Biomass Conversion

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Mechanism of Glucose Isomerization Using a Solid Lewis Acid Catalyst in Water**

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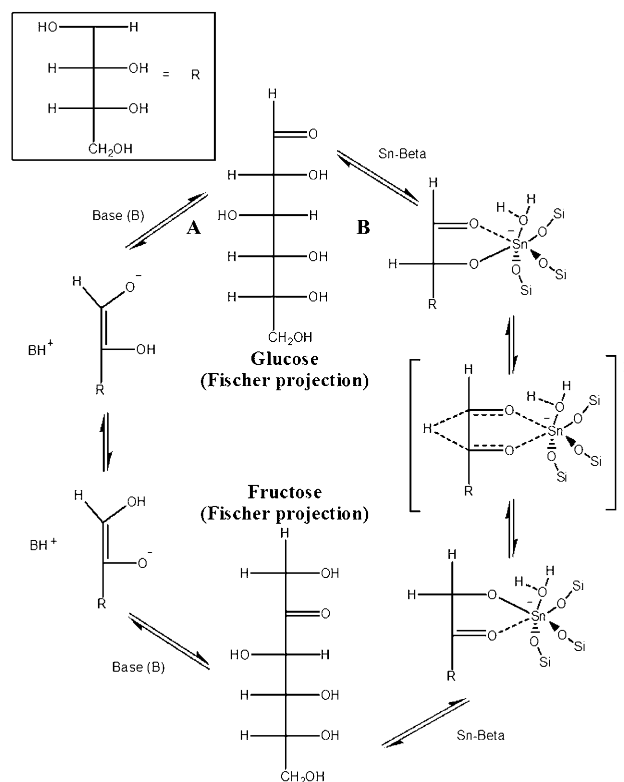
The conversion of glucose into fructose for the production of high-fructose corn syrups (HFCS) is the largest biocatalytic process in the world, and it recently has been considered as a key intermediate step in the conversion of biomass to fuels and chemicals.[1] This reaction is typically catalyzed by an immobilized enzyme, xylose isomerase, that generates an equilibrium mixture of 42 wt % fructose, 50 wt % glucose, and 8 wt % other saccharides. The enzymatic process is highly selective, but it has several drawbacks that increase processing costs, including the use of buffering solutions to maintain pH, narrow operating temperatures, strict feed purification requirements, and periodic replacement of the enzyme due to irreversible deactivation.[1a] Inorganic bases can also catalyze this reaction, albeit with low yields due to the reduced stability of monosaccharides in the presence of basic catalysts.[2] The mechanism of this aldose–ketose isomerization involves hydrogen transfer from C-2 to C-1 and from O-2 to O-1 of an α-hydroxy aldehyde to create the related α-hydroxy ketone (Scheme 1).[3] This mechanism can occur either by a proton transfer (Scheme 1 A) or by an intramolecular hydride shift (Scheme 1 B). Several studies have shown that base-catalyzed isomerizations take place by a proton transfer mechanism through a series of enolate intermediates generated after the deprotonation of the α-carbonyl carbon in water.[4] The xylose isomerase-catalyzed process is also thought to be mediated by enolate intermediates generated by histidine-directed base catalysis;[5] however, recent studies have shown that metal centers in the enzyme are responsible for the stabilization of the sugar's open-chain form and the subsequent aldose–ketose isomerization by way of an intramolecular hydride shift.[6,7]

Recently, we reported on a tin-containing zeolite (tin in the framework of a pure-silica analog of zeolite beta, denoted Sn-Beta) that is a highly active material for the isomerization



Scheme 1. Glucose isomerization mechanisms by way of A) proton transfer and B) intramolecular hydride shift.

of glucose into fructose in aqueous media.[8] This catalyst was shown to be active over a wide temperature range (343–413 K), in acidic solutions, and with glucose feeds as high as 45 wt % to give product yields equivalent to those obtained with xylose isomerase (at its preferred reaction conditions). Here, using ^{1}H and ^{13}C NMR spectroscopy on isotopically labeled glucose, we demonstrate that in the presence of Sn-Beta, the isomerization reaction in water proceeds by way of an intramolecular hydride shift. Although Lewis acidity is usually suppressed by the presence of water, verification of this mechanistic pathway confirms that framework tin centers in Sn-Beta act as Lewis acids in aqueous media. Previous reports have shown strong interactions between Lewis acid centers in zeolites and hydroxy/carbonyl moieties in reactants dissolved in organic solvents.[9] For example, Corma et al. used Sn-Beta to catalyze the Meerwein–Ponndorf–Verley (MPV) reduction of carbonyl compounds in methanol,[10] and Taarning et al. used Sn-Beta for the production of lactate derivatives from monosaccharides in methanol.[11] The MPV reaction mechanism involves the simultaneous coordination

