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Mechanism and Malleability of Glucose Dehydration to HMF: Entry Points and Water-Induced Diversions

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The stoichiometric dehydration of glucose to 5-hydroxymethylfurfural (HMF) converts an abundant substrate to a versatile chemical. HMF formation can be optimised by using suitable solvents including ionic liquids and DMSO, and by cosolvents such as water. A prerequisite for efficient glucose influx into pathways to HMF is the isomerization of glucose to a ketose, typically the Lewis acid catalysed conversion to fructose. Here, solvent control of the influx of glucose into pathways to HMF is mapped through isotope tracing assays and through kinetic in situ observations. Diversions from the path to HMF in the presence of water are described for the popular CrCl₃/DMSO system. Addition of water to this system favors the formation of a useful byproduct instead of a mixture of inert compounds. The water-enabled formation of this product is observed for a variety of catalysts and solvents.

Introduction

The use of biomolecules as sources for fuels and materials has been considered increasingly imminent, not least because of the consequences of anthropogenic CO₂ release to the atmosphere. Glucose is the principal product of CO₂ reduction in photosynthesis. The pure monomer is accessible upon hydrolysis of its glucose storage forms or structural polymers. Hence, the conversion of glucose to versatile chemicals is a top priority in sustainable chemistry. Among the most important chemicals that are accessible from glucose is 5-hydroxymethylfurfural (HMF), which is being widely explored as a prospective precursor for polymers, fuel additives, solvents, and pharmaceuticals. The mechanistic pathways from monosaccharides to 5-hydroxymethylfurfural have remained remarkably controversial, as various plausible routes through acyclic or cyclic intermediates can be envisioned. The most efficient approaches to convert glucose to HMF entail the use of suitable Lewis acidic catalysts to convert glucose to fructose prior to dehydration. In particular, chromium chloride (as CrCl₂ or CrCl₃) has been established as particularly efficient in converting glucose to HMF. The stoichiometric dehydration of cyclic fructose to HMF is a Brønsted acid catalysed reaction. In aqueous solution, the reaction suffers from poor yields, as HMF is susceptible to rehydration and decomposition to levulinic acid. However, HMF is a stable product under conditions that disfavor polymerization, for instance when using aprotic polar or ionic liquid solvents and moderate reactant concentrations. The conversion of glucose to HMF in these solvents is limited by the formation of anhydrosugars or disaccharides. These undesired side reactions can be counteracted in the presence of water. Some disagreement persists in the literature, whether the overall selectivity for HMF formation from glucose is improved or impaired by the addition or accumulation of water in the dehydration reaction.

Catalysts of interest for the conversion of carbohydrates to value-added chemicals include paramagnetic Lewis acids. At millimolar concentrations, paramagnetic catalysts constitute paramagnetic cosolutes that accelerate the T₁ relaxation of analyte nuclei nuclei. Such conditions permit sensitivity improved, quantitative in situ NMR spectroscopy with higher time resolution than experiments in the absence of paramagnetic catalysts could have. Here, this improvement on in situ spectroscopy was employed to gain insight into the entry points, kinetics and water effect in the Cr³⁺-catalysed conversion of glucose to HMF in DMSO. Isotope tracking studies show that

Scheme 1. Schematic overview of the partitioning of glucose into three initial reactions in the conversion to HMF, and of the negative (red) or positive effect of water on the reactions.
the influx of glucose into various Cr\textsuperscript{III}-catalysed pathways partitions into 1,2 H shift, 1,5 H shift and 1,2 C shift reactions approximately as 95%, 4% and 1%, respectively. This distribution is not significantly affected by the presence of water. Addition of water slows down HMF formation and especially affects the first dehydration reaction of fructose. In addition, glucose is diverted from the HMF pathway to the open chain C6 acid trans-2,5,6-trihydroxy-3-hexenoic acid (THA; Scheme 1) in the presence of water. Selectivity towards THA relative to HMF is found to increase with water content. The yield of HMF is only weakly affected by the presence (or liberation) of water in the stoichiometric dehydration of glucose to HMF in a DMSO/water solvent system containing predominantly DMSO. A significant benefit of water in such a solvent system is that only one major byproduct with potential use as a polymer building block is formed. Consequences of water addition on HMF formation kinetics have to be considered, as water obstructs the first dehydration step of fructose.

