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# Dehydration of Different Ketoses and Aldoses to 5-Hydroxymethylfurfural

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5-Hydroxymethylfurfural (HMF) is considered an important building block for future bio-based chemicals. Here, we present an experimental study using different ketoses (fructose, sorbose, tagatose) and aldoses (glucose, mannose, galactose) under aqueous acidic conditions ( $65 \text{ g L}^{-1}$  substrate, 100–160 °C, 33–300 mm H<sub>2</sub>SO<sub>4</sub>) to gain insights into reaction pathways for hexose dehydration to HMF. Both reaction rates and HMF selectivities were significantly higher for ketoses than for aldoses, which is in line with literature. Screening and kinetic experiments showed that the reactivity of the different ketoses

is a function of the hydroxyl group orientation at the C3 and C4 positions. These results, in combination with DFT calculations, point to a dehydration mechanism involving cyclic intermediates. For aldoses, no influence of the hydroxyl group orientation was observed, indicating a different rate-determining step. The combination of the knowledge from the literature and the findings in this work indicates that aldoses require an isomerization to ketose prior to dehydration to obtain high HMF yields.

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## Introduction

The replacement of fossil feedstocks with sustainable resources for energy generation, transportation fuels, bulk and fine chemicals, and materials is currently considered as a pivotal challenge, receiving increasing social and scientific interest. To achieve this, alternative sources of organic carbon need to be found. Biomass is an attractive option as it is the most abundant non-fossil source of organic carbon. Biomass mainly comprises carbohydrates, lignin, fatty acids, lipids, and proteins. Carbohydrates represent the largest fraction of biomass, predominantly present in polymeric form (cellulose, hemi-cellulose, starch, inulin) and are built up from hexoses (glucose, fructose, mannose, galactose) and pentoses (arabinose, xylose). The acid-catalyzed dehydration of pentoses<sup>[1,2]</sup> and hexoses<sup>[3]</sup> leads to the formation of furfural and 5-hydroxymethylfurfural (HMF), respectively, along with many by-products. Both molecules, and derivatives thereof, are in Bozell's 'Top 10+4' list of bio-based chemicals and are considered to be key components

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in the development of a bio-based economy.<sup>[4]</sup> This has led to an enormous increase in research published on acid-catalyzed dehydration of sugars over the last decade.<sup>[2,3]</sup>

Both furfural and 5-hydroxymethylfurfural (HMF) can be used in different application areas. Furfural has high potential in fuel and solvent applications. HMF is considered a promising platform chemical due to its high derivatization potential. It can be converted to a wide range of interesting bulk and fine chemicals, for instance, as a monomer for new bio-based polymers. Avantium is currently developing a process for the production of polyethylenefurandicarboxylate (PEF) from C<sub>6</sub> sugars as a next-generation replacement material for polyethyleneterephtalate (PET), having improved barrier properties.<sup>[5]</sup>

Attention to the development of highly efficient routes to HMF has strongly increased in recent years.<sup>[3]</sup> Glucose or glucose-based oligomers and polymers, especially those derived from lignocellulosic sources, are favored feedstocks due to their availability and presence in agricultural side streams and other waste.<sup>[6]</sup> The vast majority of experimental studies, however, show that fructose, a ketose, is much more efficiently dehydrated to HMF than glucose, an aldose. Under aqueous acidic conditions, fructose yields a maximum of around 50% HMF at best because of the formation of polymeric material, known as humins, and hydration of HMF to levulinic and formic acids (Scheme 1).<sup>[3,7,8]</sup> For glucose, the maximum HMF yield is only around 5%. Higher HMF yields from fructose (>80%) have been reported in other solvent systems, especially in ionic liquids and aprotic polar solvents such as DMSO.<sup>[3]</sup> Work on glucose dehydration with heterogeneous base/acid bi-catalytic systems,<sup>[9]</sup> chromium-catalyzed glucose dehydration in ionic liquids<sup>[10,11]</sup> and organic solvents,<sup>[12]</sup> and other catalysts,<sup>[13]</sup> indicate that, apart from an acid, an additional catalyst



