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Molecular mapping of the acid catalysed dehydration of fructose†

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Several intermediates and different reaction paths were identified for the acid catalysed conversion of fructose to 5-(hydroxymethyl)-2-furaldehyde (HMF) in different solvents. The structural information combined with results of isotopic-labelling experiments allowed the determination of the irreversibility of the three steps from the fructofuranosyl oxocarbenium ion to HMF as well as the analogous pyranose route.

Acid catalysed conversion of biomass to carbon based chemicals[1,2] including liquid fuels[3,4] will be important for the sustainability of the chemical and pharmaceutical industry,[5] and to a lesser extent the energy industry.[6] The largest part of biomass is composed of mono-, di-, oligo-, and polysaccharides,[7] which are key components of sugar,[8] starch,[8] lignocellulose,[8] and even some algae.[9] Depolymerisation of the glycosidic bonds by hydrolysis can produce monosaccharides for subsequent conversions.[10]

A frequently underestimated complication in the conversion of fructose is that it has three types of structural isomers in equilibria,[8] with each of the two cyclic types having two diastereoisomers (**1a–e**, Scheme 1).

Their concentrations in solution depend on the solvent,[11] which can in turn be affected by the presence of water.[12]

The dehydration of carbohydrates to 5-(hydroxymethyl)-2-furaldehyde has been studied for decades, and many strategies have been tested to increase the yields.[13] One of the key issues has been the formation of a variety of side-products referred to as "humins",[14] a mixture of strongly coloured, soluble and insoluble oligomers and polymers which have so far eluded detailed structural characterisation.[15] Consequently, the prevention of their formation has been practically limited to trial and error approaches, with little molecular insight. Another important issue was to understand which isomers of fructose (**1a–e**) can lead to the formation of HMF. It was proposed that fructose is a necessary intermediate in the predominant route to convert glucose to HMF, involving the fructofuranoses **1b** and **1c**.[16,17]

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† Electronic supplementary information (ESI) available: Selected spectra (Fig. S1–S7) and tabulated NMR data for all the intermediates (Tables S1–S7). Schemes S1–S4 clarify mechanistic points related to reversibility and alternate pathways to HMF. See DOI: 10.1039/c2cc31689g

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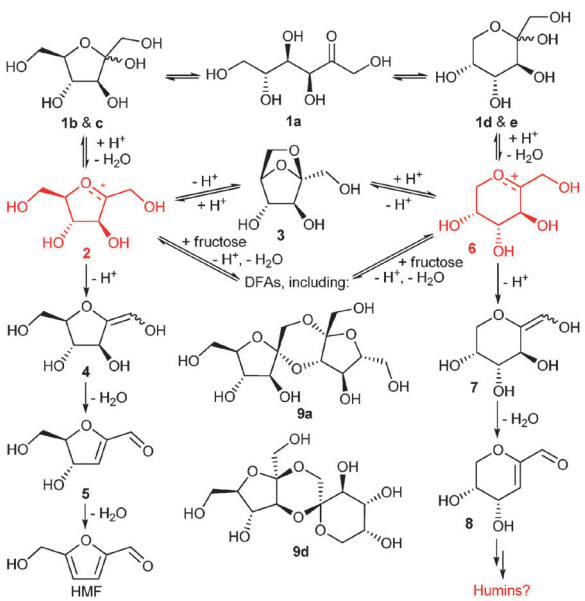
The identification of the "half of the NMR signals" of (4*S*,5*R*)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde (**5** in Scheme 1) supported the intermediacy of **1b** and **1c**.[17]

We report the first *in situ* characterisation of four intermediates in the acid catalysed dehydration of fructose, and the identification of the different reaction paths to HMF and some of the side products. In addition, the facile and reversible formation of 2,6-anhydro-β-D-fructofuranose (**3**) was observed. This might result in an intrinsic mechanistic limitation of selective HMF synthesis by providing an alternative connection between the preferred path to HMF (*via* furanoses **1b** and **1c**) and that of the formation of unwanted side-products (*via* pyranoses **1d** and **1e**).