Experimental section

Chemicals

D\textsubscript{2}O (99.9 atom % D), d\textsubscript{6}-DMSO (99.9 atom % D), 1,4 dioxane (anhydrous, >99.8%), γ-valerolactone (>99%) D(+)-glucose (>99.5%, henceforth referred to as glucose), [1-\textsuperscript{13}C] D-glucose (99 atom % \textsuperscript{13}C), and [2-\textsuperscript{13}C] D-fructose (99 atom % \textsuperscript{13}C) were obtained from Sigma–Aldrich. CrCl\textsubscript{3}·6H\textsubscript{2}O (>96%), AlCl\textsubscript{3}·6H\textsubscript{2}O (>99%), and InCl\textsubscript{3} (98%) were obtained from Merck. For simplicity, [1-\textsuperscript{13}C] D-glucose and [2-\textsuperscript{13}C] D-fructose will be referred to as [1-\textsuperscript{13}C] glucose and [2-\textsuperscript{13}C] fructose, henceforth.

Catalytic experiments

In a typical catalytic experiment, 50 mg monosaccharide and 2-4.5 mg CrCl\textsubscript{3}·6H\textsubscript{2}O (depending on whether \textsuperscript{1}H or \textsuperscript{13}C detected NMR experiments were acquired) were dissolved in 550 μl d\textsubscript{6}-DMSO at room temperature and transferred to a 5 mm NMR sample tube. In experiments probing the mechanistic effect of water, a stock solution of 1.2 ml d\textsubscript{6}-DMSO, 150 mg glucose and 7.5 mg CrCl\textsubscript{3}·6H\textsubscript{2}O was prepared. To 400 μl of this stock solution, 170 μl of d\textsubscript{6}-DMSO, 170 μl of D\textsubscript{2}O or 85 μl each of D\textsubscript{2}O and d\textsubscript{6}-DMSO was added to final fractions of 0%, 30% and 15% (v/v) water in DMSO. Sample tubes were transferred to a ceramic spinner turbine and placed into a 600 MHz Bruker NMR spectrometer equipped with a broadband probe (BBFO) SmartProbe equilibrated to the desired temperature (110-130 °C).

NMR spectroscopy

Kinetic in situ experiments were acquired as series of \textsuperscript{1}H or \textsuperscript{13}C NMR spectra in a pseudo-2D fashion using a 600 MHz Bruker Avance III NMR spectrometer equipped with a SmartProbe, using d\textsubscript{6}-DMSO as the lock substance in all circumstances. Free induction decays were sampled as 16384 complex data points using a spectral width of 16 ppm during an acquisition time of 1.7 seconds in the case of \textsuperscript{1}H spectra, while 64k complex data points (spectral width of 240 ppm) were sampled for 1.8 seconds (aq) in the case of \textsuperscript{13}C spectra. Inter-scan recycle delays of 2 seconds were used for the series of \textsuperscript{1}H spectra. Recycle delays of 3 seconds were used for \textsuperscript{13}C spectra. Automatic shimming by Bruker Topspin Topspin 3.5 pL7 software during the experiment was employed.