Scheme 1. Hydration of HMF to levulinic acid and formic acid.

is required to efficiently dehydrate glucose to HMF. This additional catalyst is generally believed to facilitate the isomerization of glucose to fructose prior to dehydration to HMF.<sup>[3]</sup>

To improve the yields, significant steps must be made in the development of catalysts, preferably heterogeneous in nature. To do so, a detailed knowledge of the reaction mechanism of the main and side reactions is required. A number of reaction mechanisms have been proposed for the dehydration reaction in water, though no definitive evidence has yet been found to confirm these.<sup>[3]</sup> The postulated mechanisms can be divided into mechanisms with cyclic (Scheme 2) or acyclic intermediates (Scheme 3).



Scheme 4. Ketoses used in this study.



Scheme 5. Aldoses used in this study.

First a high-throughput screening study was performed at a range of temperatures, acid concentrations, and reaction times to identify trends in reactivity for various ketoses and



Scheme 2. Proposed dehydration mechanism with cyclic intermediates.



Scheme 3. Proposed dehydration mechanism with acyclic intermediates.

Knowledge about the effect of the relative orientation of the hydroxyl groups of different ketoses and aldoses on the dehydration rate and selectivity to HMF is scarcely available in the literature. Seri et al. reported a lower HMF yield from sorbose than from fructose in DMSO, though no conversion data were provided.<sup>[14]</sup> Determination of the influence of the orientation of hydroxyl groups in hexoses could very well provide new insights into the mechanisms of ketose and aldose dehydration. For this reason the acid-catalyzed dehydration of fructose, sorbose, and tagatose (all ketoses, Scheme 4), as well as glucose, mannose, and galactose (all aldoses, Scheme 5) in an aqueous environment was studied by using sulfuric acid as the catalyst. A complementary, integrated research strategy was applied.

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aldoses. Subsequently, a detailed kinetic study at relevant process conditions, established in the screening, was performed to determine the kinetic constants and activation energies for the rate of reaction of the various hexose feeds. Finally, DFT calculations were performed, the results of which were compared with the experimental data.

### **Results and Discussion**

#### High-throughput screening

To determine trends in the reactivity of ketoses (fructose, tagatose, and sorbose), a highthroughput screening in a batch mode was performed. Experiments were performed at 100, 120, and 140 °C in water containing 33, 100, or 300 mM sulfuric acid at 30, 45, and 60 min reac-

tion time and a fixed initial hexose concentration of  $65 \text{ gL}^{-1}$  (0.36 M). The results for the experiments at 120 °C with 100 mM sulfuric acid are given in Figure 1 and Figure 2. In Figure 1, the conversion of the three ketoses is plotted against the reaction time. After 30 min, over 60% of the tagatose is converted, compared to around 40% conversion for fructose and sorbose. After 60 min, over 90% of the tagatose is converted, whereas around 70% of fructose and less than 60% of sorbose is converted. This shows a clear difference in reaction rates between the ketoses, with tagatose by far the most reactive. This trend was observed for the entire dataset, see the Supporting Information for more details (Figure S1–S3, the Supporting Information).



Figure 1. Conversion of fructose (▲), tagatose (■), and sorbose (●) (65 gL<sup>-1</sup>) against time at 120 °C with 100 mM aqueous sulfuric acid. Duplicate experiments are shown.



**Figure 2.** HMF yield from fructose ( $\blacktriangle$ ), tagatose ( $\blacksquare$ ), and sorbose ( $\bigcirc$ ) (65 gL<sup>-1</sup>) against time at 120 °C with 100 mM aqueous sulfuric acid. Duplicate experiments are shown.

