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# Titanium-Beta Zeolites Catalyze the Stereospecific Isomerization of D-Glucose to L-Sorbose via Intramolecular C5−C1 Hydride Shift

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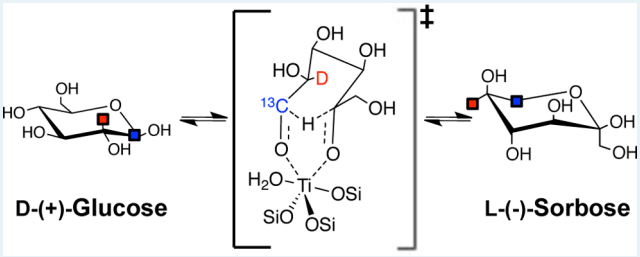
Supporting Information

**ABSTRACT:** Pure-silica zeolite beta containing Lewis acidic framework $Ti^{4+}$ centers (Ti-Beta) is shown to catalyze the isomerization of D-glucose to L-sorbose via an intramolecular C5−C1 hydride shift. Glucose−sorbose isomerization occurs in parallel to glucose−fructose isomerization on Ti-Beta in both water and methanol solvents, with fructose formed as the predominant product in water and sorbose as the predominant product in methanol (at 373 K) at initial times and over the course of >10 turnovers. Isotopic tracer studies demonstrate that $^{13}C$ and D labels placed respectively at the C1 and C2 positions of glucose are retained respectively at the C6 and C5 positions of sorbose, consistent with its formation via an intramolecular C5−C1 hydride shift isomerization mechanism. This direct Lewis acid-mediated pathway for glucose−sorbose isomerization appears to be unprecedented among heterogeneous or biological catalysts and sharply contrasts indirect base-mediated glucose−sorbose isomerization via 3,4-enediol intermediates or via retro-aldol fragmentation and recombination of sugar fragments. Measured first-order glucose−sorbose isomerization rate constants (per total Ti; 373 K) for Ti-Beta in methanol are similar for glucose and glucose deuterated at the C2 position (within a factor of ∼1.1), but are a factor of ∼2.3 lower for glucose deuterated at each carbon position, leading to H/D kinetic isotope effects expected for kinetically relevant intramolecular C5−C1 hydride shift steps. Optical rotation measurements show that isomerization of D-(+)-glucose (92% enantiomeric purity) with Ti-Beta in water (373 K) led to the formation of L-(−)-sorbose (73% enantiomeric purity) and D-(−)-fructose (87% enantiomeric purity) as the predominant stereoisomers, indicating that stereochemistry is preserved at carbon centers not directly involved in intramolecular C5−C1 or C2−C1 hydride shift steps, respectively. This new Lewis acid-mediated rearrangement of glucose to sorbose does not appear to have a metalloenzyme analog.




**KEYWORDS:** *fructose, glucose, hydride shift, isomerization, Lewis acid, sorbose, stereospecific, titanium-Beta*

## 1. INTRODUCTION

Glucose isomerization and epimerization reactions catalyzed by bases proceed via abstraction of α-carbonyl protons to form 1,2-enediol intermediates, which undergo proton transfer-mediated rearrangements to form fructose and mannose products (Lobry de Bruyn−Alberda van Ekenstein rearrangements; LdB−AvE).[1−3] Double-bond isomerization of 1,2-enediols leads to a mixture of 2,3- and 3,4-enediols that are precursors to psicose, tagatose, and sorbose ketohexoses (the C3, C4, and C5 epimers of fructose, respectively) and other aldohexoses.[4] Fructose is the preferred product of LdB−AvE rearrangements of glucose in alkaline media, but it is formed with a selectivity that decreases with increasing glucose conversion as sequential 1,2-enediol isomerization[4] and as retro-aldol fragmentation and other degradation reactions of monosaccharides[4−7] become more prevalent. In contrast to bases that initiate glucose isomerization via α-carbonyl proton abstraction, Lewis acids coordinate with lone electron pairs in oxygen atoms (O1) at glucose aldehyde carbons (C1), leading to polarization of C═O bonds and to electron-deficient C1 centers.[8] A single Lewis acid center can also coordinate with a second oxygen atom, such as those found in hydroxyl groups located along the glucose backbone; subsequent hydroxyl deprotonation forms a bound alkoxide moiety with increased electron density at its carbon center. Such bidentate coordination of aldehyde and alkoxide groups on open-chain sugars to a single Lewis acid site facilitates the nucleophilic addition of electron-rich moieties at the alkoxide carbon center to the electrophlic aldehyde C1 center preferentially over other carbon centers in the sugar backbone.

Infrared (IR) and solid-state $^{13}C$ nuclear magnetic resonance (NMR) studies, together with quantum chemical calculations, have shown that framework Sn centers in zeolite beta (Sn-Beta) mediate glucose ring-opening and coordinate with glucose O1 and O2 atoms.[9] In turn, glucose−fructose isomerization occurs via an intramolecular hydride shift from C2 to C1 carbon atoms on open glucose chains (Scheme S1, Supporting Information).[10] This isomerization mechanism is analogous to that mediated by two divalent Lewis acid metal centers (e.g., $Mg^{2+}$ or $Mn^{2+}$) within hydrophobic pockets of metalloenzymes (e.g.,

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D-xylose isomerase) that are spatially positioned to bind glucose via O1 and O2 atoms prior to intramolecular C2−C1 hydride shift steps.[11,12] Sn-Beta can also mediate glucose−mannose epimerization in methanol,[13] and in water in the presence of borate salts,[14] via a Lewis acid-mediated intramolecular carbon shift known as the Bilik reaction.[15−17] In the glucose−mannose epimerization mechanism, C3 carbon centers bound to C2 atoms behave as nucleophiles and migrate, along with the rest of the covalently bound sugar backbone, to electrophilic C1 centers (Scheme S1, Supporting Information).