DMSO has been reported to be one of the better solvents for the conversion of carbohydrates to HMF.[18,19] We have therefore first investigated the dehydration of fructose in DMSO (and/or DMSO-d_6) in the absence and presence of sulfuric acid as a catalyst. All intermediates were characterised by *in situ* NMR. For species with particularly low concentrations, it was essential to use singly ^{13}C-labelled fructoses in conjunction with 2D techniques to assign the resonances (Tables S1–S7, ESI†).

While fructose can be readily dissolved in DMSO at room temperature (Fig. S1a, ESI†), it took several days to reach equilibria between the five isomers (**1a**: D-fructoketose 2.4%,



Scheme 1 Molecular isomers of fructose (**1a–e**) and their acid catalyzed dehydration to HMF and side products.

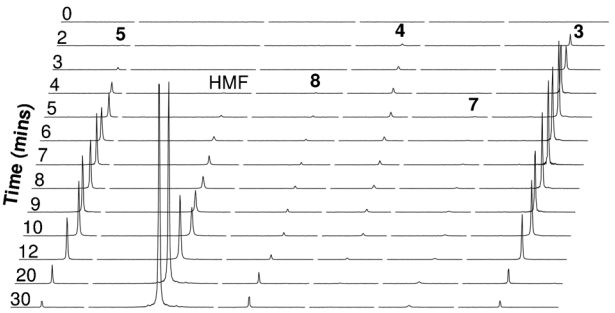


Fig. 1 Selected ^{13}C NMR spectra for the heating of 2-^{13}C-fructose in DMSO-d_6 solution at 150 °C.

1b: α-D-fructofuranose, 19.6%, **1c** β-D-fructofuranose: 46.1%, **1d**: α-D-fructopyranose 4.3%, and **1e**: β-D-fructopyranose, 27.4%) as shown by ^{13}C NMR of 2-^{13}C-fructose (Fig. S1b, ESI†). These equilibria can be established much faster at higher temperatures,[19] for example, after heating at 150 °C for 5 minutes and rapidly cooling the sample, the composition was **1a**: 2.4%, **1b**: 18.5%, **1c**: 42.9%, **1d**: 4.1%, and **1e**: 32.2% (Fig. S2, ESI†). After 5 minutes, 49% of fructose was converted, and the largest new peaks in the ^{13}C NMR spectrum were at 108.3 and 151.6 ppm (Fig. 1), due to 2,6-anhydro-β-D-fructofuranose (**3**, 12.4%) (Fig. S4 and Table S1, ESI†) and HMF (Table S2, ESI†), respectively. The new resonance at 139.2 ppm was assigned to (2*R*,3*S*,4*S*)-2-(hydroxymethyl)-5-(hydroxyl-methylene)tetrahydrofuran-3,4-diol (**4**, 0.3%) (Fig. S5 and Table S3, ESI†), formed by the deprotonation of **2**.[20] The peak at 156.5 ppm was due to **5** (0.6%) (Fig. S6 and Table S4, ESI†) which was partially characterised previously,[17] and was formed by the loss of water from **4**. Upon heating for an additional 20 minutes, the conversion of fructose increased to 86.2%, while **4** was barely detectable and the concentration of **5** increased to 0.9%. Furthermore, the concentration of **3** decreased to 1.4%, while the yield of HMF increased to 54.5%. In addition, we also observed the transient formation of (3*S*,4*R*,5*R*)-2-(hydroxymethylene)-tetrahydro-2*H*-pyran-3,4,5-triol (**7**) (Table S5, ESI†) and (3*R*,4*S*)-3,4-dihydroxy-3,4-dihydro-2*H*-pyran-6-carbaldehyde (**8**) (Fig. S7 and Table S6, ESI†), two key intermediates for the pyranose route (Fig. 1). The maximum yield of **7** was 1.9% after 30 minutes, which was gradually converted into **8** and then to side-products such as humins, since unlike **5**, **8** cannot readily aromatize to form a stable species. Peaks due to at least six difructose dianhydrides were also observed (DFAs, **9a–f**, up to 12.5%) (Fig. S3, ESI†).[21] The chemical shifts of one of the DFAs, α-D-fructofuranose β-D-fructofuranose 1,2′:2,3′-dianhydride (**9a**) (Scheme 1), were identified by comparison with an authentic sample (Table S7, ESI†). After 4 hours, the major detectable species were **9a–f** (4.3%) and HMF (79%). Although heating the reaction mixture for a total of 8 hours resulted in the complete disappearance of **9a–f**, the HMF yield also decreased. The relative reactivity of DFAs compared to fructose was studied by heating a sample of **9a** in DMSO. After 4 hours the HMF yield was only 8.7%, although this increased to 56.7% after 16 hours heating.

