versus reaction time for fructose ($\blacktriangle$), sorbose ($\bullet$), tagatose ($\blacklozenge$) and psicose ($\blacktriangledown$) at 65 g L^{-1} substrate in methanol at $100\text{ }^{\circ}\text{C}$ with (a) 17 and (b) 34 mM H_2SO_4 .

The combined yield of HMF and MMF (abbreviated as RMF) is of particular importance for this study. If the RMF yield is plotted against the sugar conversion (Figure 4), a clear trend is visible for each hexose, irrespective of the acid concentration. This reveals that the acid concentration does not have a measurable influence on the selectivity to RMF; instead, the selectivity depends on the conversion and the type of substrate. This is in line with a previous study in water.^[15] A comparison of the

Figure 4. The yields of RMF versus sugar conversion for fructose ($\blacktriangle$), sorbose ($\bullet$), tagatose ($\blacklozenge$) and psicose ($\blacktriangledown$) at 65 g L^{-1} substrate in methanol at $100\text{ }^{\circ}\text{C}$ for all reaction times with 17 or 34 mM H_2SO_4 .

results for the four hexoses reveals clearly that the selectivity to RMF is consistently higher for fructose and psicose than for sorbose and tagatose. At conversions below 80%, the selectivity to RMF is comparable for psicose and fructose. The same can be said for tagatose and sorbose at conversions below 65%. At conversions over 80%, the RMF yield from psicose is consistently higher than that for fructose. This results in a maximum RMF yield of approximately 55% from psicose, whereas the maximum yield from fructose is approximately 45%. The observed differences in selectivity between the four ketoses could be caused by the differences in the rate of RMF formation and competing side-reactions.

A known side-reaction for the dehydration of sugars is the formation of 2-hydroxyacetylfruran (Scheme 1).^[17–20] Therefore, attempts were made to identify and quantify HAF in the product samples. An additional peak in the ultra-performance liquid chromatography (UPLC) chromatogram was observed next to that of HMF with a similar UV spectrum. Spiking UPLC and GC–MS experiments with pure HAF confirmed the presence of HAF. In addition to HAF, its methyl ether (2-methoxyacetylfruran, MAF), was also observed. The formation of MAF in sugar dehydration reactions has not been reported previously, though it is a known compound.^[21]

Both HAF and MAF were only formed in significant amounts from sorbose and tagatose (Figure 5). The yields of both are consistently higher for sorbose than for tagatose. HAF is by far the major component; thus, the methylation of HAF to MAF appears relatively slow on the timescale of the experiments. This is notably different to the behaviour of HMF, which converts readily into MMF under the reaction conditions (Figures 2 and 3). The sum of the HAF and MAF yields is at a maximum of approximately 8% for sorbose at 150 min with 17 mM H_2SO_4 (Figure 5a) or at 75 min with 34 mM H_2SO_4 (Figure 5b).

In the dehydration of sugar to furanics, the yield is limited by two important side-reactions, namely, the hydration of HMF to levulinic acid (LA) and the formation of humins. Brown solid materials were not present after the reactions; therefore, any humins formed are soluble, which hampers their quantification. As the reactions were performed in methanol under

Figure 5. The yields of HAF (red) and MAF (blue) versus reaction time for sorbose (●) and tagatose (▲) at 65 g L⁻¹ substrate in methanol at 100 °C with (a) 17 and (b) 34 mm H₂SO₄.

acidic conditions, LA was mainly present as its methyl ester (ML), and the LA yields were consistently below 1%. The ML yield is a clear function of time and, as expected, ML is formed particularly at longer reaction times (Figure S1, Supporting Information). In Figure 6, the yield of ML is plotted against the

Figure 6. The yields of methyl levulinate versus the combined yields of HMF and MMF for fructose (▲), sorbose (●), tagatose (◆) and psicose (▼) at 65 g L⁻¹ substrate in methanol at 100 °C for all reaction times with 17 or 34 mm H₂SO₄.

