Conversion of Abundant Aldoses with Acetylacetone: Unveiling the Mechanism and Improving Control in the Formation of Functionalized Furans Using Lewis Acidic Salts in Water

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ABSTRACT: The exploration and exploitation of reactions extending abundant carbohydrates by multiple-bond-forming reactions has recently experienced a renaissance. Such reactions can form drug-like structural motifs from renewable substrates in water at mild temperatures. A combined reaction tracking and kinetic modeling approach was conducted here for the conversion of glucose and other simple carbohydrates with acetylacetone to densely functionalized furans in the Lewis acid-catalyzed Garcia Gonzalez reaction in water. Real-time ^{13}C NMR data was used to identify major intermediates towards furan products, and kinetic modeling supports the deduced pathway and reveals its energetics. Albeit the main dihydrofuran intermediate is bicyclic, with the C4 oxygen of glucose attached to the dihydrofuran ring, the use of C4-functionalized carbohydrate (maltose) shows that this intermediate is not the only on-pathway intermediate towards functionalized furans. The use of nearly solvent-free eutectic mixtures favors the intermolecular initial steps and renders the conversion of glucose and acetylacetone largely complete within four hours at 323 K, even in the presence of only 0.01 equivalents Zr(IV). As the conversion proceeds in an initial bimolecular and subsequent unimolecular reaction, sufficiently high substrate concentrations favor the initial bimolecular reaction to polyhydroxyalkyl furan, which equilibrates with C-glycosyl furan. The use of various Lewis acidic salt catalysts indicates that the conversion of glucose and acetylacetone is not uniquely favored by Zr(IV) catalysis. For instance, similarly efficient enolization of acetylacetone and reaction is achieved using Hf(IV) catalysis in water. Alternative media were correctly predicted to catalyze the reaction at milder temperatures along the same pathway, including a concentrated solution of $ZnCl_2$ in water that had previously been described as a nontoxic, and recyclable homogeneous reaction medium for converting polysaccharides into dehydrated chemicals.

INTRODUCTION

The change towards a sustainable society requires the transition to new materials and fuels, while currently on the order of 95% of the organic chemicals used in the chemical industry remain sourced from fossil resources.[1] The sources for new chemicals include carbon dioxide[2–4] or products derived from carbon dioxide by photosynthesis, such as lignocellulosic biomass, which primarily consists of carbohydrates. Carbohydrates are available in pure form at competitive costs and their conversion to various chemical precursors hence has been pursued. Products formed from carbohydrates often have included chemicals deriving from isomerization,[5,6] dehydration[7–12] and C-C bond cleavage,[13,14] and these products include rare carbohydrates, furanic compounds, and polyester building blocks.[15] An additional degree of freedom is provided by the functionality of carbohydrates, including the reactive aldehyde group of abundant aldoses such as glucose and xylose.[16–22]

Arguably, the upgrading of unprotected carbohydrates through reactions with other substrates has been a strangely dormant field for too long,[23,24] and recent studies have indicated that valuable compounds can be obtained in high yield under benign conditions when converting aldoses with nucleophilic reactants in water.[18,22,24–29] Chain extension of carbohydrates at the carbonyl groups is viable with reactants such as malononitrile or acetylacetone.[30] The products resulting from C-C bond formation at the aldose anomeric center may experience further conversion, including reaction cascades that encompass dehydration, cyclization, and tautomerization steps leading to the formation of several new bonds. In this manner, polyfunctional products can be formed. These compounds contain privileged scaffolds for bioactive compounds that have been employed in antimicrobial, antifungal and anticancer agents,[31,32] but also in glycomimetics,[33] fuel-like molecules and other applications.[23,27] The formed high-value chemicals include C-glycosylated furans that can be formed in the Garcia Gonzalez reaction between aldoses and β-dicarbonyl compounds.[31,33]

Optimized biomass conversion, including the conversion of carbohydrates with added substrates, suffers from the limited insight into the molecular processes through experimental methods. A plausible reason for this shortcoming is the presence of various acyclic and cyclic isomers in the polyfunctional

carbohydrates and the products formed upon conversion. NMR spectroscopy, especially when exploiting the resolution and sensitivity provided by ^{13}C NMR recorded on instruments with cryogenically cooled detection electronics, promises to fill the knowledge gap by providing insight into isomeric forms in solution, and into their dynamic change in reaction tracking. *In situ* spectroscopy of ongoing reactions is a suitable methodology for identifying kinetics, mechanisms, pathways and energetics in ongoing reactions. Arguably, the urgency for improved experimental detail grows if reaction discovery and optimization will increasingly be based on computational approaches that require reliable data sets for training.[34] Encouraged by recent successes using NMR reaction tracking for identifying unexpected pathways in the extension of glucose by malononitrile and in recognizing new catalyst systems,[19,20] we commenced to evaluate the pathway, likely mechanism, and catalyst-substrate interaction in the Garcia Gonzalez reaction. This reaction extends the carbohydrate chain upon Knoevenagel condensation of aldoses with β-dicarbonyl compounds. The conversion to polyhydroxyalkyl- and C-glycosyl furans with mono- and bicyclic structures, respectively, have previously been described for the reaction of glucose with acetylacetone in aqueous solution or nearly solvent-free conditions.[23,28] Here, we explore the mechanism, kinetics and energetics of the Lewis acid-catalyzed bimolecular reaction between aldoses and acetylacetone in water to polyhydroxyalkyl furans and C-glycosyl furans, and suggest the use of alternative media for this chain extension. Such insight facilitates the use of the reaction at moderate temperatures and catalyst loadings with high conversion and suitable reaction time.