The mechanisms for Sn-mediated glucose−fructose isomerization and glucose−mannose epimerization are similar because they first require bidentate glucose coordination to metal centers via O1 and O2 atoms; they differ, in part, because electron-rich H2 or C3 species located at glucose C2 centers respectively act as the nucleophiles that add to electron-deficient C1 centers (Scheme S1, Supporting Information). These intramolecular hydride and carbon shifts are mediated only by Lewis acidic framework Sn sites in Sn-Beta and not by base sites located on extraframework $SnO_2$ domains,[13] reflecting the requirement of Lewis acid centers to facilitate the redistribution of oxidation states between carbon atoms in organic substrates at transition states for intramolecular[10,13,18] or intermolecular[19−21] Meerwein−Ponndorf−Verley aldehyde and ketone reduction and Oppenauer alcohol oxidation (MPVO) reactions.

Here, we report the first evidence for the direct isomerization of D-glucose to L-sorbose, (the ketohexose C5 epimer of fructose), which is mediated by Lewis acidic $Ti^{4+}$ centers isolated within the framework of pure-silica zeolite beta (Ti-Beta). D-Glucose is used as feedstock in the Reichstein synthesis of L-ascorbic acid (a form of vitamin C; ∼$10^5$ tons produced annually worldwide[22]) via L-sorbose intermediates. Current routes for D-glucose-to-L-sorbose conversion involve the sequential hydrogenation of D-glucose to D-sorbitol over a nickel-based catalyst and the selective oxidation of D-sorbitol C2−OH groups using microbial enzymes to form L-sorbose.[22−25] Alkaline media can isomerize glucose into sorbose, but only among a mixture of several aldohexose and ketohexose isomers and only via indirect pathways, either via the formation of 1,2-enediols and isomerization to 3,4-enediol sorbose precursors[4] or via isomerization to fructose, retro-aldol fragmentation to triose intermediates, and recombination of sugar fragments.[26] Heterogeneous base resins (Amberlite XE-48, Amberlite IRA-400) can also convert D-(+)-glucose to a mixture of D-(+)-sorbose (∼68%) and L-(−)-sorbose (∼32%),[27] among several other hexose products, via 3,4-enediol intermediates.[28] The data and the mechanistic evidence presented herein, to our knowledge, constitute the first report of direct and stereospecific D-(+)-glucose to L-(−)-sorbose isomerization mediated by a Lewis acid center or by any catalytic entity, for that matter.

## 2. EXPERIMENTAL METHODS

**2.1. Catalyst Synthesis and Characterization.** Procedures to synthesize Ti-Beta zeolites in fluoride media with different Si/Ti ratios were adapted from reported protocols.[29] Ti-Beta samples were treated in flowing air (1.67 $cm^3$ $s^{-1}$, Air Liquide, breathing grade) at 853 K (0.0167 K $s^{-1}$) for 12 h prior to characterization and catalytic evaluation. Atomic Si and Ti contents were measured using a JEOL 8200 electron microprobe, operated in focused beam mode with a 40 μm spot size, at 15 kV and 25 nA. The Si/Ti ratio determined by electron microprobe is denoted in the suffix of sample names (e.g., Ti-Beta-79 contains a Si/Ti ratio of 79).

The crystal structures of all samples, determined from powder X-ray diffraction (XRD) patterns collected using a Rigaku Miniflex II diffractometer and Cu Kα radiation, was consistent with zeolite beta (Figure S1, section S.2, Supporting Information). $N_2$ (77 K) adsorption isotherms were measured using a Quantachrome Autosorb iQ automated gas sorption analyzer, using protocols reported elsewhere,[30] and gave micropore volumes consistent with the beta topology (Figure S2, section S.2, Supporting Information). Diffuse reflectance UV−visible spectra of Ti-Beta samples (Figure S3, section S.2, Supporting Information) showed bands centered at ∼200−220 nm, which have been assigned previously to Ti centers incorporated within zeolite frameworks.[31]

**2.2. Kinetic Studies of Glucose Reactions with Ti-Beta.** Reactions with D-glucose (Sigma-Aldrich, ≥ 99%) were conducted in 10 mL thick-walled glass batch reactors (VWR), with temperature control via an oil bath located on a digital stirring hot plate (Fisher Scientific). Typical reactions with D-glucose were carried out at a 1:50 metal/glucose molar ratio and involved contacting 4 g of a 1% (w/w) glucose solution (∼0.04 g of glucose) in water or in methanol with the catalytic solids (∼0.01−0.04 g) in a stirred glass reactor sealed with a crimp top (PTFE/silicone septum, Agilent). Kinetic studies using isotopically labeled glucose were performed using 1% (w/w) solutions of D-glucose-D2 (Cambridge Isotope Laboratories, ≥ 98%) or of D-glucose-$D_7$-1,2,3,4,5,6,6 (Cambridge Isotope Laboratories, ≥ 98%) in methanol.

Reactors were placed in the oil bath, and small aliquots (∼50−100 μL) were extracted at various time intervals via syringe (Hamilton, 700 series), filtered through a 0.2 μm PTFE filter (National Scientific), and mixed with 1% (w/w) aqueous D-mannitol (Sigma-Aldrich, ≥ 98%) solutions used as an internal standard for quantification. The composition of reaction aliquots was determined after separation of the compounds in an Agilent 1200 high performance liquid chromatograph (HPLC) equipped with an evaporative light scattering (ELS) detector (Agilent 380 LC). Glucose, sorbose, mannose, fructose, and mannitol fractions were separated using a Hi-Plex Ca column (7.7 × 300 mm, 8 μm particle size, Agilent) held at 353 K, with either ultrapure water (0.010 mL $s^{-1}$ flow rate) or a 70/30 (v/v) mixture of acetonitrile/water (0.013 mL $s^{-1}$ flow rate) as the mobile phase.