RMF yield, and the different trends for the different ketoses can be seen clearly. This relates the maximum obtainable RMF yield to the formation of levulinates. At the same RMF yield, psicose shows clearly the lowest yield of methyl levulinate (ML), followed by fructose and tagatose with comparable values and sorbose with by far the highest yield of ML relative to the RMF yield. The rate of RMF formation (Figure S2) is the highest for psicose, followed by fructose and tagatose with approximately equal values and sorbose with clearly the lowest formation rate of RMF. The combination of this information with the observations from Figure 6 shows that a high rate of RMF formation is favoured for high RMF yields. This can be explained by a simplified reaction pathway through a two-step consecutive reaction (Scheme 3) involving the dehydration of

Scheme 3. Simplified reaction network for the conversion of hexose to MMF and ML.

the sugar to MMF (step 1) and the formation of ML (step 2). The experimental data reveal that k_1 is a function of the sugar substrate. On the basis of this scheme, k_2 should not be a function of the sugar substrate. As such, a higher reactivity of the sugar (higher k_1) is expected to lead to higher RMF yields, as was also shown experimentally in this research.

The sum of all measured products (HMF, MMF, HAF, MAF, furfural, ML and LA) is plotted against the hexose conversion in Figure 7, in which the maximum attainable yield is also shown (100% mass balance). Interestingly, below 80% conversion, the trend for the sum of measured products versus conversion for

Figure 7. The sums of the yields of HMF, MMF, HAF, MAF, furfural, LA and ML versus the sugar conversions for fructose (▲), sorbose (●), tagatose (◆) and psicose (▼) at 65 g L⁻¹ substrate in methanol at 100 °C for all reaction times with 17 or 34 mm H₂SO₄. The dashed line represents 100% mass balance.

each sugar is approximately parallel to the 100% mass balance line. However, the difference between the measured yields and the 100% mass balance closure line is significant; therefore, other unidentified products are formed as well. The GC chromatograms were checked for known sugar decomposition products, and small traces of the retro-aldol products lactic acid and dihydroxyacetone were observed.^[22,23] These added up to less than 0.1% yield and, therefore, did not play a significant role.

The fructose trend is consistently 20% below the 100% mass balance line, but the total identified yield line moves closer to the 100% mass balance line at higher conversions. This is an important observation as it suggests the presence of unidentified intermediates in the early stages of the reaction that are converted later to RMF and ML rather than humin-type byproducts. Fructose forms dimers, so-called difructose dianhydrides;^[24] therefore, the other ketoses are also probably prone to dimerisation. As the reactions were performed in methanol, the initial absence of water would favour these re-

versible dimerisation reactions. This reduces the determined mass balance at low conversions, in line with the experimental data. It also suggests that the formation of humin, a major by-product in water, is suppressed considerably in methanol and that the amounts of humins are at most 20–30% at high sugar conversion (with the assumption that all unknowns are humins and not unidentified methanol-soluble compounds). For example, for psicose, the most reactive hexose with the highest attainable RMF yield, the amount of unidentified products is approximately 10–15% at psicose conversions higher than 90%; therefore, humin formation is less than 10%.

Additionally, the results in Figure 7 show that the trend in the total product yields for psicose and fructose is comparable. For psicose and fructose, the combined yields of furanics and levulinates follow approximately the same trend versus the conversion. Therefore, the lower yields of furanics at higher conversions from fructose (Figure S3) are compensated completely by the additional amount of ML formed. As levulinates are generally considered to be formed from HMF/MMF species, they should be considered as a product in the RMF reaction pathway.^[1] As only the ratio of RMF and ML differs and not their combined yield, the selectivities of psicose and fructose towards the RMF pathway are approximately identical. Therefore, the conversion rates of these two sugars to RMF have no measurable influence on the selectivity towards the RMF pathway (Scheme 1) relative to other available sugar conversion routes, such as humin formation.

