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Visualization of Pathway Usage in an Extended Carbohydrate Conversion Network Reveals the Impact of Solvent Enabled Proton Transfer

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12

13 ABSTRACT: Bio-sourced molecules should increasingly contribute to meeting societal demands
14 for energy and chemicals, while reducing net carbon dioxide release and the dependence on fossil
15 resources. Especially oxygenated chemicals can be derived from carbohydrates, and the
16 conversion of carbohydrates in protic and non-protic solvents has attracted considerable interest.
17 Here we probe chemocatalytic carbohydrate conversion in a time-resolved manner using
18 quantitative *in situ* NMR spectroscopy. A core reaction network in the carbohydrate conversion
19 by Sn(IV) in non-protic solvents is followed by identifying and quantitatively tracking ten
20 chemicals with more than 70 atomic sites. The *in situ* analysis yields nine rate constants and shows
21 that (co)solvents with labile protons strongly affect tautomerization kinetics and product
22 distributions at an upstream branch point of the reaction network. Solvent enabled tautomerization
23 and the ensuing accumulation of reactive 1,2-dicarbonyl compounds can thus be key factors
24 influencing reaction kinetics and atom economy in carbohydrate conversion.

25 KEYWORDS: Biomass conversion, Catalysis, Carbohydrate utilization, Humin formation,
26 Kinetic Model, NMR spectroscopy, Reaction Network

27

INTRODUCTION

There is a broad consensus that a future sustainable society will depend on the production of materials and fuels from abundant renewable substrates rather than fossil resources.¹ Lignocellulosic biomass, and especially carbohydrates, play a leading role as prospective natural resources for oxygenated compounds with high chemical functionality. Current progress in endeavors towards viable carbohydrate-based processes is arguably limited by restricted insight into the multiple carbohydrate conversion pathways towards different (by)products. Carbohydrate conversion pathways often encompass acid- or base-catalysed dehydration, isomerization or (retro-)aldol reactions. These pathways can encompass acyclic and cyclic forms,²⁻⁴ and free aldehyde groups whose high reactivity is difficult to control.⁵⁻⁶ Hence, various acyclic and cyclic pathways may coexist, and the factors influencing substrate influx into the different pathways remain difficult to understand and control. Most notoriously, the relative importance of various plausible pathways towards furanic compounds has remained controversial for many decades, possibly due to the involvement of different pathways towards the product.^{4, 7-9}

In the conversion of carbohydrates, different solvents and solvent systems have attracted interest. The solvents should ideally solubilize the carbohydrate at sufficiently high concentration and stabilize intermediates against aggregation reactions. Reactions in water often lead to the formation of undesired side products.¹⁰ Alcoholic solvents have a tendency to mask aldehyde groups as unreactive acetals and to covalently add to double bond functionalities¹¹ formed by dehydration reactions.¹²⁻¹³ Aprotic polar solvents and ionic liquids have therefore attracted particular interest, although product purification can be hampered in such solvents.^{3, 14-16}

Figure 1. Schematic overview of the questions addressed herein using erythrulose as an acyclic probe molecule to track usage and control of different reaction pathways that are accessible to acyclic carbohydrate substrates.

The experimental observation of carbohydrate conversion networks and their response to changes in reaction conditions has remained a challenge (Figure 1). High-field NMR spectroscopy emerges as a suitable means to obtaining definitive answers on the molecular forms and their conversion kinetics in complex reactions mixtures, without the need for sample workup.^{2, 11-13, 17-21} Here we hypothesized that *in situ* spectroscopy can shed light on the chemical pathways that are accessible to acyclic carbohydrate forms in aprotic polar solvents under mild reaction conditions. The majority of reactions that have been described for acyclic carbohydrate conversion entail intramolecular redox and dehydration reactions at C1-C4.^{4, 13, 22-26} Hence, these reactions can be probed using the C4 substrate erythrulose as the substrate. A special emphasis is placed herein on reactions that leave the carbon backbone intact or lead to self-condensation.

RESULTS AND DISCUSSION

Recently, the conversion of abundant C6 sugars by Lewis acids¹⁶ in acyclic pathways was described.^{3, 20} We undertook to enquire the Lewis acid catalyzed conversion of carbohydrates in polar environments, using erythrulose as a molecular probe for the reaction network that is accessible with the cheap and widely available Lewis acids SnCl₄ in DMSO.¹⁶ Previously elusive mechanistic details concern (1) branch points in the reaction network, (2) substrates and kinetics for self-condensation in humin formation, (3) the kinetic impact of cyclic intermediates (such as 3-deoxyglycosones) and (4) the molecular effect of water addition and choice of solvent on the reaction network (Figure 1).