**2.3. Isotopic and Stereochemical Characterization of Sugars.** Liquid NMR analysis of products formed from isotopic tracer studies using D-glucose-D2 or D-glucose-$^{13}$C-C1 (Cambridge Isotope Laboratories, ≥ 98%) reactants involved separation of the glucose, sorbose, and fructose fractions by HPLC, evaporation of $H_2O$, and dissolution in $D_2O$ (Cambridge Isotope Laboratories, 99.9%). $^1$H and $^{13}$C liquid NMR spectra were collected on a 400 MHz NMR spectrometer (Varian) in the Caltech liquid NMR facility. After collection of NMR spectra, the glucose, sorbose, and fructose solids were subsequently isolated by evaporation of $D_2O$ and dissolved in $H_2O$ prior to measurement of optical rotation at 589 nm and ambient temperature using a Jasco P-2000 polarimeter and a 100 mm path-length cell.

## 3. RESULTS AND DISCUSSION

**3.1. Kinetic Studies of Glucose Isomerization over Ti-Beta.** Monosaccharide yields resulting from the reaction of 1% (w/w) glucose solutions with Ti-Beta samples (373 K) of


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**Table 1. Monosaccharide Yields and Turnover Numbers from Glucose Reactions with Ti-Beta in Water and Methanol[a]**

| | | | monosaccharide yield (w/w %) | | | | | |
|---|---|---|---|---|---|---|---|---|
| catalyst | solvent | glucose/metal ratio | glucose | sorbose | mannose | fructose | total | turnover no.[b] |
| Ti-Beta-66 | $H_2O$ | 32 | 82 | 4 | <0.1 | 11 | 98 | 5.0 |
| Ti-Beta-79 | $H_2O$ | 60 | 81 | 3 | <0.1 | 8 | 93 | 6.8 |
| Ti-Beta-107 | $H_2O$ | 56 | 80 | 4 | <0.1 | 8 | 92 | 6.4 |
| Ti-Beta-202 | $H_2O$ | 69 | 87 | 3 | <0.1 | 6 | 96 | 5.8 |
| Ti-Beta-66 | $CH_3OH$ | 30 | 64 | 12 | 1.1 | 8 | 85 | 6.5 |
| Ti-Beta-79 | $CH_3OH$ | 63 | 79 | 8 | 0.7 | 4 | 92 | 8.4 |
| Ti-Beta-107 | $CH_3OH$ | 54 | 76 | 9 | 0.8 | 4 | 90 | 7.9 |
| Ti-Beta-202 | $CH_3OH$ | 119 | 77 | 6 | 0.6 | 4 | 88 | 13.0 |

[a]Reaction conditions: 1% (w/w) glucose solutions, 373 K, 2 h. [b]Moles of product monosaccharides formed per moles of total Ti.

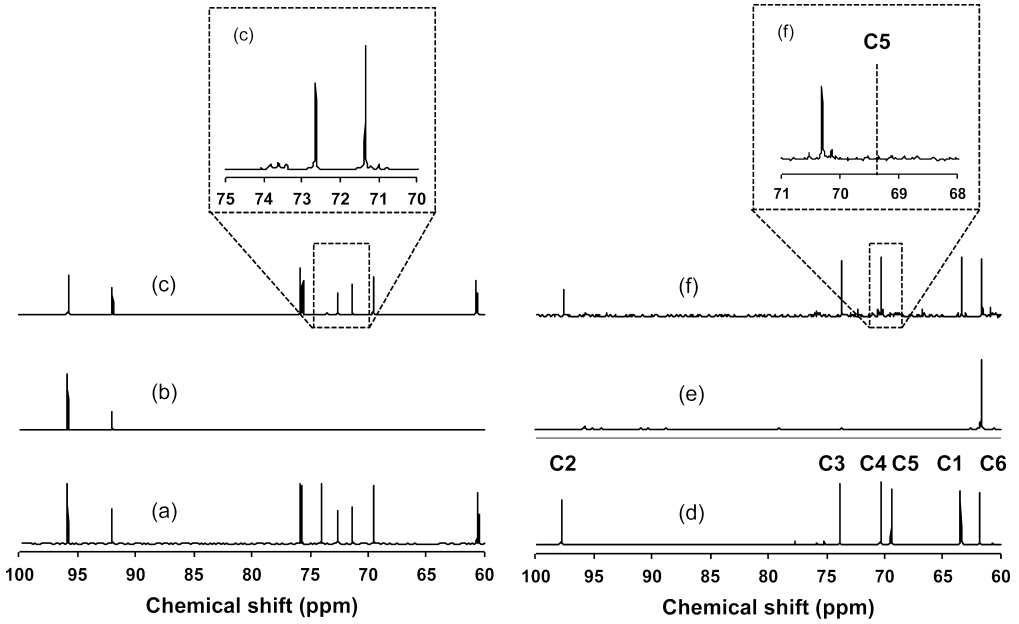


**Figure 1.** $^{13}C$ NMR spectra of (a) unlabeled glucose and of the glucose fractions isolated after reaction of (b) glucose-$^{13}C$-C1 and (c) glucose-D2 with Ti-Beta in water at 373 K for 6 h. $^{13}C$ NMR spectra of (d) unlabeled sorbose together with assignments for each carbon position in $\alpha$-L-sorbopyranose[32] and of the sorbose fractions isolated after reaction of (e) glucose-$^{13}C$-C1 and (f) glucose-D2 with Ti-Beta in water at 373 K for 6 h.