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of the carbonyl group of a ketone and the hydroxy group of an alcohol to a metal center. Adequate Lewis acidity in the metal center allows the polarization of the carbonyl group of the ketone and promotes a hydride shift from the hydroxy group of the alcohol to the carbonyl group of the ketone (see Figure S1 in the Supporting Information).[10] Corma and coworkers have shown that metal centers (Nb, Ta, and Sn) incorporated into zeolites can act as Lewis acids when used in organic solvents containing a small amount of water.[12] Christensen et al. recently reported on the isomerization of dihydroxyacetone using Sn-Beta in methanol and in water, where it was observed that no loss in activity occurred in methanol, but severe catalyst deactivation occurred in water due to the formation of large carbonaceous deposits. The mechanism of reaction in water was not explained.[13] Thus, the work reported herein is the first to describe the mechanism whereby Sn-Beta acts as a Lewis acid in a purely aqueous environment.

Glucose deuterated at the C-2 position (glucose-D2, Figure S2 A) was used to perform NMR studies on the isomerization reaction. As shown in Scheme 1, the proton at the C-2 position plays a fundamental role in the reaction mechanism regardless of which pathway is followed. Indeed, isotopic substitution at the C-2 position resulted in a two-fold decrease in the initial reaction rate ($k_H/k_D = 1.98$, Figure S3), revealing a considerable kinetic isotopic effect. Importantly, ^{13}C NMR spectra of glucose-D2 heated in water at the reaction temperature (383 K) in the absence of catalyst reveal that no isotopic scrambling occurs (Figure S2 B). This result is important because it demonstrates the inertness of the C−D bond in water at reaction conditions and indicates that any isotopic rearrangement within the molecule during the reaction is entirely due to the actions of the catalyst.

^{13}C and ^{1}H NMR spectroscopy were used to study the isomerization of glucose-D2 using Sn-Beta as the catalyst. A comparison of ^{13}C NMR spectra of unlabeled glucose and glucose-D2 feed solutions reveals that resonances observed at $\delta = 74.1$ and 71.3 ppm in the unlabeled glucose solution appear as low-intensity 1:1:1 triplets in the glucose-D2 solution (Figure 1 a,b). This effect is related to the disruption of the nuclear Overhauser enhancement (NOE) by the deuterium atoms in the C-2 positions of the two configurations of glucose-D2 in solution (β-pyranose and α-pyranose, present in a 64:36 ratio). During NOE, ^{13}C resonance intensities are enhanced up to 200 % for directly bonded ^{13}C–^{1}H pairs when ^{1}H broad-band decoupling is used to suppress C,H couplings;[14] however, this resonance amplification is not observed for ^{13}C–^{2}H pairs and resonances associated with C-2 in glucose-D2 are thus substantially diminished. After reacting a 10 wt % solution of glucose-D2 in water at 383 K for 15 min in the presence of Sn-Beta, the glucose and fructose fractions were separated using high-performance liquid chromatography (HPLC). Analysis of ^{13}C NMR spectrum for each fraction shows that after reaction, glucose-D2 remains unchanged (Figure 1 b,c), while the fructose product has significant differences compared to an unlabeled fructose standard (Figure 1 e,f). Specifically, resonances at $\delta = 63.8$ and 62.6 ppm assigned to the C-1 position of the β-pyranose and β-furanose configurations in the unlabeled fructose standard appear as low-intensity triplets for the fructose product recovered after reaction. ^{1}H NMR spectra for both sugars further confirm these results. The ^{1}H NMR spectra of glucose-D2 before and after reaction remain constant (Figure 2 b,c), while the fructose spectrum shows the disappearance of the resonance at $\delta = 3.45$ ppm due to the presence of a deuterium atom in the C-1 position