\textsuperscript{13}C \textsuperscript{T1} relaxation times had previously been measured on Cr\textsuperscript{III} containing reaction mixtures showing that the Cr\textsuperscript{III} had shortened relaxation times to below 1 s for glucose and HMF \textsuperscript{13}C spins. Such shortened relaxation times have the benefit that \textsuperscript{13}C spectra in reaction tracking were quantitative (sum of recycle delay and acquisition time corresponds to ~5·T\textsuperscript{1}) with high time resolution and sensitivity. Pseudo-2D spectra were processed in Bruker Topspin 3.5 pL7 with baseline correction and integrated using the Dynamics module of the software. Signal areas rather than intensities of the reactants, intermediates and products were considered.

Data analysis

Signal areas were fitted using pro Fit 7 (QuantumSoft, Zurich). Data and fits were plotted in pro Fit 7. For the experiment containing 30% (v/v) water in the CrCl\textsubscript{3} catalysed reaction in d\textsubscript{6}-DMSO, rates of product formation were determined as the slopes of product formation against time, while selectivity was determined as the slope of product formation relative to the slope of glucose consumption. Rate and selectivity were plotted against the reaction progress (glucose conversion) in Fig. 7 alongside trend lines to guide the eye.

Results and discussion

\textsuperscript{13}C Isotope flux analysis of pathways to HMF

Efficient influx of substrate into pathway intermediates that can be rapidly dehydrated to HMF is a prerequisite for the efficient conversion of carbohydrates. The entry point for glucose into the HMF forming pathway catalysed by CrCl\textsubscript{3} was established under conditions of HMF formation. The initial reactions of glucose (at sufficiently low concentration to disfavor humin catalysis) converts glucose to mannose as an off-pathway intermediate. Both 1,2 and 1,5 H-shift convert glucose to ketoses (fructose and sorbose, respectively), which are on-pathway intermediates towards HMF. In contrast, a 1,2 C-shift converts glucose to mannose as an off-pathway intermediate.

Isotopic isomers (isotopomers) of HMF formed from [1-\textsuperscript{13}C] glucose substrate is widely employed in metabolic research,\textsuperscript{21,22} while being considerably less widely established in chemocatalytic investigations.\textsuperscript{23} Both 1,2 and 1,5 H-shift convert glucose to ketoses (fructose and sorbose, respectively), which are on-pathway intermediates towards HMF. In contrast, a 1,2 C-shift converts glucose to mannose as an off-pathway intermediate.

Isotopic isomers (isotopomers) of HMF formed from [1-\textsuperscript{13}C] were tracked by NMR spectroscopy. HMF was found to be enriched with \textsuperscript{13}C at the positions 1, 6 and 2 respectively, while the three remaining positions contained \textsuperscript{13}C at natural abundance. [1-\textsuperscript{13}C] HMF, [6,\textsuperscript{13}C] HMF and [2-\textsuperscript{13}C] HMF derive from [1-\textsuperscript{13}C] glucose following 1,2 H-shift, 1,5 H-shift and 1,2 C-shift, respectively. This is consistent with the mechanism described above.
The kinetics of [2-13C] HMF formation upon an initial 1,2 C-shift is shown in Fig. 2B. The formation of [2-13C] HMF proceeds with a kinetics akin to the competing 1,2 H-shift pathway and at amounts comparable to the natural abundance species producing [1,2-13C] HMF. This species is formed from glucose labelled at C1 and carrying 1% natural abundance 13C enrichment at the C2 position via a 1,2 H-shift. Approximately 1% of [1-13C] glucose thus reacts through a 1,2 C-shift.

13C Isotope influx into pathways to HMF with different catalyst and substrate

When repeating the experiment with InIII instead of CrIII catalysis, no enrichment of the C2 and C5 positions were found, thus indicating that 1,2 C-shift and 1,5 H-shift are largely disfavored for some Lewis acid catalysis (Fig. 3). This
observation parallels similar observations for the isomerization reaction of glucose by In\textsuperscript{III} and Cr\textsuperscript{III} catalysis in water, which had suggested low propensity of In\textsuperscript{III} to catalyze 1,2 C-shifts in glucose.\textsuperscript{2}