varying Si/Ti content in water and in methanol are shown in Table 1; characterization data for the samples used in this study are provided in section S.2 of the Supporting Information. Reactions of glucose with Ti-Beta in water formed predominantly fructose, as reported previously,[30,31] together with a second previously unidentified hexose sugar that became the predominant product of glucose reactions with Ti-Beta in methanol solvent (Table 1). This unidentified hexose product was retained at times similar to (within 0.2 min) that of mannose during chromatographic separation with a Ca Hi-Plex column (7.7 × 300 mm, 8 $\mu$m particle size, Agilent) using water as the mobile phase (0.6 mL $min^{-1}$, 353 K). Mannose and the unidentified hexose product were resolved, however, upon changing the mobile phase to a 70/30 (v/v) mixture of acetonitrile/water (0.8 mL $min^{-1}$, 353 K). $^1H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra of this previously unidentified hexose product were identical to that of authentic sorbose,[32] the C5 epimer of fructose.

Kinetic studies of glucose reactions with Ti-Beta (373 K) performed in batch reactors using 1% (w/w) glucose solutions in water and in methanol showed that the evolution of liquid-phase fructose and sorbose concentrations with reaction time were consistent with that expected from product formation rates that are first-order in glucose concentration (details in section S.3, Supporting Information). Fructose and sorbose were formed at nonzero initial turnover rates and in essentially constant molar ratios as glucose conversion increased from 0 to 36% (Figures S4a and S4b, section S.3, Supporting Information) and as the number of isomerization turnovers (per total Ti) increased from 0 to ~13 (Table 1), reflecting the formation of both products from primary, parallel reactions of glucose. This kinetic behavior is inconsistent with the formation of sorbose via 3,4-enediol intermediates formed upon sequential rearrangements of 1,2-enediols, or via sequential retro-aldol fragmentation, isomerization, and recombination of triose fragments, as has been reported with homogeneous[4,26,33] or heterogeneous[27,28] bases. Other ketohexoses (e.g., psicose, tagatose) and trioses were absent in solution after glucose reactions with Ti-Beta (Table 1), also inconsistent with their expected formation during base-catalyzed glucose reactions.[4−7,26−28]

**3.2. Isotopic Tracer Studies of Glucose Isomerization over Ti-Beta.** Isotopic tracer studies using glucose reactants labeled with $^{13}C$ at the C1 position (glucose-$^{13}C$-C1) or with D at the C2 position (glucose-D2), together with $^1H$ and $^{13}C$ NMR spectroscopic analysis of sugar products isolated by


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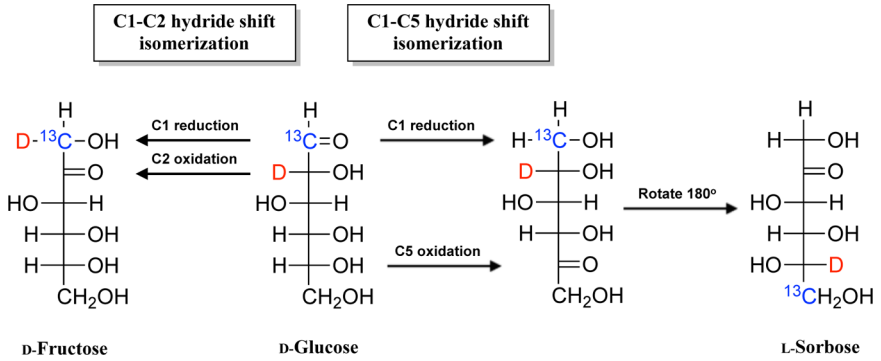
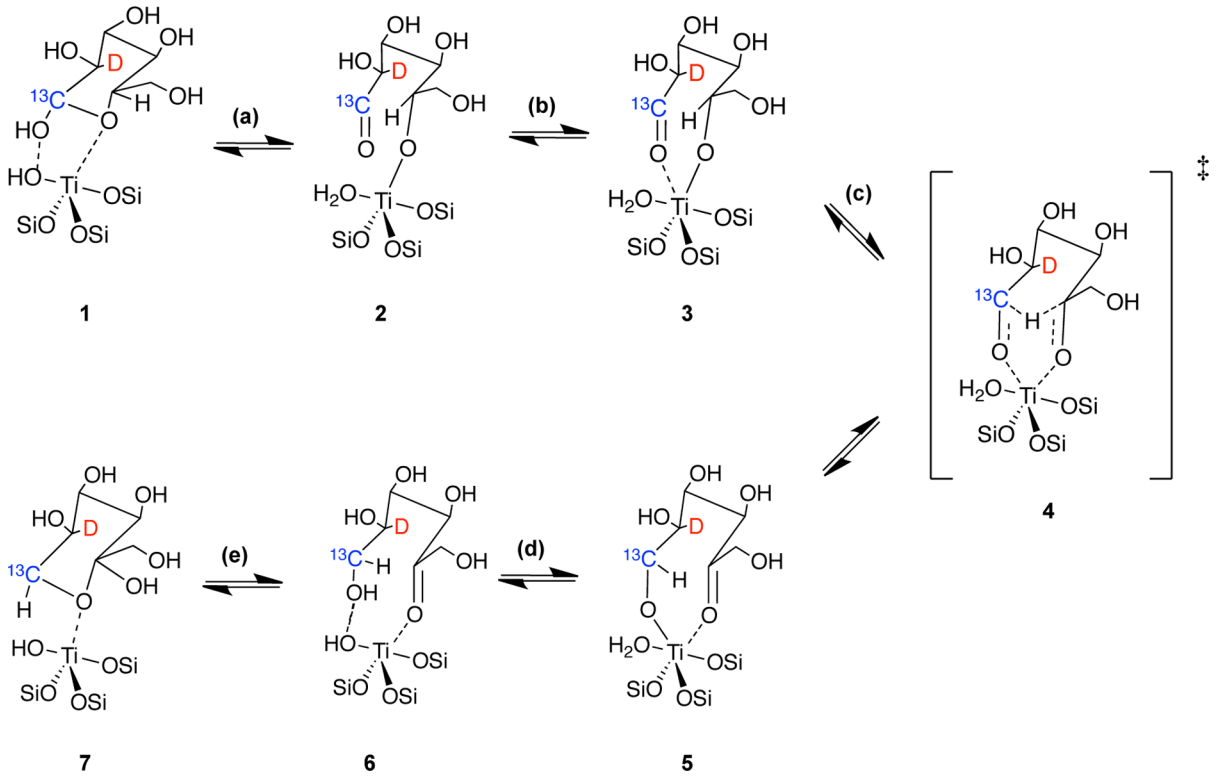
**Scheme 1. Parallel Reaction Scheme for Glucose−Fructose and Glucose−Sorbose Isomerization Mediated by Lewis Acidic $Ti^{4+}$ Centers in Ti-Beta[a]**