Rationale for using an acyclic probe in aprotic solvent. The use of erythrulose in aprotic solvent promises to efficiently channel substrate into the reaction network for the conversion of acyclic carbohydrates. Opposite to acyclic erythrulose, the C6 analogue fructose has an open chain population of only approximately 2.4 % in DMSO near room temperature,¹⁷ thus decreasing substrate population interactions with the Lewis acidic catalyst (Figure 2). As a consequence, erythrulose was found to be converted substantially faster than fructose, as shown by reaction tracking with a time series of ¹³C NMR spectra (Figure 2a). In this sense, fructose and other longer ketoses mask the reactive carbonyl group through intramolecular hemiketal or hemiacetal formation to cyclic forms. Similarly, conversion of carbohydrates in alcoholic solvents leads to the formation of hemiketals/hemiacetals or ketals/acetals that mask the carbonyl groups as solvent adducts. Use of erythrulose in aprotic solvents thus stands as a particularly strong means of populating reaction pathways that involve the coordination of free carbonyl groups to Lewis acidic catalysts.

Figure 2. (a) Conversion of a mixture of fructose and erythrulose shows the higher reactivity of erythrulose due to the higher acyclic population. (b) Schematic overview of higher acyclic fraction leading to higher populations of complexes with the schematically depicted Lewis acid (here Sn^{IV} , Ligands are indicated as L due to the possibility of partial SnCl_4 hydrolysis). Reaction conditions: L-erythrulose (27 mg), D-fructose (40 mg) and $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ (10 mg) in d_6 -DMSO (550 μL) at 313 K.

Tracking of an extended reaction network. Subsequently, the conversion of erythrulose by SnCl_4 in polar aprotic solvent (DMSO) was followed using quantitative *in situ* NMR at high magnetic field (800 MHz spectrometer equipped with a TCI cryoprobe to maximize the signal-to-noise ratio in the resultant spectra). In addition to the more trivial isomerization products erythrose and threose, nine dehydration products could be tracked in a time resolved manner (Figure 3 and Figure 4). Kinetic profiles of the resultant reaction progress curves supported the full assignment of the chemical compounds shown in Scheme 1. The assignments were completed by the use of homo- and heteronuclear assignment spectra, specifically ^1H - ^1H TOCSY, ^1H - ^1H COSY, ^1H - ^{13}C HSQC and ^1H - ^{13}C HMBC spectra, which also yielded ^1H NMR shifts for all non-labile protons.

The detected chemical species emerged with kinetics that were indicative of the plausible reaction pathways as shown in Scheme 1, while Figure S2 depicts the corresponding complexation of the metal center. Aldotetrose signals decayed with a kinetics akin to erythrulose and were treated as part of the carbohydrate substrate pool (Figure S3). The first detected dehydrated intermediate is the enol **2**, which corresponds to the enol form of a 3-deoxythreosone (4-hydroxy-2-oxobutanal, the cyclic keto tautomer is entry **5**). The keto tautomer **5** forms subsequently, in parallel to vinyl glyoxal (**3**), which readily rehydrates at the C1 position and is detected as the hydrate. Vinyl glyoxal (**3**) is an unstable intermediate that reacts to vinyl glycolate (**4**) through a 1,2-hydride shift of the C1-hydrated form. In contrast, the 3-deoxythreosone intermediate **5** proves more resilient to hydride shifts, forming a fairly stable product at 313 K that only slowly converts to the hydroxybutyrolactone (**6**), and the corresponding acyclic esters (**9**).

Figure 3. Conversion of erythrulose and some of the major carbonyl- and carboxyl-containing reaction products that were formed. Reaction conditions: L-erythrulose (27 mg), D-fructose (40 mg) and SnCl₄·5H₂O (10 mg) in d₆-DMSO (550 μL) at 313 K.

Scheme 1. Conversion of erythrulose through a reaction network entailing two branch points. Chemical shifts were assigned using reaction-progress curves and two-dimensional assignment spectra.