The kinetic experiment of carbohydrate conversion to HMF was repeated using a 1:1 substrate mixture of [1-\textsuperscript{13}C] glucose and [2-\textsuperscript{13}C] fructose. Here, [2-\textsuperscript{13}C] HMF and [5-\textsuperscript{13}C] HMF arise as the main product species from [2-\textsuperscript{13}C] fructose with kinetics as shown in Fig. 4. The formation of [2-\textsuperscript{13}C] HMF from fructose is distinctly faster than formation of HMF from glucose and follows a different kinetic profile.\textsuperscript{26} The fraction of [2-\textsuperscript{13}C] HMF reacting to [5-\textsuperscript{13}C] HMF is smaller than the fraction of [1-\textsuperscript{13}C] glucose reacting to [6-\textsuperscript{13}C] HMF, possibly due to the 1,5 H-shift competing with the faster conversion of fructose to HMF. In addition, the formation of [5-\textsuperscript{13}C] HMF is considerably slower than the formation of [2-\textsuperscript{13}C] HMF, as the conversion of fructose to aldoses by a 1,5 H shift introduces additional reaction steps for the formation of HMF via this pathway.

**Influence of water on kinetics and selectivities**

The Cr\textsuperscript{III} catalysed conversion of glucose to HMF has previously been described in water, DMSO and mixtures of the solvents.\textsuperscript{11,18} The isotopic distribution in HMF formed from [1-\textsuperscript{13}C] glucose was thus probed with \textsuperscript{13}C NMR spectra upon Cr\textsuperscript{III} catalysis in DMSO and water. Cr\textsuperscript{III} catalysis showed approximately twofold lower propensity for 1,2 C-shift in water than in DMSO (Fig. S3). Different binding behavior to the paramagnetic Cr\textsuperscript{III} center in response to altered solvent composition can be corroborated by probing the Cr\textsuperscript{III}-induced paramagnetic relaxation\textsuperscript{20} of different chemicals at different solvent compositions. These observations indicate changes in binding behavior of oxygen-containing compounds upon altered solvent composition (Fig. S4) and stipulated the enquiry of further solvent-induced changes to the catalytic pathway towards HMF.

Conflicting views have been held on the water effect on the Cr\textsuperscript{III}-catalysed glucose conversion to HMF.\textsuperscript{3,18,27} The conversion of glucose to HMF is a dehydration process, whose efficient progress has been linked to the water removal methods.\textsuperscript{28} Some recent studies have nevertheless emphasised a neutral or even beneficial effect of 15-50% water on HMF formation,\textsuperscript{29} as water suppresses the sequestration of glucose into unreactive disaccharides and anhydroglucose forms.\textsuperscript{18,19} The effect of water in the Cr\textsuperscript{III}-catalysed glucose conversion to HMF was thus scrutinised in more detail using in situ NMR.