The HMF yield over time at 120 °C with 100 mM sulfuric acid is given in Figure 2. The graph shows that, under these conditions, the HMF yield is consistently the highest for tagatose. The HMF yield increases in time up to about 40% at a conversion of around 85% (Figure 1) and then remains constant as a result of the subsequent decomposition of HMF to levulinic acid and formic acid. The HMF yields from fructose and sorbose are equal after 30 min (around 22%) and increase to 35% and 28%, respectively, after 60 min reaction time.

The experimental results for the high-throughput screening of the ketoses, exemplified by Figure 1 and Figure 2, indicate that tagatose possesses the highest reactivity for the acid-catalyzed dehydration in the entire process window. The difference in reaction rate between fructose and sorbose is very small and within the error of experimentation. The key difference between the ketoses tested is the orientation of hydroxyl groups on the C3 and C4 position. This is a strong indication that the stereochemistry at C3 and C4 has a significant influence on the reactivity.

Under reaction conditions in which hexose conversion is complete, the HMF yield from tagatose is consistently lower than the HMF yield from fructose and sorbose under the same conditions (Figure S4, the Supporting Information). This can be explained by the higher reaction rate of tagatose. As a result, the subsequent HMF decomposition to, among others, levulin-



**Figure 3.** HMF yield against conversion for fructose ( $\blacktriangle$ ), tagatose ( $\blacksquare$ ), and sorbose ( $\bigcirc$ ). Experiments were performed at 100, 120 and 140 °C with 33, 100, or 300 mM H<sub>2</sub>SO<sub>4</sub> at 30, 45, and 60 min reaction time. Duplicate experiments are shown.

ic and formic acid also occurs to a larger extent, leading to lower HMF yields.  $^{\left[7,8\right]}$ 

Figure 3 provides an overview of all experimental data obtained in the high-throughput screening. The experimental error in some cases is rather large because of the fact that this was a screening with the purpose of identifying general trends for detailed kinetic experiments. The maximum attainable yield of HMF is about the same for all three ketoses within the margin of error, and is around 40–45% at 90% conversion. This is in the lower range of the general trends reported in the literature for acid-catalyzed fructose dehydration in water.<sup>[3]</sup>



**Figure 4.** Levulinic acid yield against conversion for fructose ( $\blacktriangle$ ), tagatose ( $\blacksquare$ ), and sorbose ( $\bullet$ ). Experiments were performed at 100, 120 and 140 °C with 33, 100 or 300 mM H<sub>2</sub>SO<sub>4</sub> at 30, 45 and 60 min reaction time. Duplicate experiments are shown.

Figure 4 shows a strong increase in levulinic acid yield at high conversions. Together with the decrease in HMF yield at high conversions (Figure 3), this confirms that, at high conversion, the HMF yield is reduced by a consecutive reaction to levulinic acid and formic acid, as described in the literature.<sup>[3,7,8]</sup>

Apart from the ketoses discussed above, three aldoses were also screened in batch mode at similar conditions as for the ketoses. Glucose, mannose, and galactose were reacted at 120, 140, and 160 °C with 33, 100, and 300 mM sulfuric acid for 30–60 min. A higher temperature range was selected because glucose is known to be less reactive than fructose.<sup>[3]</sup> The observed maximum HMF yield was around 5%, at conversions of 30–70%, which is in line with the majority of the literature.<sup>[3]</sup>

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Furthermore, no clear differences in aldose conversion rates or selectivities to HMF were observed for the three aldoses. This indicates that the orientation of the hydroxyl groups does not affect the dehydration rate of the aldoses, which suggests that the acid-catalyzed aldose dehydration possesses a different rate-determining step than the acid-catalyzed ketose dehydration.