The accumulation of hydrated **3** and cyclic hemiacetal **5** contrasts the much lower accumulation of the free corresponding 1,2-dicarbonyl compounds, indicating a kinetic impact of hemiacetal and hydrate forms that are more stable than their 1,2-dicarbonyl counterparts. The predominance of the cyclic structure **5** was evident from characteristic chemical shifts, especially for ^1H and ^{13}C at the C4-H4 position, and from long-range connections in the ^1H - ^{13}C HMBC experiment (Figure S4). The observation is consistent with previous observations that 85% of compound **5** exist as a cyclic form even in purely aqueous solution.²⁷ Only upon addition of water to the reaction mixture could acyclic forms **7** and **8** of the 3-deoxythreosone be observed. In the conversion of **5** to **6**, kinetic experiments at varying temperatures indicated that the acyclic form **9** was formed prior to **6**, followed by equilibration of **9** and **6** (Figure S5). This observation is

consistent with the interpretation that the cyclic form **5** accumulates as the least reactive form of 3-deoxythreosone.

Kinetic model consistent with the reaction network

The reaction pathway of Scheme 1 was incorporated into a simple kinetic model and the experimental reaction progress data for the main intermediates was fitted to the kinetic model. Fitting quantitative experimental data for seven molecular species (Figure 4) supported the simple reaction model of Scheme 1 and Figure 5. Previous observations had shown that the conversion of 1,2-dicarbonyl compounds (such as **3** and **5**) to α -hydroxy acids was irreversible.^{11, 28} Spectroscopic data likewise indicated that the conversion of **3** was quantitative (Figure 4) and would have a small reversible reaction rate constant. The parallel formation of

Figure 4. Integrals of carbon signals in compounds **1-6** alongside residual other species (especially oligomers and polymers), for the conversion of erythrulose under the conditions of Figure 3. The experimental data shown as black squares were in agreement with a kinetic model of Figure 5. Red lines depict from kinetic modelling calculations.

Figure 5. Kinetic model that is consistent with kinetic reaction progress data for the erythrulose conversion at 313 K. Reactions were treated as irreversible steps in order to avoid overfitting of the data set. The data indicated slow oligomerization of the alpha carbonyl aldehydes **3** and **5** (red arrows).

compounds **3** and **5** from **2** indicates the formation in largely irreversible competitive steps in the absence of added water (red values in Figure 4 designate rate constants in the absence of water). The weakly accumulating open enol form **2** was elusive to previous observation. Allowing for reversibility of the first step did not significantly improve the fitting and did not affect the obtained constants.

These rate constants show erythrulose conversion to compound **2** with a rate constant that is approximately eightfold lower than the conversion of **2** to **3**, and one order of magnitude lower than the enol-to-ketone conversion of **2** to **5** (red values in Figure 5). The conversion of intermediates **3** and **5** through hydride shifts is orders of magnitude slower than the formation of **3** and **5** from **2** (Figure 5). Kinetic fits indicated that the alpha-carbonyl aldehyde forms **3** and **5** are precursors for oligomers and polymers (humins), consistent with recent suggestions that alpha-

carbonyl aldehydes undergo aldol condensation to form humins.⁶ This conversion was faster from vinyl glyoxal (**3**) than from the circular hemiacetal **5** (Figure 5). The instability of vinyl glyoxal was further witnessed by the observation of formic acid forming in parallel to vinyl glycolate (**4**) upon accumulation of the 1,2-dicarbonyl species **3** (Figure S6). Rather notably, liberation of formic acid from a β - γ unsaturated α -hydroxy-carbonyl intermediate is analogous to the proposed mechanism in the conversion of HMF to levulinic acid via β - γ unsaturated α -hydroxy-carbonyl intermediate.²⁹

The slower conversion of compound **5** as compared to compound **3** is a hallmark in the conversion of the 1,2-dicarbonyl compounds **3** and **5** to the respective α -hydroxy acids. The observation of a fairly rapid formation, but slow turnover of the 3-deoxythreosone intermediate stipulated the search for conditions that disfavour the conversion of compound **5** in favour of enolization and conversion through the acyclic pathway to compound **4** that has been considered the more useful chemical due to its vinyl functionality.

Water-enabled tautomerization affects the branch point between cyclic and acyclic routes.