EXPERIMENTAL SECTION

Chemicals. D-glucose (96%), acetylacetone (99%), L-fucose (99%), D-xylose (99%), maltose monohydrate (99%) and isotope-enriched [1-^{13}C]glucose (99 atom % ^{13}C) were purchased from Sigma Aldrich (St. Louis, MA, USA). Lewis acidic salts $ZrCl_4$ (99.5%), $ZnCl_2$ (98%) and $Sc(OTf)_3$ (99%) were likewise purchased from Sigma Aldrich. $HfCl_4$ (98%) was purchased from ThermoScientific (Waltham, MA, USA). Deuterated water (D_2O) was purchased from Deutero GmbH (Kastellaun, Germany).

General Reaction Procedure. The typical reaction procedure consisted of weighing glucose and acetylacetone into a 1.5 mL Safe-lock Eppendorf (Hamburg, Germany) microcentrifuge tube to yield the desired final concentration (in a 0.5 mL reaction), using 1.0 equivalent of acetylacetone. The reactions were started with the desired amount of catalyst. Reactions in water-poor medium at highest glucose concentration (1 mmol glucose and acetylacetone, 100 µl D_2O) were conducted after producing the deep eutectic medium by shaking the reaction mixture in the absence of catalyst for 24 hours at 323 K.[23] Also reactions in this medium were started with the desired amount of catalyst.

NMR Samples. For *in situ* ^{13}C NMR experiments, the reaction mixture was typically transferred to a 5 mm NMR sample tube prior to tuning and matching, pulse calibration, and shimming. Subsequently, NMR spectroscopic observations were started as detailed below. Reactions employing isotope-labeled [1-^{13}C]glucose were performed on a scale of 175 µL using 3 mm NMR sample tubes.

NMR Spectroscopy. NMR spectra were acquired on an 800 MHz Bruker (Fällanden, Switzerland) Avance III instrument equipped with an 18.7 T magnet and a 5 mm TCI cryoprobe. The time-resolved reaction tracking was conducted by implementing a time series of 1D ^{13}C NMR spectra (zgig30) as a pseudo-2D experiment. An inter-scan relaxation delay d1 of 1.5 s was used, and 128–200 transients of the FID were accumulated, subject to the sensitivity required. The FID was sampled during an acquisition time of 0.68 s. ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and ^{1}H-^{1}H TOCSY were employed for structure determination and chemical shift assignments. All spectra were acquired, processed and analyzed using Bruker Topspin 3.5 pl6. Integrals of signals for the detected species were extracted from pseudo-2D experiments using the Dynamics module of the same software.

Kinetic Fitting and Plotting. Kinetic profiles of the time-dependent ^{13}C NMR integrals were fitted by setting up molar balances as ordinary differential equations and were solved numerically in Matlab 2018 using the Runge–Kutta 2–3 method as previously described.[35] Reaction rate constants were varied to match experimental and modelled data by the regression analysis, where C_{glu}, C^{aac}, C_{int}, and C_p represent concentrations of glucose (**1**), acetylacetone (**2**), polyhydroxyalkyl furan **3**, and the C-glycosyl furan **4**, respectively.

(i) $$\frac{dc_{glu}}{dt} = -k_1 C_{glu} \times C_{aac}$$

(ii) $$\frac{dc_{aac}}{dt} = -k_1 C_{glu} \times C_{aac}$$

(iii) $$\frac{dc_{int}}{dt} = k_1 C_{glu} \times C_{aac} - k_2 C_{int} + k_3 C_p$$

(iv) $$\frac{dc_{pro}}{dt} = k_2 C_{int} - k_3 C_p$$

The set of ordinary differential equations was then solved in Matlab 2018 with the Runge-Kutta 2-3 method, while the Nelder–Mead method was employed as a regression method to minimize the objective function (equation (v) below). The Levenberg–Marquardt method was additionally utilized to derive the Jacobian matrix and to calculate 95 % confidence intervals. NMR data sets were further integrated and fitted repeatedly to validate the robustness of the determinations.

(v) $$\left(k_{i-j}\right) = \sum_{exp=1}^{EXP} \sum_{j=1}^{J} \left(C_{exp} - C_{mod}\left(k_{i-j}\right)\right)^2$$

Spectra of acetylacetone with 0.1 equivalents Lewis acids. To an Eppendorf-tube was added 400 µL of demineralized water, to which Lewis acid (98 µmol, 0.1 eq; either $ZrCl_4$, $ZnCl_2$, $Sc(OTf)_3$, or $HfCl_4$) was added and dissolved. To this solution, acetylacetone (100 µL, 980 µmol, 1 eq) was added to the solution and homogenized. Of the mixture 500 µL was added to a 5 mm NMR-tube doped with 40 µL D_2O. A reference sample with no Lewis acid added was likewise prepared. 1D ^{13}C NMR Spectra were acquired on a 400 MHz Bruker Avance III HD NMR instrument equipped with an Ascend magnet and a BBO Prodigy probe.