#### **Kinetic study**

The screening results indicated clear differences in the reactivity of the three ketoses. In the next step, kinetic experiments were performed to quantify the differences in reactivity of the ketoses at 137 °C with 33, 100, and 300 mM sulfuric acid in a time frame of 0–90 min. The experiments were performed in a batch mode using glass ampoules. At t=0 min, the ampoules were placed in an oven at 137 °C and allowed to react for a predetermined time. The experimental data were modeled using a simple kinetic expression assuming first order in sugar concentration and acid concentration [Eqs. (1) and (2)].

$$r = -k[Sugar][H_2SO_4]$$
(1)

$$k = k_{rot} e^{-\left(\frac{E_s}{R}\right) \times \left(\frac{1}{T_{rest}} - \frac{1}{T_{rest}}\right)}$$
(2)

$$T_{\text{real}} = T_{\text{ref}} - (T_{\text{ref}} - T_{\text{i}}) \mathbf{e}^{(-\text{ht})}$$
(3)

Here,  $k_{ref}$  describes the reaction rate constant at 137 °C ( $T_{ref}$ ) and  $T_i$  is the initial temperature (25 °C). At the initial stage of the reaction, the temperature is not constant as it takes typically 5–10 min to reach 137 °C. This effect was compensated for by extending the model with an energy balance. After integration, Equation (3) is obtained, which, combined with the mass balances in batch for the hexoses, allows calculation of the concentration and the temperature as a function of the batch time. The value for the parameter *h* [0.2135 min<sup>-1</sup>, Eq. (3)] was determined independently.<sup>[7]</sup>

In Figure 5 the experimental data points (137 °C, 33 mm sulfuric acid) and the model line for the three ketoses are provided. Agreement between model and experimental data is very satisfactory (c.f.  $R^2$  values and the error in  $k_{1ref}$  as seen in Table 1). The results from the kinetic study are in line with the screening experiments, with tagatose being the most reactive



**Figure 5.** The concentration of sugar in time at  $137 \degree C$  with 33 mM sulfuric acid, with the points describing the experimental results [fructose ( $\blacktriangle$ ), tagatose ( $\blacksquare$ ), and sorbose ( $\bigcirc$ )] and the lines describing the model.

Table 1. Kinetic data for the acid-catalyzed dehydration of different ketoses.						
Ketose $k_{ref}$ [Lmol <sup>-1</sup> min <sup>-1</sup> ]		$E_a$ [kJ mol <sup>-1</sup> ]	R <sup>2</sup>			
sorbose	0.9±0.2	138±41	0.976			
fructose	$0.9 \pm 0.1$	$124\pm22$	0.989			
tagatose	2.0±0.6	89±15	0.990			

ketose. This is clearly illustrated by the significantly higher  $k_{\rm 1ref}$  value and significantly lower  $E_{\rm a}$  value for acid-catalyzed dehydration of tagatose than for the acid-catalyzed dehydration of fructose and sorbose. The  $k_{\rm 1ref}$  and  $E_{\rm a}$  values for sorbose and fructose dehydration are essentially equal within the experimental error.

Figure 6 shows the yield against the conversion for all kinetic experiments. For fructose and tagatose, the general trend is the same as for the experiments in the high-throughput



**Figure 6.** The HMF yield plotted against conversion for the kinetic studies using the three ketoses at 137 °C with 33, 100, and 300 mM acid at 0–90 min [fructose ( $\blacktriangle$ ), tagatose ( $\blacksquare$ ), and sorbose ( $\bigcirc$ )].

screening, with approximately 55% selectivity up to around 60% conversion and a maximum HMF yield of just over 40% at around 85% conversion. The trend for sorbose, however, is different. At conversions higher than 30%, the HMF yield line for sorbose is below that of the other two ketoses. This indicates that additional reactions are involved in sorbose dehydration. This effect was not observed in the screening, presumably due to analytical issues (e.g., overlapping product peaks). Further research is in progress to identify additional reaction products.