The competing conversions of the previously elusive enol intermediate **2** involve tautomerization steps. Water is known to have a noteworthy catalytic impact on Tautomerization reactions, because it can mediate necessary intramolecular proton transfer.³⁰⁻³¹ Added water should additionally facilitate populating the hydrated vinyl glyoxal **3**. Hence, water was added to the reaction mixture at fractions of 7.5 % (v/v) or 15 % (v/v) and the effects on reaction progress were monitored by *in situ* NMR spectroscopy (Figure 6). The resultant experiments indeed showed that the population of **5** could be diminished by the addition water, while influx of intermediate **2** into the hydrated acyclic form **3** was favored. Accumulation of intermediate **3** and

Figure 6. Conversion of erythrulose to central intermediates and products in the presence of varying amounts of water. Reaction conditions: L-erythrulose (27 mg), D-fructose (40 mg) and $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ (10 mg) in $\text{d}_6\text{-DMSO}/\text{D}_2\text{O}$ of the indicated ratio (v/v added water, total 550 μL) at 313 K.

product formation of **4** were accelerated as a consequence. In contrast, accumulation of molecule **2** declined upon addition of water. Only in the presence of water did the kinetic profiles of **3** and **5** deviate from kinetically controlled competitive formation, consistent with water catalysis facilitating reversible tautomerization.

Overall, the observations indicated that water addition noticeably favored the conversion of **2** to **3** over its cyclization to **5**. These observations provide a mechanistic basis for previous coincidental observations, which indicated that pathways to C6-analogues of **4** can be favored over pathways to cyclic compounds by the addition of water.³ As anticipated, water catalysis had a strong effect on the kinetics of tautomerization reactions, where the rate constant for the conversion of **2** to **3** was more strongly enhanced than the rate constant rate constant for conversion of **2** to **5** (see blue values in Figure 5 above for a comparison of the rate constants).

Water effect on self-condensation. Further studies of the water effect were conducted to monitor the composition of post reaction material obtained in the presence of increasing water content. These experiments validated a decrease of compound **5**, but increase of compound **4** at low water content. In addition, a new compound emerged at increased water content, especially for higher temperatures (Figure S6). The additional compound yielded eight correlating ^{13}C signals of identical area. This C8 compound with characteristic chemical shifts was subsequently identified as erythropyrone **10**, formed from the condensation of two C4 compounds. A plausible mechanism for the condensation is schematically depicted in Scheme 2.³² The accumulation of erythropyrone is in agreement with the accumulation of vinyl glyoxal. The role of Brønsted acidity

Figure 7. ^{13}C NMR spectra of post reaction material for reactions with varying water content and added Brønsted acid. Reaction conditions: L-erythrulose (40 mg) and $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ (10 mg) in d_6 -DMSO/ D_2O (v/v as indicated, 550 μL) at 313 K for 24 hours. A reference reaction was conducted in d_6 -DMSO (550 μL) containing 50 mM HCl (aq). Asterisks indicate erythropyrone (10) signals.

Scheme 2. Plausible reaction pathway for the conversion of erythrulose to a self-condensed C8-product, erythropyronone, by reaction with vinyl glyoxal intermediate.^{32 33}

in the formation of erythropyronone was validated by repeating the experiment in the presence of 50 mM HCl in the reaction mixture of SnCl₄ in DMSO, again causing the accumulation of erythropyronone **10** (Figure 7). In addition, accumulation of the reactive vinyl glyoxal intermediate (**3**) was observed in the presence of added water (Figure 6). Discoloration and the formation of insoluble material in the post-reaction mixture were aggravated by increasing temperature and water content, both of which favour the conversion of **2** to vinyl glyoxal (**3**) (Figure S11 and S12).

Distinct solvent influence of protic versus aprotic media. Considering the apparent role of free carbonyl groups in coordinating the Lewis acidic catalyst, and the role of labile protons in catalyzing tautomerization reactions, polar protic solvents and polar aprotic solvents were expected to show significantly different reaction progress curves. Polar protic solvents such as short chain alcohols have a tendency to add to aldehyde and olefinic groups and should interfere with some of the reactions of Scheme 1. In order to evaluate, if reaction progress in polar protic and polar aprotic solvents falls into two distinct categories, the reaction progress in DMSO was thus finally compared to reaction progress in aprotic polar DMF and in the protic polar methanol and ethanol solvents.