RESULTS AND DISCUSSION

Main molecular species in the Garcia Gonzalez reaction. The Garcia Gonzalez reaction proceeds by catalysis with different water-tolerant Lewis acid catalysts under mild conditions, where especially the catalysis by transition metal salts has garnered attention. Among the salts of transition metals, especially catalysis by $CeCl_3 \cdot 7H_2O$[28] and more recently by $ZrCl_4$[23] have been reported to result in high yields of substituted furans from

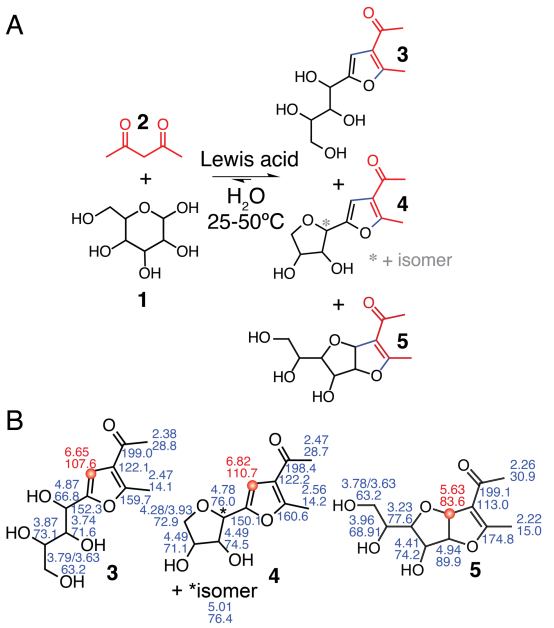

Figure 1. (A) The Garcia Gonzalez reaction, proceeding under mild conditions in near solvent free conditions or aqueous solution. Acyclic and various bicyclic forms were identified, including newly described species that provide mechanistic insight. (B) Chemical shift assignments of three structural forms observed in reaction mixtures.

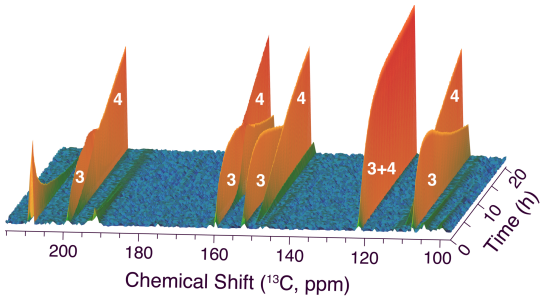

Figure 2. Reaction conditions: 2.2 M glucose and 2.2 M acetylacetone in H_2O, 298 K, $ZrCl_4$ (0.1 eq), in the presence of an external ^2H lock capillary containing D_2O.

glucose (**1**) and acetylacetone (**2**), albeit these two catalysts have been reported to yield different main products (polyhydroxyalkyl furans **3** and C-glycosyl furans **4**, using $CeCl_3 \cdot 7H_2O$ and $ZrCl_4$, respectively). Using high-field NMR spectroscopy on ongoing reaction and non-purified reaction mixtures, we identified four compounds beyond glucose and acetylacetone. These compounds include **3** and **4** in addition to an isomeric C-glycosyl furan **4'** with the configuration at one carbon atom inverted, and a bicyclic dihydrofuran **5** (Figure 1A) that was formed rapidly but only at low levels as an intermediate during reaction progress. The chemical shift assignments of the formed compounds are compiled in Figure 1B. In addition to these species, some acetate and minor furanic byproducts were detected, which could be ascribed to the loss of the 3-acetyl substituents from the substituted (dihydro)furans **3-5**.

Dynamic reaction progress was monitored using ^{13}C NMR tracking. Previous studies of this reaction have predominantly been based on single timepoint analysis, without considering the dynamic reaction progress. Mechanistic insights for improving existing reactions and devising new ones were therefore sought using time-resolved observations of the Garcia Gonzalez reaction. Figure 2 displays the reaction progress of a reaction between 2.2 M glucose and 2.2 M acetylacetone in water at 298 K in the presence of 0.1 eq. $ZrCl_4$. Reaction progress was tracked in real-time as a series of ^{13}C NMR spectra. Conditions that were conducive to conversions showed the presence of a symmetric enolate adduct with Lewis acid catalyst for acetylacetone (signal near 195 ppm in Figure 2, in addition to the signal near 210 ppm for the diketone form). The rapid conversion using substoichiometric amounts of catalyst in this reaction was somewhat surprising, considering that higher temperatures had previously been considered necessary for the reaction using glucose as the substrate.

In addition to the dihydrofuran intermediate **5**, a minor intermediate form with a similar kinetic profile was observed and chemical shifts allowed tentative assignment to a bicyclic dihydrofuran with a six-membered instead of a five-membered ring attached to the dihydrofuran (Figure S1). Time-resolved data indicated that the monocyclic compound **3** formed faster than the bicyclic variant **4** and its isomer (Figure S2), consistent with reports that have described the polyhydroxyalkyl furan **3** as the main product at lower temperatures and C-glycosyl furan **4** as the main product for higher temperatures[23,24] and longer reaction times[23] in the Garcia Gonzalez reaction.