The total product yields for tagatose and sorbose follow a similar trend, though the total yields of identified products are consistently lower than those for psicose and fructose. Both tagatose and sorbose form significant amounts of HAF and MAF, whereas only traces of HAF and MAF were observed for psicose and fructose. This indicates the existence of a parallel reaction pathway to HAF/MAF for tagatose and sorbose. As such, the lower amount of total identified products for tagatose and sorbose compared with those for psicose and fructose could be (partly) caused by additional side-reactions in the HAF formation pathway.

It is of interest to compare the results from the current study with the results we reported recently for the dehydration of three of the four ketoses in water, catalysed by sulphuric acid.^[15] The reactivity of the ketoses is clearly higher in methanol than in water. In methanol, significantly less severe conditions were applied (100 °C, 17 or 34 mm H₂SO₄) to obtain comparable conversion levels to those in the previous study in water (120 °C, 100 mm H₂SO₄). In water, the experiments were performed with tagatose, fructose and sorbose. Tagatose was far more reactive than fructose and sorbose, which is in line with the data reported here for the reaction in methanol. Thus, the reactivity patterns for the three ketohexoses in methanol

are in line with the results obtained previously in water. The study in water was combined with DFT calculations to relate the structures of the ketoses to their reactivity. The DFT calculations were in line with the experimental reactivity data for tagatose, fructose and sorbose, and psicose was predicted to be the least reactive ketose. These conclusions were based on the differences in the calculated stabilities of the proposed intermediate carbocations. The current experimental study shows that psicose is not the least reactive in methanol but is as reactive as tagatose.

An important difference between the reactions in water and methanol can be found in the rate of RMF formation from fructose relative to that from tagatose. In water, the HMF yields at the same reaction time were higher for tagatose than for fructose, whereas the RMF yields in methanol over time are comparable. This could be caused by the difference of the orientation of the hydroxy group at C4, which is the key difference (Scheme 2). The formation of HMF is slower in water than in methanol.^[15] This suggests that the interaction of the sugar with water has a stronger negative effect on the HMF formation rate if the hydroxy group at C4 is pointed down than if it is pointed up (Scheme 2). The same relative drop in rate would be expected for psicose relative to tagatose for the reactions in water. Water has a higher capacity to form hydrogen bonds than methanol and is, therefore, more likely to disrupt intramolecular hydrogen bonds within the sugars. This makes it plausible that an intramolecular hydrogen bond with the C4 hydroxy group is important for the formation of HMF.

Mechanistic considerations and ¹³C labelling experiments with sorbose

The observed differences in reactivity of the four ketoses to furanics in methanol are remarkable. The ketoses differ only in the orientations of the hydroxy groups at C3 and C4 (Scheme 2). If the hydroxy groups are *cis*-oriented in the Fischer projection and, therefore, also in the furanose structures, the conversion rate is higher than that for the *trans* orientation of these hydroxy groups. This implies that the relative orientation of the hydroxy groups at C3 and C4 is a key factor for the conversion rate of the sugars and that it plays a major role in the rate-determining step of the reaction sequence. This suggests strongly that the C3–C4 bond lacks free rotation in the rate-determining step. As such, reaction mechanisms with cyclic intermediates (Scheme 4) make more sense than reaction mechanisms with acyclic intermediates, as the relative orientation of the latter is of less importance owing to the free rotation of the C–C bonds. This cyclic mechanism was also considered the most appropriate to explain the differences in

Scheme 4. The dehydration of fructose through cyclic intermediates, as proposed in Ref. [1].

the reactivity of ketohexoses and aldohexoses in water with sulfuric acid as the catalyst.^[15]

The formation of HAF and MAF was only observed in significant amounts for tagatose and sorbose, both of which have the same orientation of the hydroxy group at C4 (Scheme 2). This suggests that the orientation of the hydroxy group at C4 plays a key role in the formation of HAF and MAF.