The reaction profiles in DMSO and DMF were similar, but were significantly different from the reaction profiles in methanol and ethanol (Figure 8 and Figure S15). Rather notably, the conversion of erythrulose substrate was faster in protic solvents facilitating tautomerization (Figure S15). In the alcoholic solvents, none of the intermediates **2**, **3** or **5** accumulated to significant amounts. In contrast, the alcohol rapidly added to the vinyl glyoxal intermediate forming a C4 ether variant of 3-deoxythreosone, predominantly found as a hemiacetal with the

Figure 8. Reaction progress in various aprotic (a) and protic (b) solvents. Reaction conditions: L-erythrulose (40 mg) and $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ (10 mg) in 550 μL d_6 -DMSO, protonated DMF containing 5% d_6 -DMSO, methanol or ethanol containing 5% (v/v) d_4 -methanol at 333 K.

alcohol at the C1 position (Figure 8b). The changes in pathway usage are thus consistent with the effect of water addition on reaction kinetics in DMSO: protic polar solvents favor the pathway through the transient vinyl glyoxal intermediate, while disfavoring the pathway through 3-

deoxythreosone as compared to aprotic polar solvents. As a result, the product composition in alcoholic solvents is simpler than the product composition in the polar aprotic solvents, which enable two pathways of similar propensity for C4 substrates.

CONCLUSION

An extensive reaction network was observable in a time-resolved manner for the Lewis acid catalysed conversion of a model carbohydrate in DMSO. Rate constants for the central reactions could be determined, including those of reactions that led to the formation of insoluble products. The product distribution, including the formation of (usually undesired) humins, was affected by the addition of water. Kinetic curves indicated that two competing products, 3-deoxythreosone and vinyl glyoxal, formed in competing reactions under kinetic control in the absence of added water. Addition of water and higher temperature changed the reaction control at the branch point, thus also favouring self-condensation and humin formation. Reaction kinetics of upstream tautomerization steps and ensuing accumulation of intermediates and products can thus be strongly affected by the presence of solvent containing labile protons. The observations further show that the hydration and intramolecular ring formation of free carbonyl groups affect pathway kinetics. *In situ* reaction tracking and structural identifications reported herein may facilitate the implementation of conditions that disfavour undesired pathways in carbohydrate upgrading.

EXPERIMENTAL SECTION

Materials. D-(-)-fructose ($\geq 99\%$), L-(+)-erythrulose (85%), tin(IV) chloride pentahydrate (98%), tin(II) trifluoromethanesulfonate, aluminium(III) chloride hexahydrate (%), titanium(IV)

chloride (99.9%), *d*₆-dimethylsulfoxide (%), and D₂O (%) were purchased from Sigma-Aldrich (Andover, MA, USA). HCl (4 M in H₂O) was purchased from Fluka and used as a stock solution in probing the effect of Brønsted acidity. Different metal salts were used in an initial screening approach (Figure S1) to show that Tin(IV) catalysed reactions described herein equivalently occur under Al(III) catalysis and to some extent with Tin(II) catalysis.

Reaction procedures. Carbohydrates were dissolved in *d*₆-DMSO at the indicated concentrations in 1.5 ml Eppendorf safelock tubes. Deuterated water (D₂O) was added to a final volume ratio (v/v) as indicated. Tin(IV) chloride or other metal salt catalysts were added from a stock solution, usually to a final carbohydrate:catalyst molar ratio of ~12:1 (40 mg erythrose and 10 mg SnCl₄·5H₂O, unless stated otherwise). Subsequently, reaction mixtures were (a) either transferred to 5 mm NMR sample tubes for *in situ* reaction tracking or (b) the Eppendorf tubes containing 550 µl of reaction mixture were incubated on a Hettich Thermo Shaker MHR13 equipped with a thermoblock at 298 K, 313 K, 323 K, 333 K or 363 K and the indicated times for compositional analysis and chemical shift assignments of post reaction material.

NMR spectroscopy. NMR spectra were acquired with a Bruker Avance II 800 MHz NMR spectrometer equipped with an 18.7 T magnet (Oxford, United Kingdom) and a TCI z-gradient cryoprobe (Bruker, Karlsruhe, Germany). For the assignment of chemicals in post reaction material, samples were transferred to 5 mm NMR tubes for NMR analysis. A suite of 2D NMR assignment spectra was acquired, including TOCSY with a 10 kHz spin lock field that was applied for 60 ms (1024×128 complex data points with 128 ms and 16 ms acquisition times), a sensitivity enhanced ¹H-¹³C HSQC (1024×128 complex points, sampling 107 ms and 3.2 ms acquisition

times), ^1H - ^{13}C HMBC (1024×256 complex data points, sampling 128 and 5.7 ms acquisition times) and a ^1H - ^{13}C HSQC TOCSY with adiabatic decoupling (2048×128 complex points with 160 ms and 3.9 ms acquisition times). ^{13}C NMR spectra were acquired by sampling the ^{13}C FID during an acquisition time of 1.36 seconds with 64k complex data points with an inter-scan relaxation delay of 10 seconds between 256 accumulations.