#### **DFT calculations**

To gain insights into the origin of the experimentally observed differences in reactivity between the three ketoses, model DFT calculations were performed. It has previously been proposed that the reactivity and selectivity of the acid-catalyzed hexose conversion is determined by the regeoselectivity of the initial protonation and the accompanying dehydration step.<sup>[15]</sup> A characteristic aspect of fructofuranose dehydration by Brønsted acids is the preferred protonation of the OH group at the anomeric C2 carbon (Figure 7a) that initiates a sequence of fast reactions towards HMF. In the case of glucose conversion, the initial protonation site is the anomeric hydroxyl at C1. Howev-



**Figure 7.** (a) Furanose dehydration initiated by the preferred protonation of the anomeric hydroxyl group and (b) the optimised structures of the cationic dehydration products originating from psico-, sorbo-, fructo-, and tagatofuranose and the respective DFT-computed average Gibbs free energies of dehydration of alpha- and beta-anomers of the sugars (kJ mol<sup>-1</sup>). The arrows depict the direction of the dipole moment in the cations.

er, its activation does not lead to the desired products but rather opens pathways towards humin precursors. In both cases, the reactivity is determined by the stability of cationic intermediates resulting from the dehydration of the initial protonated complex.

Reaction Gibbs free energies ( $\Delta G^{\circ}_{298K}$ ) of the dehydration of alpha- and beta-anomers of fructo-, sorbo-, psico-, and tagato-furanose in water resulting from protonation of the anomeric hydroxyl group were calculated at the B3LYP/6-311 + G(d,p) level of theory using the Gaussian 09 program.<sup>[16]</sup> Bulk solvent effects were approximated using the polarized continuum solvent (PCM) model within the conductor reaction field (COSMO) approach.<sup>[17]</sup> The Brønsted acid was modeled as a H<sub>5</sub>O<sub>2</sub><sup>+</sup> cation.<sup>[15]</sup>

The optimized structures of the cationic sugar dehydration products and the respective  $\Delta G^{\circ}_{298K}$  values are summarized in Figure 7 b. The most favorable reaction is predicted for tagato-furanose. The free energies of fructofuranose and sorbofuranose dehydration are very similar and are substantially higher than that computed for psicofuranose, which was not included in the experimental study. Interestingly, it appears that the computed  $\Delta G^{\circ}_{298K}$  values correlate with the direction of the dipole moment in the dehydration products. The most stable cationic species is formed when the dipole moment is oriented parallel to the furanose ring (tagatofuranose). Deviations from such an orientation lead to the destabiliza-

tion of the dehydrated cation (Figure 7b).

#### **Mechanistic aspect**

The experimental data from both the screening and kinetic experiments clearly show differences in reactivity of the different ketoses. The kinetic models obtained for the three ketoses at different acid concentrations are consistent and fit well with the experimental results. A possible explanation for the differences in reactivity of the ketoses is the relative orientation of their hydroxyl groups at the C3 and C4 position.

DFT calculations on acid-catalyzed furanose dehydration indicate that the carbocation formed by dehydration at C2 is most stable for tagatose, followed by fructose and sorbose. This is also the order of decreasing reactivity as found in the kinetic study, suggesting a relationship between the determined activation energies and the calculated  $\Delta G$  from the DFT calculations (Figure 8).

The studies provided above imply that the differences in reaction rate of the different ketoses are due to the orientation of the hydroxyl groups on C3 and C4. This suggests that the reaction follows a mechanism with cyclic intermediates



**Figure 8.** The observed  $E_{\rm a}$  plotted against calculated  $\Delta G^{\circ}_{\rm 298K}$  of the single dehydrated ketose carbocations.

(Scheme 2). For a dehydration mechanism with acyclic intermediates (Scheme 3), it is more difficult to explain the significant differences in reactivity of the different ketoses. The mechanisms are based on a series of ß-dehydrations. According to literature, intermediates are generally not observed in water-based acid-catalyzed fructose dehydration, which implies that the formation of the 1,2-enediol would be the rate-determining step in the case of a mechanism with acyclic intermediates, as shown in Scheme 6. This shows that the orientation of the hydroxyl group on the chiral C3 of the 1,2-enediol relative to the double bond between C1 and C2 is not relevant, as C2 and C1 are both achiral. The same can be said for C4 in 3-deoxyhexosulose. This means that any differences in reactivity between the ketoses can only be explained on the basis of the interactions between groups on C3 with those on C4 and C5, which are connected with free-rotating carbon-carbon bonds, which in turn makes large differences in reaction rates less likely.