An experiment with L-[6-¹³C]sorbose was performed to gain insights into the reaction pathways from sorbose to HAF and HMF/MMF. Sorbose was used because it yielded the highest amount of HAF/MAF of all ketohexoses tested. The experiments were performed with 17 mM H₂SO₄ for 150 min at 100 °C, as these conditions gave the highest HAF yields (7%, MAF 2% and MMF ≈ 25%). A ¹³C NMR spectrum of the reaction mixture after workup is shown in Figure 8. The largest peak at δ = 66.3 ppm is attributed to MMF, the major product of hexose dehydration in methanol under these conditions. As expected from previously proposed dehydration mechanisms,^[1] the label at C6 in sorbose ends up in the CH₂ unit of the methoxymethyl group of MMF. The significant peak at δ = 29.8 ppm corresponds to the methyl group next to the carbonyl moiety of LA. Thus, the carbonyl group of HMF/MMF is converted into formic acid. Both observations agree with NMR studies by Zhang and Weitz for fructose in water and DMSO and suggest that the formations of HMF from sorbose in methanol and fructose in water follow similar reaction pathways.^[25] The smaller peak at δ = 66.6 ppm is assigned to the hydroxymethyl group of HAF (see also Figure S4a); therefore, the label at C6 of the sorbose ends up in the hydroxymethyl group of HAF. In addition to HAF, MAF is also formed in the reaction.

The C6 peak of a representative sample of MAF is present at δ = 76 ppm (see Figure S4b). Indeed, the clear presence of this peak in the NMR spectrum of the reaction mixture indicates that the label is also present in the etherified hydroxymethyl group of MAF (Figure 8).

If the labelling is present in the furan ring, HAF resonances are expected at δ ≈ 147 ppm. Here, no significant peak was observed, and the presence of only a cluster of small peaks excludes the possibility that these originate from HAF. It is more likely that the peaks at δ ≈ 147 ppm originate from minor furan-like products, such as furfural,^[26] furan dimers and trimers, and soluble humin byproducts.^[22]

The group of very small peaks in the δ = 60–64 ppm area are expected to arise from sorbose and methyl sorbosides.^[27,28]

The interpretation of the NMR spectroscopy results for HAF formation is not straightforward. The reaction mechanism for HAF formation proposed previously involves an isomerisation to a 2,3-enediol, which would have the ¹³C label in the furan ring (Scheme 5).^[18,29]

The labelling experiments presented here do not agree with this mechanism, as the label ends up in the CH₂OR side-chain. On the basis of the observation that the orientation of the hydroxy group at C4 of the ketose plays a key role in the selectivity towards HAF formation, it is hypothesised that the pathway to HAF proceeds through a 1,4-anhydroketose (Scheme 6).

The hydroxy groups at C1 and C4 can be oriented in such a way that they are in close proximity to allow the formation of a second five-membered ring through etherification, particularly in the pyranose (six-membered ring) form but also in the α -furanose form. The hemiacetal bond in the pyranose ring

Figure 8. ¹³C NMR spectrum of the reaction mixture for the acid-catalysed dehydration of L-[6-¹³C]sorbose in methanol.

Scheme 5. Reaction mechanism for HAF formation from fructose with acyclic intermediates, as proposed in Ref. [17].

Scheme 6. Proposed formation of HAF with the involvement of a 1,4-anhydrosorbitose.

could then potentially open owing to the ring strain to form 1,4-anhydrosorbitose. This would place the labelled carbon atom (C6) at the proper position to end up in the CH₂OR side-chain of HAF. A mechanism that explains the conversion of 1,4-anhydrosorbitose to HAF is not straightforward.