The reaction was repeated using [1-^{13}C]glucose as the reactant to track the fate of this position and to validate the structural assignments of Figure 1B. The time-resolved tracking of the Zr(IV)-catalyzed Garcia Gonzalez reaction using [1-^{13}C] glucose is shown in Figure 3. These data not only identified the ^{13}C-labeled positions in compounds **3-5**, but also their neighbors through the splitting of adjacent sites through the $^1J_{CC}$ coupling. The ^{13}C-labeled positions and their neighbors agreed with the chemical shift assignments of Figure 1B and the data validated the faster appearance of the monocyclic polyhydroxyalkyl furan **3** as compared to the bicyclic C-glycosyl furan **4**. End-point analysis indicated that polyhydroxyalkyl furan **3** and C-glycosyl furan **4** form in an equilibrium mixture, where the equilibrium in the presence of Zr(IV)-catalysis vastly favors the C-glycosyl furan form at room temperature.

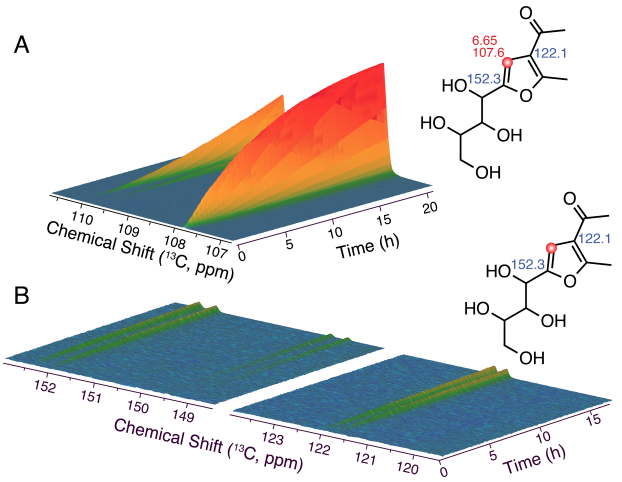

Figure 3. Time series of ^{13}C NMR spectra in the Garcia Gonzalez reaction using [1-^{13}C]glucose substrate to identify the site deriving from C1 (A) and its neighbors (B). Reaction conditions: 1 M [1-^{13}C]glucose and 1 M acetylacetone in D_2O, 298 K, 0.1 eq. $ZrCl_4$.

These observations indicated that polyhydroxyalkyl furan **3** was a kinetically somewhat stable intermediate at room temperature, while C-glycosyl furan **4** was the thermodynamic product of the reaction.

Kinetic model in agreement with experimental reaction tracking. Subsequently, the reaction was repeated at 323 K and 1 M substrate concentration to ensure full solubility of the reactants, especially of acetylacetone, for reaction tracking and kinetic fitting. The resultant time courses of **1**-**4** are shown in Figure 4. The time courses were subsequently fitted to a kinetic model assuming the largely irreversible bimolecular conversion of glucose (**1**) and acetylacetone (**2**) to **3**, and subsequent unimolecular conversion of **3** to **4**. The experimental ^{13}C NMR data supported this mechanism as evidenced by the excellent agreement between the fits of the kinetic model and data. The rate constants for the bimolecular first step and for the unimolecular second step in the kinetic model were determined to be 0.0024 $M^{-1}min^{-1}$ and 0.0025 min^{-1}, respectively. These values are consistent with a maximum accumulation of **3** to less than 30% within 4 hours of reaction time, followed by a decline at the expense of highly selective formation of **4** with a selectivity of approximately 90% (Figure 4). The bimolecular nature of the initial step implies that full conversion of substrates slows down more drastically than for a first-order reaction during the reaction progress. Hence, full conversion of substrate in the Garcia Gonzalez reaction, even with highly active catalysts and at elevated temperatures, is a time-consuming endeavor. Accordingly, optimized protocols employing continuous substrate supply or increasing temperature during reaction progress may be needed to ensure exhaustive conversion.

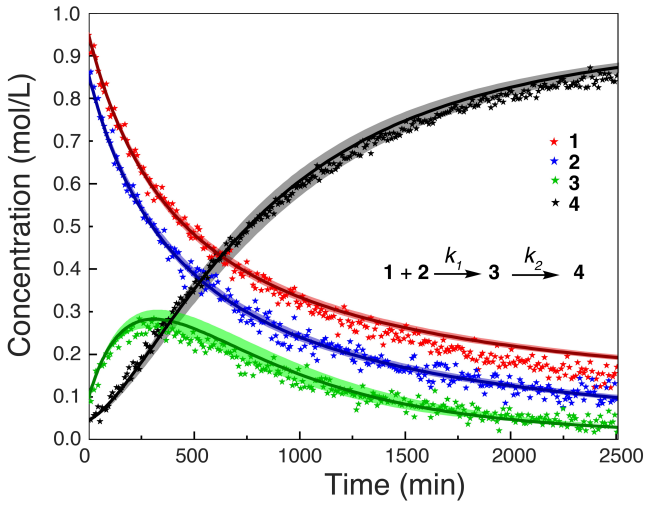

Figure 4. Fit of ^{13}C NMR integrals in the Garcia Gonzalez reaction to the shown kinetic model, yielding rate constants for the bimolecular and unimolecular reactions as indicated. The 95 % confidence intervals are shown. Monocyclic furan **3** does not accumulate strongly under these conditions. Reaction conditions: 1 M glucose (**1**) and 1 M acetylacetone (**2**) in D_2O, 323 K, 0.1 eq. $ZrCl_4$.