Scheme 6. Formation of HMF from hexose through acyclic intermediates.



Scheme 7. Possible tautomers of ketohexoses.

Since a cyclic reaction mechanism requires the ketose to react through its furanose form, it is important to take the tautomeric distribution into account. The different tautomeric forms of ketohexoses are shown in Scheme 7. The tautomeric distribution of the ketohexoses in water was studied by Que and Gray (Table 2),<sup>[18]</sup> showing that, of the ketoses addressed in

Table 2. Proportions of pyranose and furanose forms of ketoses at equilibrium in aqueous solutions at 30 $^\circ\text{C}.^{[18]}$							
Ketose	$\alpha$ -Pyranose	β-Pyranose	$\alpha$ -Furanose	$\beta$ -Furanose			
fructose	0	72	5	23			
tagatose	71	15	5	9			
sorbose	95	0	5	0			
psicose	26	21	38	15			

this research, fructose has the largest fraction present in the furanose forms (28%) at equilibrium at 30 °C, followed by tagatose (14%) and sorbose (5%). There is no relationship between these values and the differences in reaction rate observed in our study. A study on galactopyranose tautomerization in water showed that at slightly acidic conditions (pH 4.3) equilibrium can be reached after about 1 h at room temperature.<sup>[19]</sup> At increasing temperatures and acid concentrations, this rate will increase. Therefore, it can be safely assumed that the tautomerization rate is much higher than the dehydration rate under the conditions studied in this research. This, in combination with the data in Table 2, excludes the tautomeric distribution as an important factor in the dehydration rate.

The difference in HMF yield between sorbose and the other two ketoses is difficult to explain. The DFT calculations did indicate that the proposed carbocation intermediate for sorbose is less stable than for fructose and, especially, for tagatose. This could be favorable for a parallel reaction pathway that results in the formation of other products. This phenomenon is currently under investigation.

Another important observation in this study is that the orientation of the hydroxyl groups on the aldoses has no influence on their dehydration rate, indicating that this orientation has no effect on the rate-determining step. It suggests that aldose dehydration to HMF involves a different rate-determining step than ketose dehydration to HMF, which likely demands a different type of catalyst. As a number of researchers have found evidence that suggests that an isomerization cocatalyst is required in the glucose dehydration to HMF,<sup>[3,9,10]</sup> this could mean that the rate-determining step in aldose dehydration under acidic conditions is the isomerization to a ketose. The so-called Lobry de Bruyn–Alberda Van Eekensteijn transformation for aldose–ketose isomerization is base-catalyzed.<sup>[20]</sup> It is thus not surprising that the HMF yield in dehydrations from aldoses under acidic conditions is so low. This information furthermore suggests a cyclic dehydration mechanism starting from the ketofuranose form, as 1,2-enediol formation appears to be favored in the presence of basic catalysts.

## Conclusions

In this study, the combination of high throughput screening and detailed kinetic studies was successfully applied to determine the differences in reactivity between hexoses in the acidcatalyzed dehydration to HMF. The screening showed that different ketoses have different reactivities in acid-catalyzed dehydration to HMF, which must be caused by the different orientation of the hydroxyl groups on C3 and C4. Tagatose showed significantly higher conversion rates than fructose and sorbose. Differences between fructose and sorbose were much smaller. For these ketoses (sorbose, fructose, and tagatose) k and  $E_a$ values were successfully determined from kinetic experiments.

Between the aldoses tested (glucose, mannose, and galactose), no differences in reactivity were observed. This indicates that HMF formation from ketoses and aldoses involves different rate-determining steps.