[a]Mechanistic evidence from isotopic tracer studies using D and $^{13}C$ labels shown in reactants and products, which are depicted using Fischer projections.

**Scheme 2. Plausible Intermediate (1−3, 5−7) and Transition State (4) Structures Involved in the Proposed Intramolecular C5−C1 Hydride Shift Reaction Mechanism for Glucose−Sorbose Isomerization on Open Sites in Ti-Beta**




fractionation, were used to confirm the presence of Lewis acid sites on Ti-Beta and to probe the mechanism of glucose−sorbose isomerization. The $^{13}C$ NMR spectrum of unlabeled glucose is shown in Figure 1a for reference. The glucose fraction isolated after reaction of glucose-$^{13}C$-C1 with Ti-Beta in water (373 K) showed resonances at $\delta$ = 95.8 and 92.0 ppm (Figure 1b), which correspond to C1 positions in the $\beta$-pyranose and $\alpha$-pyranose anomers respectively, of glucose. The $^{13}C$ NMR spectrum of the glucose fraction collected after reaction of glucose-D2 with Ti-Beta in water (373 K) showed low-intensity triplets present in place of sharp resonances at $\delta$ = 74.1 and 71.3 ppm (Figure 1c), which correspond to the C2 positions in $\beta$-glucopyranose and $\alpha$-glucopyranose, respectively. Deuterium atoms bonded to carbon centers suppress the nuclear Overhauser enhancement (NOE) of carbon resonances in $^{13}C$ NMR spectra collected using proton broad-band decoupling[34] and lead to the appearance of low-intensity triplets, confirmed in the case of glucose-D2 by the absence of resonances for C2−H atoms in the corresponding $^{1}H$ NMR spectrum (Figure S5, section S.4, Supporting Information). These data (Figures 1b, 1c) confirm that $^{13}C$ and H/D scrambling in glucose reactants does not occur during reaction or chromatographic separation.

The fructose products formed from the reaction of glucose-$^{13}C$-C1 and glucose-D2 with Ti-Beta in water contained a $^{13}C$ label at its C1 position (fructose- $^{13}C$-C1) and a D label at its C1 position (fructose-D1) (Figures S6 and S7, section S.4, Supporting Information), respectively, as also observed on Lewis acidic Sn-Beta.[10,13] These isotopic tracer studies confirm that glucose−fructose isomerization occurs via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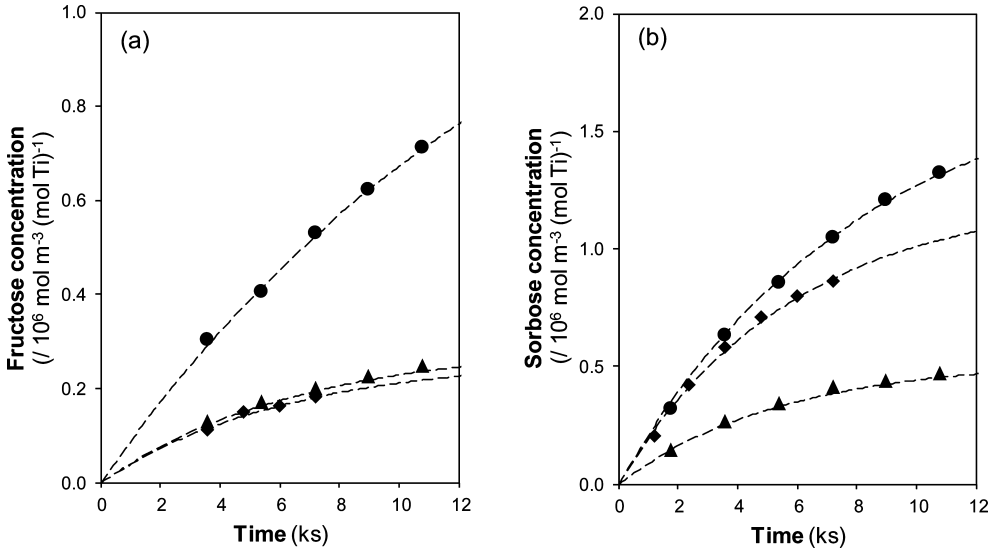