If the reaction was monitored at one minute intervals, **3** and **4** were easily observable as the first two new species (Fig. 1), followed by the formation of **5**, **7**, **8** and HMF, as expected.

The three steps from **2** leading to HMF are irreversible. This was demonstrated by the stereospecificity of the intermediates, and the lack of deuterium incorporation in experiments where the fructose hydroxyls were previously replaced with deuterium, or, with the addition of 1.7–22.4 equivalents of D_2O (Scheme S1, ESI†).

The same deuterium labelling experiments also allowed us to rule out the formation of HMF from the linear isomer **1a**. This requires the formation of the intermediate 3-deoxy-D-erythro-hexos-2-ulose (**12**, Scheme S4, ESI†),[22] which in turn requires the acquisition of a proton from solution to form the CH_2 at C-3. Less than 1% deuterium was measured at the C-3 position of HMF.

Although some mechanisms have shown that **4** must first tautomerise to form a 2,5-anhydro-D-aldofuranose,[16] we could detect only trace quantities of it in the later stages of the reaction. An authentic sample was found to be more robust than fructose, requiring 16 h to be completely converted and reach a maximum HMF yield.

No scrambling of any of the carbon atoms of all the possible singly ^{13}C-labelled fructoses was observed, indicating that no C–C bond cleavage occurred during the reaction. Once the reaction mixture had equilibrated, the relative proportions of the isomers did not change significantly, indicating that isomerisation was faster than any of the fructose-consuming reactions.

Trace amounts of formic acid (FA),[23] 2-furyl hydroxymethyl ketone[24] and furfural[23] were also detected. Of the intermediates described, it was only possible to isolate crude **3** and HMF (4 : 1 CH_2Cl_2 : MeOH), and a mixture of DFAs (after acetylation) by column chromatography due to their higher stability in solution and in the presence of silica.[25]

Since DMSO could decompose to various products including CH_3SO_3H and H_2SO_4 at higher temperatures,[26] the *in situ* formed acids served as the catalysts for the dehydration.[27] This was confirmed by heating a mixture of fructose, DMSO-d_6 and $NaHCO_3$ at 150 °C for 2 hours, after which only trace quantities of HMF were detected. Further evidence was provided by studying the reaction in the absence and presence of added H_2SO_4 at 120 °C. The HMF yield started to increase significantly when the concentration of H_2SO_4 was higher than 10^{-6} mol L^{-1} and reached a maximum value of 80% at 10^{-2} mol L^{-1} H_2SO_4 (Fig. 2). Higher acid concentrations resulted in the formation of levulinic acid (LA) and FA.

A wide range of solvents have been tested for the dehydration of fructose, so our study was broadened to include other polar aprotic systems (dimethylacetamide (DMA)/LiCl,[28] 1-butyl-3-imazolium chloride (BMIMCl), γ-valerolactone (GVL)/BMIMCl mixtures and an aqueous acidic (D_2O/D_2SO_4) system. In DMA/LiCl, the product distribution is superficially similar to that in DMSO/DMSO-d_6, except that none of the DFAs were present. This is an interesting result, which suggests that the chloride anion plays a critical role in either breaking up the fructose oligomers formed *in situ* or preventing their formation. When using unlabelled fructose in BMIMCl or GVL/BMIMCl mixtures **5** and **7** were easily detectable.