Initial screening experiments using UPLC analyses indicated a maximum HMF yield of around 40% at around 85% conversion. The kinetic experiments in combination with HPLC analyses, however, showed that the maximum HMF yield from sorbose was only 30%, which leads to the conclusion that a different parallel pathway is available for sorbose. This aspect is still under investigation.

DFT calculations on the ketoses indicate that tagatose forms the most stable furanose carbocation upon single dehydration at the anomeric carbon (C2), followed by fructose and sorbose. As this is also observed to be the order of decreasing reactivity, the calculations provide a plausible explanation for the obtained results; a dehydration mechanism with cyclic intermediates.

The results of the experimental data in combination with DFT calculations are best explained by the formation of HMF through a ketose dehydration mechanism with cyclic intermediates. This means that for aldose conversion to HMF, an isomerization to a ketose would be required prior to dehydration. The fact that this is typically base-catalyzed explains why the acid-catalyzed dehydration of aldoses is much less efficient than the acid-catalyzed dehydration of ketoses.

## **Experimental Section**

Screening: Glucose (99%), fructose (99%), sulfuric acid (96%), 1,4dioxane (99.8%), and saccharine (98%) were purchased from Sigma–Aldrich, galactose (99%), and mannose (99%) were purchased from Acros and sorbose (99.6%) and tagatose (99.8%) were purchased from Carbosynth. Milli-Q quality water was used for all experiments and sample preparations. All experiments were per-

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formed at a 1 mL scale under 20 bar  $N_2$  in batch on an Avantium Quick Catalyst Screening system with a substrate concentration of  $65 \text{ g L}^{-1}$  (0.36 M) in water. Sulfuric acid concentrations of 33, 100, and 300 mm were tested. The ketoses were reacted at 100, 120, and 140°C and the aldoses were reacted at 120, 140, and 160°C. After the appropriate reaction time, the reactor blocks were cooled in an ice bath. The analysis of sugars and furans was performed on a Waters Acquity UPLC with an Acquity ULPC BEH C18 2.1 $\times$ 5.0 mm, 1.7 µm column (the Supporting Information, Table S1). The sugars were detected using an evaporative light scattering detector and HMF was detected on a photodiode array detector at 230 nm. Saccharine was used as external standard. The analysis of levulinic acid was performed on an Interscience TraceGC with an Agilent J&W FactorFour VF-WAXms,  $30 \text{ m} \times 0.25 \text{ mm}$ , 0.25 µmcolumn with a flame ionization detector and 1,4-dioxane as the external standard. The standard mixture was added to the reaction mixture upon opening of the reactor. This was followed by the appropriate dilutions for UPLC and GC analyses.

**Kinetic experiments:** Fructose (99%), sorbose (98%), tagatose (98%) and sulfuric acid (96%) were purchased from Sigma–Aldrich. Milli-Q quality water was used for all experiments and sample preparations. All experiments were performed at a 0.5 mL scale in sealed glass ampoules which were heated in an oven at 137 °C. A substrate concentration of 65 gL<sup>-1</sup> (0.36 M) in water was used. Sulfuric acid concentrations of 33, 100, and 300 mM were used. The ampoules were cooled in cold water after the appropriate reaction time. The reaction mixture was then filtered over a 0.45  $\mu$ m PTFE syringe filter and diluted 7–9 times in water for analysis on an Agilent 1200 HPLC with a Bio-rad Aminex HPX-87H column. 5 mM sulfuric acid was used as the eluent with a flow rate of 0.55 mL min<sup>-1</sup>. Refractive index and UV (210 nm) detection were used.

**Determination of the kinetic parameters**: The kinetic parameters were determined using a maximum likelihood approach, which is based on minimization of errors between the experimental data and the kinetic model. For each hexose, the datasets obtained at the three different acid concentrations were solved simultaneously. Error minimization was performed using the MATLAB toolbox lsqnonlin.

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