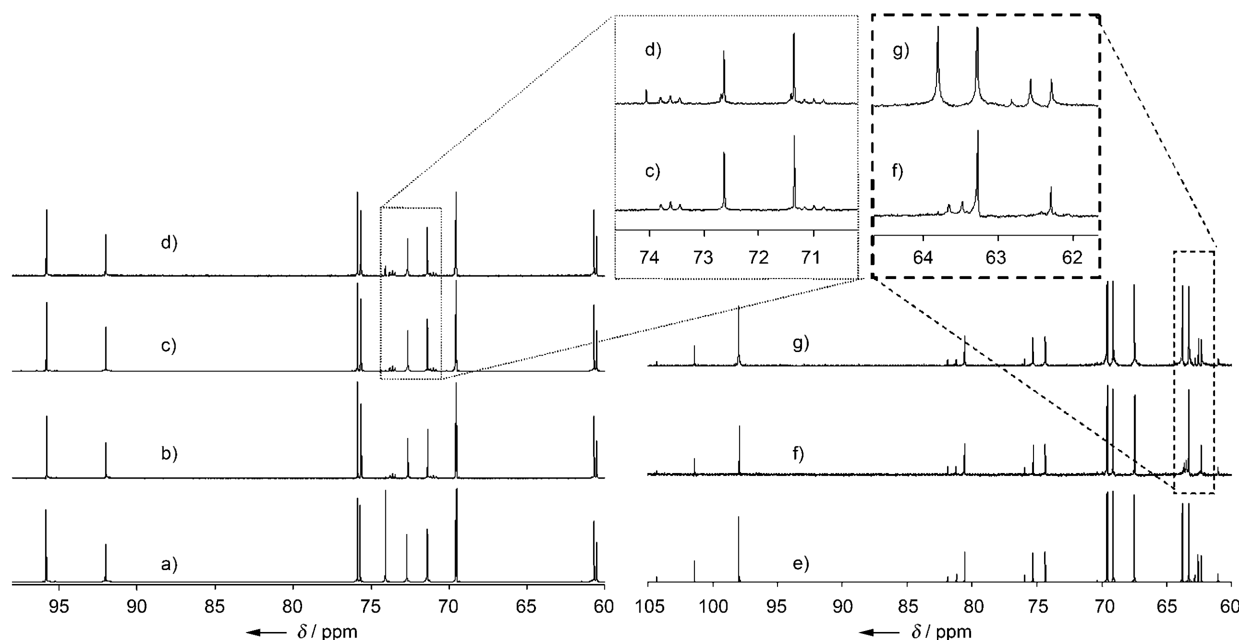

Figure 1. ^{13}C NMR spectra of a) unlabeled glucose, b) labeled glucose-D2, c) glucose fraction obtained after reacting glucose-D2 with Sn-Beta, d) glucose fraction obtained after reacting labeled glucose-D2 with NaOH, e) unlabeled fructose, f) fructose fraction obtained after reacting labeled glucose-D2 with Sn-Beta, and g) fructose fraction obtained after reacting labeled glucose-D2 with NaOH.

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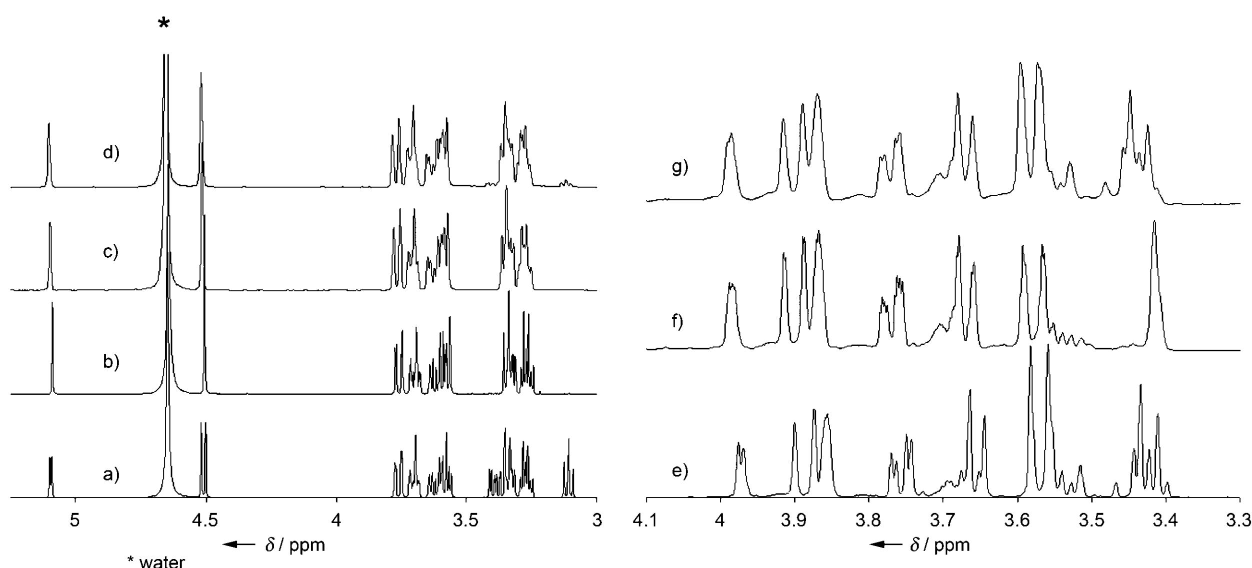

Figure 2. ^{1}H NMR spectra of a) unlabeled glucose, b) labeled glucose-D2, c) glucose fraction obtained after reacting glucose-D2 with Sn-Beta, d) glucose fraction obtained after reacting labeled glucose-D2 with NaOH, e) unlabeled fructose, f) fructose fraction obtained after reacting labeled glucose-D2 with Sn-Beta, and g) fructose fraction obtained after reacting labeled glucose-D2 with NaOH.