Conclusions

The Brønsted acid catalysed conversions of four different 2-ketohexoses (fructose, sorbose, tagatose and psicose) in methanol were investigated to identify the most suitable precursor for 5-hydroxymethylfurfural/methoxymethylfurfural (HMF/MMF) formation and to establish hexose structure–yield relationships. Significant differences in the reactivities and selectivities were observed and quantified through kinetic experiments. Psicose and tagatose were the most reactive, and psicose gave the highest selectivity towards HMF and MMF ($\approx 55\%$ combined yield at $\approx 96\%$ conversion). As such, psicose would be the ideal monosaccharide for the production of HMF and its derivatives. However, psicose is a rare sugar, present in small amounts in wheat, *Itea* plants, processed sugar cane and beet molasses.^[30–33] For a techno-economically viable process, either a psicose-producing organism or an isomerisation process to obtain psicose from readily accessible sugars would need to be developed.^[34]

The significant differences in the reactivities of the four ketohexoses were related to their molecular structures. The hexoses differ only in the orientation of the vicinal hydroxy groups at C3 and C4; therefore, these structural differences are significant for the dehydration to both HMF/MMF and 2-hydroxyacetylfuluran (HAF). The reactivity of the sugar is determined by the relative orientation of these hydroxy groups, and the *cis* orientation leads to faster conversion than the *trans* orientation. This is best explained by a dehydration mechanism with cyclic intermediates.

The formation of HAF depends on the orientation of the hydroxy group at C4 of the ketohexose, which consequently also affects the selectivity for the HMF/MMF formation. The reaction mechanism of HAF formation was proposed to involve a 1,4-anhydroketose as an intermediate. This would have all of the carbon atoms in the right positions to form HAF, as evidenced by dehydration experiments with ¹³C-labelled sorbose.

Experimental Section

Chemicals: D-Fructose, L-sorbose, D-tagatose (>99%), sulfuric acid (96%), 1,4-dioxane (99.8%), CDCl₃ (99.8%) and saccharin (98%) were purchased from Sigma–Aldrich; D-psicose and L-[6-¹³C]sorbose (99.9%) were purchased from Carbosynth; 2-hy-

droxyacetylfuluran (HAF, 95%) was purchased from Otava Ltd.; acetonitrile (HPLC-S grade) was purchased from Biosolve; and methanol (HPLC grade) was purchased from Fisher. Milli-Q quality water was used for all sample preparations.

High-throughput experiments: All experiments were performed with a substrate concentration of 65 g L^{−1} (0.36 M) and with two sulfuric acid concentrations (17 and 34 mM) at 1 mL scale in methanol under 20 bar N₂ at 100 °C. An Avantium Quick Catalyst Screening system was used. After the appropriate reaction time, the reactor blocks were cooled in an ice bath. The reactors were opened, and an external standard solution (4 mL) containing saccharin (UPLC, 5.63 g L^{−1}) and 1,4-dioxane (GC, 3.75 g L^{−1}) in 1:1 acetonitrile/water was added to each reactor. These mixtures were analysed by GC and diluted in water (25 times) for UPLC analysis. For GC analysis, the mixtures were neutralised with aqueous NaOH solution (1 M, 10–30 μ L, depending on the acid content of the sample). The level of neutralisation was checked with pH paper.

Synthesis of 2-methoxyacetylfuluran: 2-Methoxyacetylfuluran (MAF) was synthesised by reacting 2-hydroxyacetylfuluran (HAF) under the reaction conditions described for the high-throughput experiments, except that H₂SO₄ concentrations of 17, 34 and 67 mM were applied at a fixed reaction time of 60 min. The reaction mixtures were analysed by GC–MS to confirm MAF formation. These mixtures were used subsequently to confirm the retention time of MAF under the UPLC and GC conditions.