In situ experiments were performed as time series of ^{13}C 1D NMR spectra by immediately transferring reaction mixtures to 5 mm NMR tubes and equilibrating the NMR tubes to the desired temperature in the spectrometer. Time series of ^{13}C spectra were recorded in a pseudo-2D fashion to facilitate the integration of signal areas in the Dynamics Module of Bruker Topspin 4.0.6. The ^{13}C FID was sampled by acquiring 32k complex data points during an acquisition time of 0.68 seconds. An inter-scan relaxation delay of 10 seconds ($\sim 5 \times T_1$) per time point was used for reaction tracking. All protonated (non-quaternary) ^{13}C sites of each analyte molecule were used for integration. The identical kinetic profile of four carbon sites (of comparable signal area) in each of the C4-molecular species **1–9** aided and validated the assignment of the molecular species as depicted in Scheme 1 below.

All NMR spectra were recorded, processed with ample zero filling in all spectral dimensions, and analysed with Bruker Topspin 4.0.6 software (Fällanden, Switzerland).

Data Analysis. A kinetic model was devised of sequential reactions for the signal areas of core compounds **1–6** as well as signal area that is lost in undetectable polymeric forms. Nonlinear least-squares fitting of the time-dependent signal areas was conducted in MATLAB using the `fmincon` function for the following differential equations:

$$\frac{d[1](t)}{dt} = -k_1 \times [1](t) \quad (1),$$

$$\frac{d[2](t)}{dt} = k_1 \times [1](t) - k_2 \times [2](t) - k_5 \times [2](t) + k_{-2} \times [3](t) + k_{-5} \times [5](t) \quad (2),$$

$$\frac{d[3](t)}{dt} = k_2 \times [2](t) - k_3 \times [3](t) - k_4 \times [3](t) - k_{-2} \times [3](t) \quad (3),$$

$$\frac{d[4](t)}{dt} = k_3 \times [3](t) \quad (4),$$

$$\frac{d[5](t)}{dt} = k_5 \times [2](t) - k_6 \times [5](t) - k_7 \times [5](t) - k_{-5} \times [5](t) \quad (5),$$

$$\frac{d[6](t)}{dt} = k_6 \times [5](t) \quad (6), \text{ and}$$

$$\frac{d[\text{oligomers}](t)}{dt} = k_4 \times [3](t) + k_7 \times [5](t) \quad (7).$$

337

338 Square brackets indicate the signal areas, while k denotes first order rate constants. Satisfactory
 339 fits were only obtained when invoking the loss of detected signal from the 1,2-dicarbonyl
 340 compounds **3** and **5**. Previous observations had shown that the conversion of 1,2-dicarbonyl
 341 compounds (such as **3** and **5**) to α -hydroxy acids (such as **4**) was irreversible,^{11, 28} Spectroscopic
 342 data likewise indicated that no NMR-detectable equilibrium between **3** and **4** was formed. Kinetic
 343 data showed that reversibility of upstream tautomerization reaction plays an increasingly important
 344 role in the presence of protic solvent.

345

346 ASSOCIATED CONTENT

347 **Supporting Information.** Supplementary figures include NMR spectra of product mixtures
 348 derived upon catalyst screening; assignment spectra for the identification of 3-deoxythreosone
 349 forms; time-resolved in situ NMR spectra for reaction tracking at varying water content and

temperature; detailed depiction of kinetic fits in the absence and in the presence of water;
comparison of substrate conversion in various protic and aprotic solvents

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Author Contributions

The manuscript was written through contributions of all authors. All images in Schemes and
Figures were created by the authors. All authors have given approval to the final version of the
manuscript.

Notes

The authors declare no competing financial interests.

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TOC Entry:

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480 A reaction network for carbohydrate valorization was observed, revealing the impact of solvent
481 protons on the desired process, and on aggregation and degradation reactions.

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