Mechanism. The kinetic model supporting the formation of polyhydroxyalkyl furan **3** and and C-glycosyl furan **4** by sequential second- and first-order reactions, respectively, alongside the formation of bicyclic dihydrofuran and the formation of diastereomeric product **4** and **4'**were subsequently used to propose the mechanism that is detailed in Figure 5. Notably, initial Knoevenagel addition and condensation products do not

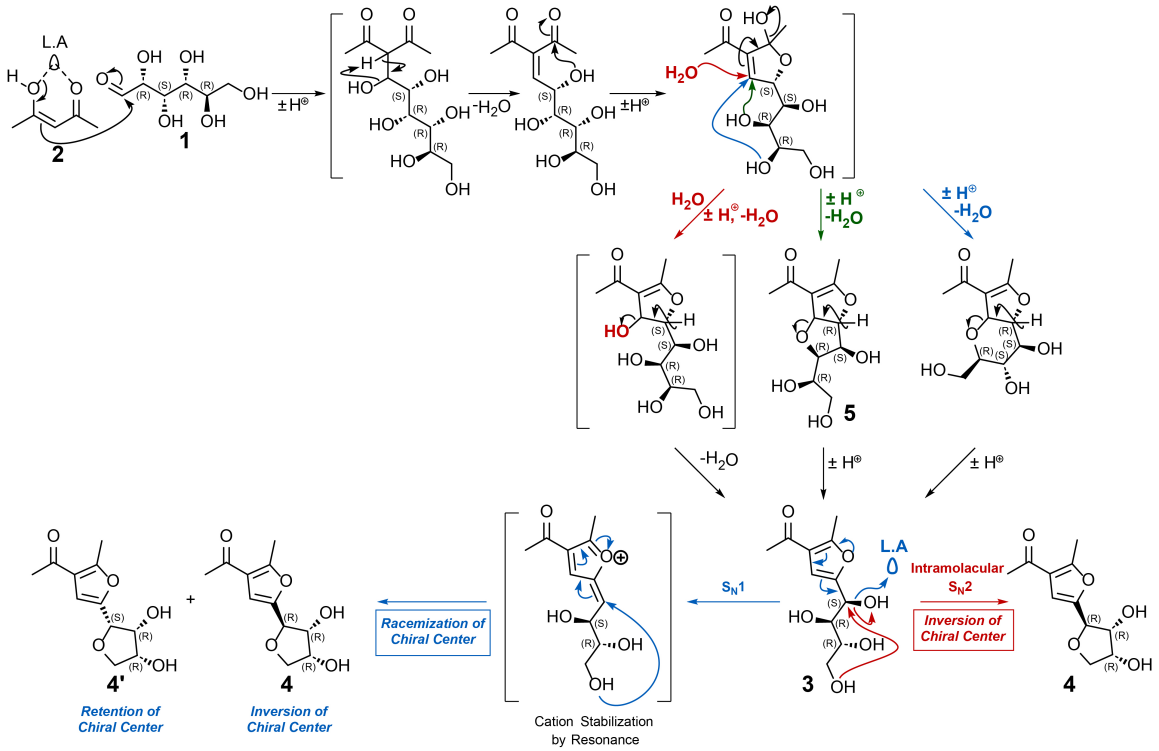

Figure 5. Plausible mechanism based on real-time NMR tracking data and kinetic modelling.

accumulate in significant amounts. Hence, cyclization of these species and subsequent dehydration was rapid relative to the chain elongation on glucose. This formation of dihydrofuran can plausibly entail the formation of monocyclic forms or bicyclic forms containing five- or six-membered rings (Figure 5). Among these plausible forms, only the bicyclic variant containing a five-membered ring fused to the furan ring was experimentally detected at appreciable amounts. This observation led us to probe the reaction with maltose as the substrate, as the glucose unit at the reducing end is protected at the C4 position by the α–1-4-glycosidic bond in maltose. Using maltose as a substrate and probe molecule for the proposed mechanism, the reaction toward C4 glycosylated forms of first **3** and then **4** was still observed and the glycosidic bond was found to remain intact (Figure S3). We hence concluded that the bicyclic dihydrofuran **5**, albeit the only intermediate upstream of **3** to accumulate at appreciable amounts, is not an obligatory on-pathway intermediate in the $ZrCl_4$-catalyzed Garcia Gonzalez reaction in water. Competition between equimolar maltose and glucose concentrations in the Garcia Gonzalez reaction showed that the conversion of glucose was more rapid than the conversion of maltose (Figure S4) and that this trend was reflected in the slower formation of C4 glycosylated forms of **3** and **4**, relative to the formation of **3** and **4** themselves.

The reaction was subsequently also visualized with other substrates to support the mechanism. Using xylose and fucose (Figure S5) as the substrates simplified the reaction outcome as expected, as these compounds lack the C6 methoxy functionality and hence cannot form the C-glycosyl furans. The conversion of xylose was largely complete within two hours at room temperature in the presence of 1 M substrates and 0.1 eq. $ZrCl_4$. By contrast, the use of hexoses complicates the accumulation of these monocyclic furans (**3**) when employing Zr(IV) catalysis due to the rapid cyclization between the C3 and C6 hydroxy groups. A viable approach to favor the accumulation of **3** is the use of high-concentration and largely solvent-free conditions in the conversion of unprotected aldose sugars, consistent with recently described reaction systems.[23,28] Using higher concentrations indeed elicited the higher accumulation of **3** from glucose and acetylacetone owing to the higher concentration dependence of the bimolecular formation of **3** relative to the unimolecular conversion of polyhydroxyalkyl furan **3** to C-glycosyl furan **4**. Notably, the use of largely solvent-free conversion of glucose and acetylacetone still afforded the formation of **4** within four hours at 323 K, even in the presence of as little as 0.01 eq. $ZrCl_4$ catalyst (Figure S6).