Chromatographic analysis: The analysis of sugars and furanics was performed with a Waters Acquity UPLC instrument equipped with an Acquity UPLC BEH C18 (2.1 $\times$ 5.0 mm, 1.7 μ m) column. A mobile phase (0.6 mL min^{−1}) with acetonitrile/methanol (1:1, A) and water (0.2 wt % TFA, B) was used with a gradient from 98% A and 2% B to 2% A and 98% B. The sugars were detected with an evaporative light scattering detector (ELSD), and HMF was detected with a photodiode array detector (PDA) at $\lambda = 230$ nm. Saccharine was used as the external standard and was measured at $\lambda = 250$ nm and in the ELSD for sugar analysis. As the reactions were performed in alcohols, the remaining sugars were mostly present in methylated form. These methylated sugars were categorised as unconverted sugars, as they are known to convert to furanics.^[13] Levulinic acid and methyl levulinate were analysed with an Inter-science Trace GC instrument with an Agilent J&W FactorFour VF-WAXms (30 m $\times$ 0.25 mm, 0.25 μ m) column with a flame ionisation detector (FID) and 1,4-dioxane as the external standard. The GC was operated at a temperature of 250 °C at a constant flow of 2 mL min^{−1}. GC–MS (Thermo Scientific traceGC, DSQ II mass detector) was used to confirm the formation of HAF and MAF. Ion-source and transfer-line temperatures of 250 °C were used. The equipment was calibrated with pure compounds. The UPLC response factor for MAF was estimated from the known response factors for HAF, HMF and MMF. The response factors of the latter two were shown to be related to the molecular weights, and the response-factor ratio of the two was equal to their molecular-weight ratio. Therefore, the response factor of MAF was calculated from that of HAF by using a correction for the difference in molecular weight.

Experiments with L-[6-¹³C]sorbose: Three experiments with L-[6-¹³C]sorbose were performed at 1 mL scale with the substrate (65 g L^{−1}) and 17 mM H₂SO₄ in methanol for 150 min at 100 °C and 20 bar N₂. After the reaction, the samples were combined and neu-

tralised with NaOH_(aq) (8.1 mg, 50 wt%, 0.10 mmol) in methanol (1.5 mL). All volatiles were then removed under reduced pressure (5 mbar, 35 °C) to afford a brown residue. CDCl₃ (1.0 mL) was added to the residue, and the resulting suspension was filtered through a syringe filter (Millex FH 0.45 µm) before measurement. The ¹H and ¹³C (inverse-gated decoupled) NMR spectra of samples in CDCl₃ were recorded with a Bruker Avance 500 (125.78 MHz for ¹³C, 2048 scans, 2.0 s delay time) digital NMR spectrometer with a Cryo Platform. The signal of the residual hydrogen atoms of CDCl₃ (δ = 7.22 ppm) was used to reference the spectra.

Acknowledgements

The majority of the work was performed with financial support from the European Community under the seventh framework programme (Project SPLASH, contract no. 311956). Part of the work was financed by Avantium Chemicals.

Keywords: biomass • carbohydrates • oxygen heterocycles • isotopic labelling • reaction mechanisms