By contrast in D_2O in the presence of 0.18–0.47 mol L^{-1} D_2SO_4 at 95 °C, **3**, none of the DFAs, and none of the intermediates **4**, **5**, **7**, and **8** were observed. It is plausible that

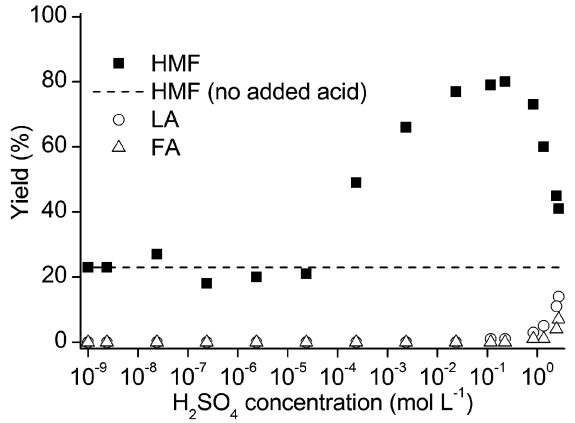


Fig. 2 Product yields from fructose in DMSO as a function of H_2SO_4 concentration.

in the presence of large quantities of water, the fructosyl oxocarbenium can easily react with water to reform fructose. Thus, maintaining a higher concentration of free fructose increases the rate of side product formation. No deuterium was incorporated into HMF, consistent with previous work,[29] and consistent with the mechanism being largely solvent-independent. HMF was also hydrated to form levulinic and formic acids, the formic acid being almost exclusively derived from the fructose C-1, as expected.[30]

Based on our results, we can draw a detailed reaction map to describe the acid-catalysed conversion of fructose. Its protonation and dehydration lead to fructosyl oxocarbenium ions (Scheme 1), among which, the formation of **2** is probably more energetically favoured than **6**.[30] Reversible intramolecular nucleophilic attack of **2** by the terminal OH-6, followed by deprotonation could yield **3**. Alternatively, intermolecular nucleophilic attack by other fructose molecules could form DFAs, which in turn can act as a reversible fructose "reservoir". In the later stages of the reaction the water concentration is also high enough to compete for **2** by hydrating it to re-form **1b** and **1c**.

Alternatively, **2** can be deprotonated to form **4**, and then readily lose water to yield **5**, which can then dehydrate to form HMF. Similar arguments can be made for the conversion of **6** to **7** and **8**, but in this case **8** presumably decomposes to side products such as humins. In the early stages of the reaction, the concentration of **3** was high, and that of **4**, **5** and HMF was low, showing that the loss of a proton from **2** at O-6 by breaking the O–H bond is more energetically favoured than from C-1 by C–H bond cleavage. In the later stages, the concentrations of both **3** and **4** were low, coinciding with an increase in the water concentration promoting the reverse reaction of **2** to **1b** or **1c**. Experiments with varying water concentrations did not show significant changes in the rate of formation of HMF, leading us to the conclusion that under both anhydrous and "hydrous" conditions the deprotonation of **2** to form **4** is always the rate limiting step.

The concentrations of intermediates **4**, **5**, **7** and **8** were too low to be detected in the presence of added acid, indicating that their dehydration is even more sensitive to acid catalysis than the rate-limiting deprotonations of **2** and **6**.

In conclusion, several intermediates and different reaction paths were identified for the acid catalysed conversion of fructose to HMF. The structural information combined with isotopic-labelling allowed the determination of the irreversibility of the three steps from the fructofuranosyl oxocarbenium ions to HMF as well as the analogous pyranose route.

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