**Figure 2.** Liquid-phase concentrations of (a) fructose and (b) sorbose as a function of reaction time during reaction of a 1% (w/w) solution of glucose (●), glucose-D2 (♦), or glucose-$D_7$-1,2,3,4,5,6,6 (▲) with Ti-Beta-79 in methanol solvent (1:50 glucose/Ti molar ratio, 373 K). Corresponding initial turnover rates are given in Table 2. Dashed curves represent best fits of the experimental data to kinetic models derived, assuming parallel isomerization reactions and rates that are first-order in glucose concentration (details in section S.3, Supporting Information).

an intramolecular C2−C1 hydride shift, reflecting the sole involvement of Lewis acidic framework $Ti^{4+}$ sites in Ti-Beta for glucose isomerization. In contrast, base sites would otherwise have mediated reversible enolization to cause H/D scrambling at the C2 position of glucose and, in turn, fructose products formed without D atoms retained at their C1 position.[10,13]

The $^{13}C$ NMR spectrum of unlabeled sorbose is provided in Figure 1d, together with positional assignments for each carbon atom in $\alpha$-L-sorbopyranose.[32] The $^{13}C$ NMR spectrum of the sorbose fraction isolated after reaction of glucose-$^{13}C$-C1 with Ti-Beta in water showed a single resonance at $\delta$ = 61.7 ppm (Figure 1e), which corresponds to the C6 position. In contrast, isotopic tracer studies using radioisotopically labeled glucose-$^{14}$C-C1 reactants showed that base-mediated isomerization via symmetric 3,4-enediol intermediates form sorbose with $^{14}C$ labels at both the C1 and C6 positions,[28] whereas base-mediated isomerization via retro-aldol fragmentation and recombination reactions redistribute the $^{14}C$ label throughout the sorbose backbone.[4,28] The $^{13}C$ NMR spectrum of sorbose formed form reaction of glucose-D2 with Ti-Beta showed resonances for all carbon atoms except that for the C5 position at $\delta$ = 70.3 ppm (Figure 1f), whose NOE is suppressed by D atoms bound to C5 centers. In contrast, base-mediated glucose isomerization initiated via $\alpha$-carbonyl proton abstraction would have caused H/D scrambling at C2 positions of glucose and the incorporation of H atoms at C5 positions of sorbose. Thus, we conclude that C and H atoms at glucose C1 and C2 locations are retained at C6 and C5 locations, respectively, in sorbose upon isomerization with Lewis acidic $Ti^{4+}$ centers in Ti-Beta (Scheme 1). The atom rearrangements involved in glucose−sorbose isomerization occur between opposite ends of ring-opened glucose chains; at first glance, they appear to require several skeletal rearrangement steps but, in fact, require only glucose C1 aldehyde-to-alcohol reduction and C5 alcohol-to-ketone oxidation (Scheme 1) in a concerted step, as we discuss next.

**3.3. Proposed Mechanism for Glucose−Sorbose Isomerization on Ti-Beta.** We propose that glucose−sorbose isomerization occurs via a concerted intramolecular MPVO step mediated by a hydride shift from the C5 to the C1 position over open glucose chains (Scheme 2), analogous to the intramolecular MPVO mechanism for glucose−fructose isomerization mediated by a C2−C1 hydride shift. Quantum chemical studies of glucose−fructose isomerization on Sn-Beta and Ti-Beta open sites (three framework −OSi bonds and one −OH group)[9] have shown that coordination of oxygen atoms in C1−O−C5 hemiacetal linkages of cyclic glucose at Lewis acidic framework metal (M = Sn, Ti) sites (**1**, Scheme 2) and subsequent metal-mediated ring-opening (**2**, Scheme 2) results in open-chain glucose bound to metal centers via O1 and O5 atoms (**3**, Scheme 2). These theoretical studies indicate that intramolecular C2−C1 hydride shifts in glucose−fructose isomerization, in fact, require proton transfer from M−($OH_2$) groups to glucose O5 atoms in intermediate **3** (Scheme 2) to form C5−OH groups, desorption of C5−OH groups from M sites, adsorption of C2−OH moieties after rotation of glucose coordinated solely via its O1 atom, and deprotonation of C2−OH groups by M−OH moieties to enable bidentate coordination of O1 and O2 atoms.[9]

Glucose−sorbose isomerization instead would require only an alternate reaction sequence beginning with intermediate **3** (Scheme 2). In this alternate sequence, an intramolecular C5−C1 hydride shift (**4**, Scheme 2) would form an open-chain sorbose bound via O2 and O6 atoms (**5**, Scheme 2), and subsequent protonation of sorbose O6 atoms to C6−OH groups (**6**, Scheme 2) and ring-closing would form bound cyclic sorbose (**7**, Scheme 2), analogous to the steps required to close glucose−fructose isomerization cycles. In this proposal, the reaction coordinates for glucose−fructose and glucose−sorbose isomerization share common elementary steps for binding and ring-opening of cyclic glucose at framework metal centers (steps a and b, intermediates **1**, **2**, and **3**, Scheme 2). These mechanistic features are consistent with the sole formation of fructose and sorbose with Lewis acidic Ti-Beta (Table 1) and the absence of psicose and tagatose isomers, which are otherwise formed concomitantly with fructose and sorbose via interconvertible enediol intermediates on homogeneous[4,26,33] or heterogeneous[27,28] base catalysts. The purported


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open Ti site structures depicted in Scheme 2, which contain an −OH group that mediates proton transfer steps with oxygenated moieties on adsorbed sugars, are present in water solvent; yet, Ti sites may differ in structure in methanol solvent, which can coordinate with Lewis acidic Ti centers and dissociate to form bound methoxy ($-OCH_3$) groups, according to EXAFS[35] and Raman[36] studies. We *speculate* that structural differences prevalent among active Ti sites in water and methanol solvent may influence the isomerization selectivity differences observed with these two solvents (Table 1).