- [1] R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev.* **2013**, *113*, 1499.
- [2] J. J. Bozell, G. R. Petersen, *Green Chem.* **2010**, *12*, 539.
- [3] B. Girisuta, L. P. B. M. Janssen, H. J. Heeres, *Green Chem.* **2006**, *8*, 701.
- [4] B. Girisuta, L. P. B. M. Janssen, H. J. Heeres, *Chem. Eng. Res. Des.* **2006**, *84*, 339.
- [5] B. Girisuta, L. P. B. M. Janssen, H. J. Heeres, *Ind. Eng. Chem. Res.* **2007**, *46*, 1696.
- [6] Y. Román-Leshkov, C. J. Barrett, Z. Y. Liu, J. A. Dumesic, *Nature* **2007**, *447*, 982.
- [7] A. J. J. E. Eerhart, A. P. C. Faaij, M. K. Patel, *Energy Environ. Sci.* **2012**, *5*, 6407.
- [8] E. de Jong, M. A. Dam, L. Sipos, G. J. M. Gruter in *ACS Symposium Series 1105: Biobased Monomers, Polymers, and Materials* (Eds.: P. B. Smith, R. Gross), American Chemical Society, Washington, DC, **2012**, pp. 1–13.
- [9] S. K. Burgess, J. E. Leisen, B. E. Kraftschik, C. R. Mubarak, R. M. Kriegel, W. J. Koros, *Macromolecules* **2014**, *47*, 1383.
- [10] B. Girisuta, PhD thesis, University of Groningen, **2007**.
- [11] I. van Zandvoort, Y. Wang, C. B. Rasrendra, E. R. H. van Eck, P. C. A. Bruijninx, H. J. Heeres, B. M. Weckhuysen, *ChemSusChem* **2013**, *6*, 1745.
- [12] G. J. M. Gruter, F. Dautzenberg (Avantium International BV), WO2007104514, **2007**.
- [13] A. S. Dias, R.-J. van Putten, G. J. Gruter (Furanix Technologies), WO2012091570, **2012**.
- [14] R.-J. van Putten, J. G. Winkelman, F. Keihan, J. C. van der Waal, E. De Jong, H. J. Heeres, *Ind. Eng. Chem. Res.* **2014**, *53*, 8285.
- [15] R.-J. van Putten, J. N. M. Soetedjo, E. A. Pidko, J. C. Van der Waal, E. J. M. Hensen, E. De Jong, H. J. Heeres, *ChemSusChem* **2013**, *6*, 1681.
- [16] M. Bicker, D. Kaiser, L. Ott, H. Vogel, *J. Supercrit. Fluids* **2005**, *36*, 118.
- [17] R. E. Miller, S. M. Cantor, *J. Am. Chem. Soc.* **1952**, *74*, 5236.
- [18] D. W. Harris, M. S. Feather, *Tetrahedron Lett.* **1972**, *13*, 4813.
- [19] K. Heyns, R. Hauber, *Liebigs Ann. Chem.* **1970**, *733*, 159.
- [20] L. Rigal, A. Gaset, *Biomass* **1983**, *3*, 151.
- [21] R. M. Moriarty, O. Prakash, M. P. Duncan, R. K. Vaid, H. A. Musallam, *J. Org. Chem.* **1987**, *52*, 150.
- [22] T. M. Aida, K. Tajima, M. Watanabe, Y. Saito, K. Kuroda, T. Nonaka, H. Hattori, R. L. Smith Jr., K. Arai, *J. Supercrit. Fluids* **2007**, *42*, 110.
- [23] I. V. Delidovich, A. N. Simonov, O. P. Taran, V. N. Parmon, *ChemSusChem* **2014**, *7*, 1833–1846.
- [24] T. J. Christian, M. Manley-Harris, R. J. Field, B. A. Parker, *J. Agric. Food Chem.* **2000**, *48*, 1823.
- [25] J. Zhang, E. Weitz, *ACS Catal.* **2012**, *2*, 1211.
- [26] R. K. M. R. Kallury, C. Ambidge, T. T. Tidwell, D. G. B. Boocock, F. A. Agblevor, D. J. Stewart, *Carbohydr. Res.* **1986**, *158*, 253.
- [27] S. J. Angyal, G. S. Bethell, *Aust. J. Chem.* **1976**, *29*, 1249.
- [28] K. Bock, C. Pedersen, *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27.
- [29] B. F. M. Kuster, *Starch/Stärke* **1990**, *42*, 314.
- [30] B. S. Miller, T. Swain, *J. Sci. Food Agric.* **1960**, *11*, 344.
- [31] W. W. Binkley, *Int. Sugar J.* **1963**, *65*, 105.
- [32] A. Hossain, F. Yamaguchi, T. Matsunaga, Y. Hirata, K. Kamitori, Y. Dong, L. Sui, I. Tsukamoto, M. Ueno, M. Tokuda, *Biochem. Biophys. Res. Commun.* **2012**, *425*, 717.
- [33] S. H. Baek, S. J. Park, H. G. Lee, *J. Food Sci.* **2010**, *75*, H49.
- [34] K. Izumori, M. Yamakita, T. Tsumura, H. Kobayashi, *J. Ferment. Bioeng.* **1990**, *70*, 26.

Received: February 25, 2016

Published online on June 17, 2016