The conversion of glucose to polyhydroxyalkyl furan **3** and to C-glycosyl furan **4** was in previous studies often conducted at higher temperatures than 323 K. We hence repeated the kinetic experiment at higher temperatures from identical stock solution to compare the temperature dependence of reaction kinetics and of product distribution. Previous reports often had described polyhydroxyalkyl furan **3** as the predominant product at lower temperatures, but this observation may well have been the result of the initial formation of **3** and subsequent conversion to **4**. Kinetic experiments at 333 K and 343 K are shown in Figure 6A and 6B, respectively. These experiments showed that the equilibration between polyhydroxyalkyl and C-glycosyl furan could not be disregarded at temperatures above 323 K from the kinetic model. The kinetic model including a reversible conversion of polyhydroxyalkyl and C-glycosyl furan yielded excellent

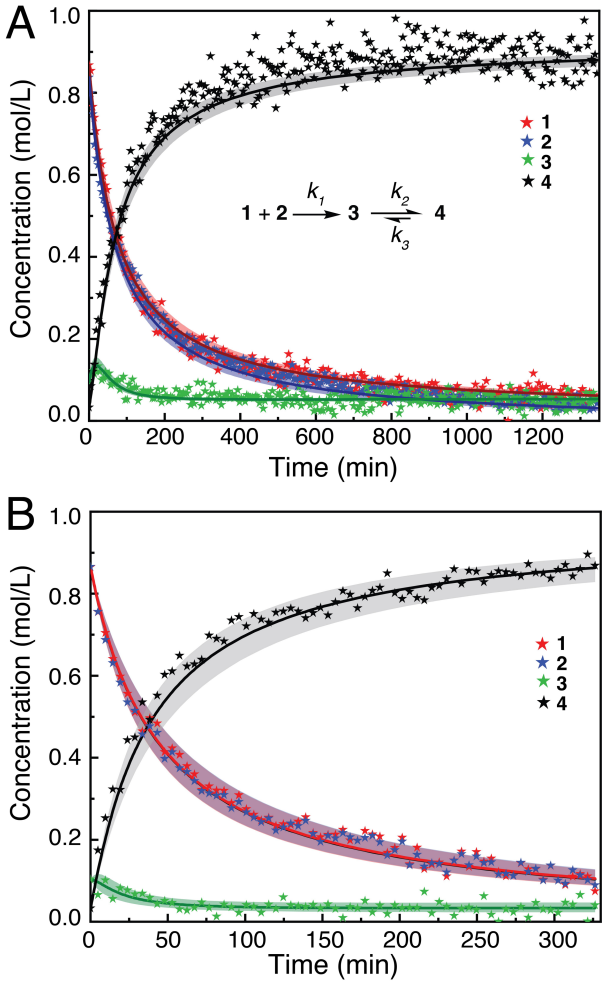

Figure 6. Fit of ^{13}C NMR integrals (recalculated to molar concentrations) in the Garcia Gonzalez reaction at 333 K (A) and 343 K (B) showing decreasing accumulation of **3** as a kinetic intermediate but increasing formation as a thermodynamic byproduct in equilibrium at increasing temperature. Reaction conditions: 1 M glucose (**1**) and 1 M acetylacetone (**2**) in D_2O, 333 K, 0.1 eq. $ZrCl_4$.

agreement between experimental and fitted data for reactions at 333 K and 343 K. The temperature range was limited by solubility considerations for acetylacetone and by hardware restrictions. The temperature dependence of rate constants k_1-k_3 allows an approximation of the energy barriers for the individual reaction steps to between 61 and 82 kJ/mol, comparable to previous determinations of the activation energy to ~67 kJ/mol in the conversion of ribose with acetylacetone using a Zr-based metal-organic framework (UiO-66).[36] Equilibrium ratios of **3** and **4** in the experiments of Figure 6 showed that the equilibrium was close to thermoneutral.

Alternative Lewis acidic media with equivalent performance. Finally, we set out to compare different Lewis acidic media beyond Zr(IV)[23] and Ce(III)[28,37] for their ability to catalyze the Garcia Gonzalez reaction with non-protected glucose in water at mild temperatures. According to computational predictions, the initial catalytic function of Lewis acids in the Garcia Gonzalez may be ascribed to the coordination to acetylacetone and its activation to an enolate form.[41] Hence, we probed if the distinct ability of different Lewis acidic salts to catalyze the Garcia Gonzalez reaction was reflected by their ability to coordinate

acetylacetone in a suitable binding regime according to Sabatier's principle. For this purpose, spectra of 1 M acetylacetone were acquired in the presence of 0.1 eq. of various Lewis acidic salts (Figure 7A) to probe catalyst/substrate interaction strength prior its comparison with the catalytic prowess. The catalytic proficiency of Zr(IV) encouraged us to probe other tetravalent Lewis acids with an emphasis on Hf(IV), in addition to Zn(II) and Sc(III) that had been previously employed for the reaction between β-dicarbonyls and aldoses.[23,25]

Coordination of 1 M acetylacetone by Zn(II) was weak, and no evident change to the ^{13}C NMR spectrum of acetylacetone was observed in the presence of 0.1 eq. $ZnCl_2$. By contrast, the addition of 0.1 eq. $Sc(OTf)_3$ led to intermediate fast exchange and changes in spectral positions of acetylacetone, while the addition of 0.1 eq. Hf(IV) or Zr(IV) chloride resulted in stronger binding, as evidenced by intermediate slow exchange and the appearance of an additional spectral species of a symmetric acetylacetone enol tautomer (highlighted with arrows Figure 7A). Repetition at higher temperatures indicated an intermediate exchange rate between Zr(IV)-bound and free enol form near 300 s^{-1} at 313 K and correspondingly slower exchange rates below and faster rates above 313 K.