Initial turnover rates (per total Ti; 373 K) for glucose isomerization to sorbose and isomerization to fructose with Ti-Beta in methanol were determined from the evolution of fructose (Figure 2a) and sorbose (Figure 2b) concentrations with reaction time (additional details given in section S.3, Supporting Information). Measured first-order isomerization rate constants derived from these initial turnover rates (Figure 2a, b) with glucose reactants containing different locations and amounts of isotopic deuterium labels are shown in Table 2.

**Table 2. Measured First-Order Rate Constants and H/D Kinetic Isotope Effects (373 K) for Glucose−Fructose and Glucose−Sorbose Isomerization in Methanol[a]**

| | measured rate constant (373 K) ($/10^{-6}$ mol (mol Ti)$^{-1}$ s$^{-1}$ ((mol glucose) m$^{-3}$)$^{-1}$) | | KIE[b] | |
|---|---|---|---|---|
| reactant | fructose | sorbose | fructose | sorbose |
| glucose | 11 ± 0.6 | 27 ± 1.3 | | |
| glucose-D2 | 5.0 ± 0.2 | 25 ± 1.2 | 2.2 ± 0.3 | 1.1 ± 0.1 |
| glucose-$D_7$-1,2,3,4,5,6,6 | 5.4 ± 0.3 | 12 ± 0.6 | 2.0 ± 0.2 | 2.2 ± 0.2 |

[a]Calculated from turnover rates measured on Ti-Beta-79 (shown in Figure 2). [b]Given by the ratio of the rate constant for unlabeled glucose relative to that for deuterated reactants.

Rate constants for glucose−fructose isomerization were higher by a factor of ∼2.2 for glucose than for glucose-D2 (Table 2) on Ti-Beta in methanol, consistent with isomerization via kinetically relevant intramolecular C2−C1 hydride shift (section S.5, Supporting Information), as also observed on Sn-Beta and Ti-Beta in water.[9,10,13] Initial turnover rates for glucose−sorbose isomerization were essentially identical (within a factor of ∼1.1, Table 2) for glucose and glucose-D2 reactants in methanol, indicating that C2−D bonds remain intact during such isomerization cycles. The reaction of fully deuterated glucose (glucose-$D_7$-1,2,3,4,5,6,6) led to an observed H/D KIE for glucose−fructose isomerization of ∼2.0 in methanol solvent (Table 2) because C2−D bonds are broken in kinetically relevant steps and also led to a similar KIE of ∼2.3 for glucose−sorbose isomerization (Table 2). The KIE values of ∼1.1 and ∼2.3 for glucose−sorbose isomerization when glucose reactants are deuterated at the C2 position and at all positions, respectively, reflect the kinetic relevance of C−D bond-breaking steps at a position other than C2. Although we are unable to probe C5−D cleavage directly because glucose-D5 reactants are unavailable, the KIE of ∼2.3 observed with fully deuterated glucose reactants is expected from kinetically relevant C5−D bond cleavage (section S.5, Supporting Information), as required for the proposed intramolecular C5−C1 hydride shift mechanism (Scheme 2), and consistent with the isotopic tracer studies (Scheme 1) that led to this proposal.

**3.4. Stereospecific Isomerization Mediated by Lewis Acid Sites.** The proposed glucose−sorbose isomerization mechanism involves the reduction of C1 centers and the oxidation of C5 centers in D-glucose, but does not change the formal oxidation states or stereochemistry at C2, C3, and C4 centers (Scheme 1). Thus, D-glucose isomerization via a C5−C1 hydride shift should selectively form L-sorbose, and isomerization via C2−C1 hydride shift should, by a similar argument, selectively form D-fructose. The glucose, sorbose, and fructose fractions isolated after reaction of a 10% (w/w) aqueous solution of glucose-D2 with Ti-Beta (373 K, 6 h) and after collection of $^1$H and $^{13}$C NMR spectra (Figures 1, Supporting Information S5−S7) and replacement of $D_2O$ with $H_2O$ as the solvent were tested for optical activity at 589 nm and at ambient temperature. The specific optical rotations of the glucose, sorbose, and fructose fractions were 44.7 ± 0.1°, −19.8 ± 0.6°, and −67.6 ± 2.7°, respectively (Table 3),

**Table 3. Specific Rotation and Enantiomeric Compositions of Glucose, Sorbose, and Fructose Fractions Isolated After Reaction of Glucose-D2 with Ti-Beta in Water[a]**

| fraction | specific rotation[b] (deg) | ee[c] (%) | D-enantiomer (%) | L-enantiomer (%) |
|---|---|---|---|---|
| glucose | 44.7 ± 0.1 | 85 ± 0.3 | 92 ± 1 | 8 ± 1 |
| sorbose | −19.8 ± 0.6 | 46 ± 1.5 | 27 ± 1 | 73 ± 1 |
| fructose | −67.6 ± 2.7 | 73 ± 3 | 87 ± 2 | 13 ± 2 |

[a]Reaction conditions: 10% (w/w) aqueous glucose-D2 solution, Ti-Beta-79 (300:1 glucose/Ti ratio), 373 K, 6 h. [b]Specific optical rotations at 589 nm and ambient temperature. [c]Calculated assuming each sugar fraction contained only a mixture of the two enantiomers and the following pure enantiomer optical rotation values: D-(+)-glucose, 52.7°; L-(−)-sorbose, −42.7°; D-(−)-fructose, −92.4°.

reflecting the presence of predominantly D-(+)-glucose, L-(−)-sorbose, and D-(−)-fructose stereoisomers within the respective fractions. Table 3 also shows estimated values for the enantiomeric excess and composition of each sugar fraction, indicating that isomerization reactions of D-(+)-glucose-D2 (92% enantiomeric purity) with Ti-Beta formed L-(−)-sorbose-D5 (73% enantiomeric purity) and D-(−)-fructose-D1 (87% enantiomeric purity) with high stereospecificity.