(Figure 2 f). Integration of the areas in these spectra confirms the presence of six C–H pairs for the glucose and fructose fractions in contrast to the seven C–H pairs found in unlabeled glucose or fructose. These results clearly indicate that the deuterium atom located in the C-2 position of glucose-D2 has moved to the C-1 position of fructose, thereby unequivocally demonstrating that the glucose isomerization reaction with a solid Lewis acid catalyst in pure water proceeds by means of an intramolecular hydride shift.

A similar spectroscopic study was performed using sodium hydroxide (NaOH) as a basic catalyst. A 10 wt% aqueous solution of glucose-D2 was reacted in the presence of NaOH (0.1M) at 383 K for 2 min. ^{13}C NMR and ^{1}H NMR spectra of the glucose and fructose fractions show considerable differences when compared to the results obtained with Sn-Beta. First, the ^{13}C and ^{1}H NMR spectra for the unlabeled fructose and for the fructose fraction isolated after reaction show no differences, indicating that the fructose fraction does not contain deuterium atoms (Figure 1 e,g and Figure 2 e,g). Second, the ^{13}C NMR spectrum of the glucose fraction shows glucose-D2 mixed with a small amount of regular glucose, as indicated by the presence of a small resonance at $\delta = 74.1$ ppm (see inset in Figure 1 d). The presence of unlabeled glucose is corroborated by the appearance of a resonance at $\delta = 3.1$ ppm in the ^{1}H NMR spectrum, which is assigned to a proton in the C-2 position (Figure 2 d). These results clearly indicate that the basic catalyst operates by a proton-transfer mechanism whereby the deuterium atom is removed from the α-carbonyl carbon of glucose-D2 to form the corresponding enolate, and a proton from solution is subsequently re-incorporated into the molecule, yielding some unlabeled glucose along with the unlabeled fructose (Scheme 1 A).

This study proves that Sn-Beta can act as a Lewis acid capable of catalyzing the isomerization of glucose in a pure aqueous medium. Further studies are necessary in order to understand the nature of the interactions amongst the active site in Sn-Beta, the sugar and the solvent during the isomerization reaction. Previous reports by Corma and co-workers have shown (using ^{119}Sn-NMR) that isolated framework tin centers in zeolites are responsible for drastically enhancing the rates of certain reactions.[15] For glucose isomerization in water, we observed that framework tin centers are necessary for Sn-Beta to catalyze the reaction. Sn-Beta synthesized by a procedure known to fully incorporate tin into the framework ($SnCl_4$ as the tin source) is highly active for the isomerization reaction, whereas Sn-Beta synthesized using SnO_2 as the tin source is completely inactive (Figure S4 A). The diffuse reflectance UV/Vis spectrum for the active material shows a single band centered at 220 nm, assigned to tetrahedrally coordinated metal, while the spectrum for the non-active material shows a band centered at 300 nm, assigned to octahedrally coordinated metal in extra-framework positions (Figure S4 B). Indeed, SnO_2 is known to be highly stable in acidic and basic media and probably does not participate in the zeolite crystallization process (thereby providing extra-framework SnO_2 nanoparticles within the zeolite pores). It has been suggested that the actual active site in Sn-Beta is a partially hydrolyzed framework tin species (i.e. a $(SiO)_3Sn(OH)$ center).[16] Interestingly, Kovalevsky et al. show that analogous hydrolyzed metal species in xylose isomerase play a fundamental role in protonation–deprotonation sequences with water and glucose molecules during the isomerization process.[7] Identifying similarities between the active sites in the biological and the Sn-Beta catalyst systems is one of our current objectives.

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Experimental Section

Sn-Beta was synthesized following procedures previously reported in the literature (see Supporting Information for details).[15] Isomerization experiments were carried out in 10 mL thick-walled glass reactors (VWR) heated in a temperature-controlled oil bath. 1.5 g of a 10 wt% glucose-D2 (Cambridge Isotopes Corp.) solution and the corresponding catalyst amount to achieve a 1:50 metal:glucose molar ratio were added to the reactor, sealed, and heated. Further information about the catalytic tests and characterization techniques can be found in the Supporting Information.

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