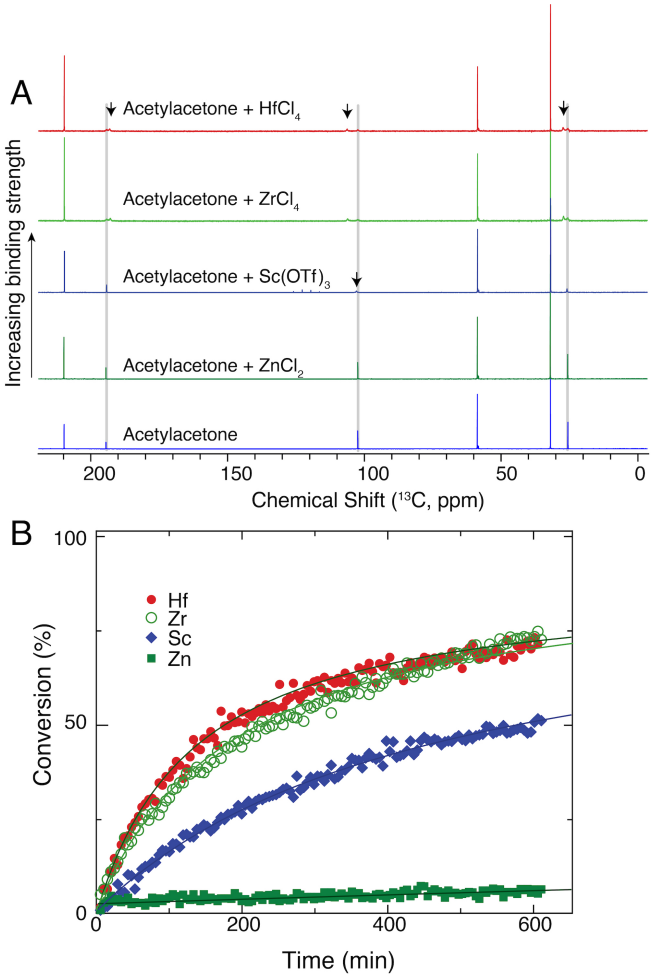

Figure 7. (A) ^{13}C NMR (101 MHz) of 1 M acetylacetone in the absence and in the presence of 0.1 eq. $ZnCl_2$, $Sc(OTf)_3$, $HfCl_4$ and $ZrCl_4$ (bottom to top) at 298 K. (B) Corresponding conversion of acetylacetone in the presence of 1 M glucose at 323 K.

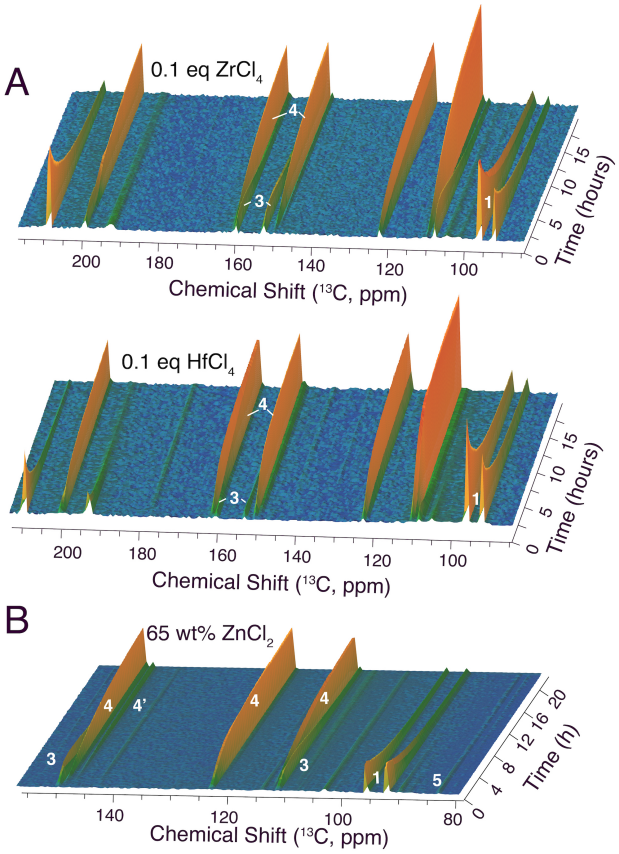

Figure 8. Time series of ^{13}C NMR spectra in the Garcia Gonzalez reaction. (A) Reaction catalyzed by 0.1 eq. $ZrCl_4$ (top) or $HfCl_4$ (bottom) at 323 K. (B) Reaction in $ZnCl_2$ medium (65 wt % $ZnCl_2$ solution in water) at 303 K. Reaction conditions: 1 M glucose (**1**) and 1 M acetylacetone (**2**) in D_2O.