Resultant spectra of glucose conversion to HMF in the absence and in the presence of water are shown in Fig. 5. Excellent signal to noise ratios were rapidly obtainable with \textsuperscript{13}C NMR spectroscopy due to the rapid relaxation of the nuclei in the presence of Cr\textsuperscript{III} catalyst. In the absence of water, fructose and compound 1 (4(R,5R)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde intermediate)\textsuperscript{29} were detected in a time-resolved manner, in addition to the formation of disaccharides and anhydroglucose forms (Fig. S5-S7). Addition of water reduced formation of disaccharides and anhydroglucoses as expected.\textsuperscript{18} Under the used reaction conditions, the hydrothermal reaction reference led to the formation of anhydroglucose forms in the absence of added water, while other reactions only included spurious formation of HMF, which was negligible compared to reactivity in the presence of Cr\textsuperscript{III} catalyst (Fig. S8). Additional changes to reaction progress in the presence of water included the accumulation of fructose, while accumulation of compound 1 was reduced in the presence of water (Fig. 5, 6). Glucose conversion rates were minutely affected and conversion proceeded only marginally slower upon addition of up to 30% water (Fig. 5). Isotope distributions among HMF formed through initial 1,5 H-shift and 1,2 C-shift was not significantly affected by the addition of water. Overall, the addition of water primarily reduced the rate of the first step of fructose dehydration (Fig. 5C). This observation is consistent with the prediction that solvation of substrates with larger numbers of hydroxyl groups leads to higher activation energies and more strongly reduced dehydration rates in the presence of water (for instance slowing the dehydration of fructose as compared to the dehydration of...
selectivity of glucose conversion to THA and HMF are depicted in Fig. 7 as functions of substrate conversion. These plots indicate that the selectivity of THA formation remains largely constant during the reaction, albeit at continuously reduced reaction rates. In contrast, selectivity for the formation of HMF increases from a low initial level, as glucose initially is converted to intermediates (fructose and compound 1), and possibly as the consequence of effects from Brønsted acidic products such as THA. The selectivity for HMF thus remains high at conditions, where reaction rates have declined to approximately 10% (Fig. 7). Selectivities determined from real-time qNMR data are consistent with literature data describing ~80% selectivity to HMF in the CrCl₃/DMSO system in the presence of water. In addition, the selectivity for THA formation remains slightly below 20%. These analyses paint a picture of glucose conversion to HMF and THA side products, with a very minor contribution of other side products in the presence of water.

**Water-enabled THA formation with other catalysts and solvents**

The CrIII-catalysed conversion of glucose to HMF has attracted interest for use in various solvent systems, including pure water and pure DMSO. Figure 8 uses ¹H-¹³C HSQC spectra to show the gradual compositional changes of post-reaction material formed from glucose by CrIII catalysis in solvent systems containing 0-100% water in DMSO. The water-enabled THA formation increases in selectivity relative to HMF with increasing water content. Rehydration and degradation of HMF contributes to the shift in selectivity and becomes significant under the chosen reaction conditions above 60% water, as signified by the increased formation of formic acid under these conditions. Figure 8 indicates that THA formation can constitute a rather major pathway in CrIII-catalysed glucose conversion.

**Selectivity during reaction progress**

In the reaction of carbohydrates to HMF, stochiometric dehydration and the formation of various organic acid side products affects the water content and the pH of the reaction medium. Mechanistic changes during reaction progress are thus to be expected. The experiments of Fig. 6 were used to extract kinetics and selectivity of CrIII-catalysed glucose conversion during reaction progress. Changes in the rate and in the
Water-enabled THA formation was likewise observed when employing In\texttextsuperscript{III} or Al\texttextsuperscript{III} catalysts, or when using other organic solvent systems such as \(\gamma\)-valerolac-tone or 1,4-dioxane (Fig. S11-S13). Overall, the pathway to THA thus emerges as a rather widely relevant competitive pathway in the formation of HMF.

**Conclusions**

The malleability and control in the popular Cr\texttextsuperscript{III} catalysed conversion of glucose to HMF in DMSO was followed using quantitative *in situ* NMR. For commercialization, the formation of value-added side products in this reaction may become similarly important as changes to the HMF yield itself. The prospective polyester building block THA is the dominant side product in the presence of water, while a mixture of inert compounds constitutes the side products in the absence of water. Isotope distributions in HMF permit quantifying the initial influx of glucose into Cr\texttextsuperscript{III}-catalysed reactions under reaction conditions to HMF. Initial hydride shift reactions are only little affected by the presence of water, while 1,2 C-shift is noticeably reduced in water. In contrast, fructose dehydration is strongly hindered in the presence of water, consistent with theoretical considerations. Various solvent systems and catalysts indicate that the pathway to THA is a widely relevant competitive pathway in the formation of HMF.

**Conflicts of interest**

There are no conflicts to declare.

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**References**

A water-enabled reaction to a polyester building block is found to widely occur in the conversion of glucose to HMF.