Distinct Lewis acid complexation by acetylacetone was then correlated to the conversion of the acetylacetone at 323 K in the presence of 0.1 equivalents Lewis salts, upon addition of 1.0 equivalent glucose (Figure 7B). The kinetic observations indicated that the conversion in the Garcia Gonzalez reaction correlated to the binding strength of the Lewis acids to acetylacetone in the order Hf(IV)≈Zr(IV)>Sc(III)>Zn(II). These observations were consistent with DFT calculations on multiple-bond forming reactions, which have previously indicated that the enol tautomer is more reactive than its keto counterpart as the nucleophilic species attacking the aldehyde group.[41] Hence, catalyst/substrate interactions appeared too weak for optimal catalytic performance using Sc(III) and Zn(II).

The spectra of Figure 7A and the conversion kinetics of Figure 7B on the other hand suggested that zirconium catalysis is not unique in glucose upgrading to C-glycosyl furan at low temperature and catalyst loading. As was evident from the detailed comparison of the reaction progress with tetravalent zirconium and hafnium salts (Figure 8A), the catalytic activity of zirconium is paralleled by hafnium, where the latter accumulated less polyhydroxyalkyl furan as a kinetic intermediate due to faster conversion of polyhydroxyalkyl furan to C-glycosyl furan (Figure 8A). Hence, Hf(IV) emerges as a catalyst with even slightly superior formation of C-glycosyl furan relative to Zr(IV). Kinetic data of Figure 7B further indicated that the substrate conversion in the Garcia Gonzalez reaction proceeds approximately tenfold slower with Zn(II) catalysis than with Zr(IV) or

Hf(IV) catalysis. Considering this degree of catalytic activity when using 0.1 eq. Zn(II), we finally explored the ability of a concentrated salt medium of $ZnCl_2$ (65 wt % $ZnCl_2$ solution in water) to catalyze the conversion of glucose and acetylacetone near room temperature. This medium had previously been described as a non-toxic, and recyclable homogeneous reaction medium for converting polysaccharides and lignocellulosic or chitin biomass into dehydrated chemicals, such as 5-hydroxymethylfurfural or levulinic acid.[39–41] Owing to the high concentration of Zn(II) in this medium (~4.8 M), we anticipated that the Garcia Gonzalez reaction may proceed faster at milder temperatures than when using 0.1 equivalents (0.1 M) Zr(IV) or Hf(IV). We tested this hypothesis by conducting the reaction near room temperature in 65 wt % $ZnCl_2$, as shown in Figure 8B. As predicted, the reaction proceeded more rapidly in 65 wt % $ZnCl_2$ near room temperature than in medium using catalytic amounts (0.1 eq.) of $ZrCl_4$ at 20 K higher temperature. The reaction followed a reaction pathway that resembled the $ZrCl_4$ catalyzed pathway, as the compounds **3-5** were observed in the conversion in the concentrated solution of $ZnCl_2$ in the same order as with $ZrCl_4$ catalysis (Figure 8A). Thus, the ^{13}C NMR screening of metal-enolate interactions, of reactivity in the presence of aldose and of quantitative concentration changes reaction pathway emerge as a suitable toolbox to developing carbohydrate upgrading methods to valuable, bioactive compounds.

CONCLUSION

Time series of ^{13}C NMR spectra show that carbon chain extension of the aldehyde group in aldoses with acetylacetone proceeds with bimolecular kinetics. Rapid dehydration and cyclization steps follow, such that the acyclic Knoevenagel addition and condensation products are not significantly populated. Real-time ^{13}C NMR data were used to identify bicyclic dihydrofuran intermediates, while the use of protected substrate, specifically maltose, indicated that the main dihydrofuran intermediate is not an obligate on-pathway intermediate. Kinetic data supported the proposed mechanism and provided insight into the energetics of the pathway. Specifically, the Knoevenagel addition proceeds to a polyhydroxyalkyl furan via low populated intermediates. The polyhydroxyalkyl furan equilibrates with C-glycosyl furan in a reaction that favors the C-glycosyl furan ($\Delta G^0 \approx$ -8.4 kJ/mol). Reaction tracking provides further insight into the catalytic system by highlighting that the reaction between glucose and acetylacetone in nearly solvent-free eutectic mixtures can proceed at catalyst loadings as low as 0.01 eq. Zr(IV) within four hours at 323 K. Owing to its strong complexation of β-dicarbonyls, Hf(IV) emerges as a catalyst that similarly potent as Zr(IV) in the reaction. The conversion by Zn(II) was an order of magnitude lower than conversion by Zr(IV) and Hf(IV). Nevertheless, it was correctly predicted that a concentrated solution of $ZnCl_2$ can catalyze the reaction at similar rate using 20 K lower temperatures than for the Zr(IV) and Hf(IV) catalyzed reactions. We finally note that the initial part of the reaction mechanism via transient and low-populated Knoevenagel adducts and cyclized dihydrofurans largely resembles the base-catalyzed reaction pathway of unprotected aldoses with CH acids such as malononitrile,[18–20,26] with the principal difference that Lewis acids catalyze the cyclization of sufficiently long polyol tails deriving from the aldose.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

PDF with detailed spectroscopic data. Assignment of minor intermediate, 2D NMR of products including isomeric bicyclic furan, time series of spectra using maltose substrate, conversion of glucose and maltose in a competition experiment, time series of spectra using fucose and xylose substrate, time series of spectra using various substrate concentrations and catalyst loadings

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TOC Figure