The predominant formation of L-(−)-sorbose and D-(−)-fructose from reactions of D-(+)-glucose with Ti-Beta is consistent with intramolecular hydride shift isomerization mediated by Lewis acidic Ti centers and specifically with the intramolecular C5−C1 hydride shift proposed for glucose−sorbose isomerization (Scheme 2). Such stereochemical specificity is in sharp constrast to that expected from base-catalyzed D-glucose isomerization via 3,4-enediol intermediates, which leads to the predominant formation of D-(+)-sorbose (68%) over L-(−)-sorbose (32%).[27] Such stereospecificity also contrasts sharply the racemization expected from base-mediated retro-aldol fragmentation to L-glyceraldehyde and recombination with dihydroxyacetone, which would also form similar amounts of L-(−)-sorbose and L-(+)-fructose.[27]

Direct glucose−fructose isomerization via intramolecular C2−C1 hydride shifts mediated by Ti-Beta has known metalloenzyme analogs (e.g., D-xylose isomerase), in which two divalent cations in the enzyme active site pockets must interact in a concerted manner to coordinate with glucose O1 and O2 atoms prior to isomerization.[11,12] In contrast, direct glucose−sorbose isomerization via intramolecular C5−C1 hydride shifts mediated by Ti-Beta does not appear to have a


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known metalloenzyme analog. The lack of enzymes that mediate direct glucose−sorbose isomerization appears evident in currently known routes for D-glucose to L-sorbose isomerization, which require sequential reduction to a sugar alcohol and oxidation to sorbose by a metal and an enzyme[22−25] or by two different enzymes[37] operating in series. This observation suggests that enzymatic active sites that selectively bind glucose via O1 and O5 atoms may not be as prevalent as those that bind glucose via O1 and O2 atoms and, in part, may be an underlying factor contributing to the rarity of L-sorbose found in nature.[37] These findings indicate that Lewis acidic metal centers in synthetic molecular sieve frameworks that can coordinate selectively with two oxygenated moieties along sugar backbones may be able to facilitate direct and stereospecific sugar rearrangements that occur rarely in biological systems.

## 4. CONCLUSIONS

Lewis acidic $Ti^{4+}$ centers in the framework of pure-silica zeolite beta (Ti-Beta) mediate the isomerization of glucose to sorbose in a direct step involving intramolecular C5−C1 hydride shift (Scheme 2), consistent with isotopic tracer studies in which $^{13}C$ and D labels placed at the C1 and C2 positions of glucose are retained at the C6 and C5 positions, respectively, of sorbose. Glucose−fructose and glucose−sorbose isomerization reactions are catalyzed in parallel by Ti-Beta in water and methanol solvent (373 K), with the former reaction predominating in water and the latter in methanol. Turnover rates of glucose−fructose and glucose−sorbose isomerization sequences are limited by a kinetically relevant intramolecular C2−C1 hydride shift and intramolecular C5−C1 hydride shift steps, respectively, consistent with observed H/D kinetic isotope effects (373 K) of 2.0−2.3 for the former reaction with both glucose-D2 and fully deuterated glucose reactants, and for the latter reaction only with fully deuterated glucose reactants. Intramolecular C2−C1 or C5−C1 hydride shift steps preserve the stereochemistry at unreacted glucose carbon centers (C3, C4, and C5 or C2, C3, and C4, respectively, Scheme 1), leading to the isomerization of D-(+)-glucose (92% enantiomeric purity) to D-(+)-fructose (87% enantiomeric purity) and to L-(−)-sorbose (73% enantiomeric purity) with high stereospecificity. The stereospecificity for D-glucose to L-sorbose isomerization is inaccessible to base-catalyzed isomerization initiated via $\alpha$-carbonyl proton abstraction.

This is the first report, to our knowledge, for direct or stereospecific D-(+)-glucose to L-(−)-sorbose isomerization in a single step mediated by a Lewis acid catalyst or by any catalytic entity. Catalytic routes for direct D-glucose to L-sorbose isomerization have useful applications in the Reichstein synthesis of L-ascorbic acid, which currently requires sequential conversion of D-glucose to D-sorbitol via metal-catalyzed hydrogenation and conversion of D-sorbitol to L-sorbose via enzyme-catalyzed selective oxidation C2-OH. In contrast with Lewis acid-mediated glucose−fructose isomerization, for which known metalloenzyme analogs (e.g., D-xylose isomerase) exist, there does not appear to be a metalloenzyme analog for glucose−sorbose isomerization. The demonstration that Ti-Beta can mediate stereospecific D-glucose to L-sorbose isomerization via intramolecular MPVO catalytic cycles offers promise for the development of synthetic catalyst structures with Lewis acid function that can mediate new sugar rearrangements via intramolecular MPVO cycles. We expect that further insights into the active site structural features responsible for glucose−sorbose isomerization on Ti-Beta and how these features may differ from those responsible for glucose−fructose isomerization will provide specific guidance for the synthesis of active site ensembles that selectively mediate intramolecular sugar rearrangements.

## ■ ASSOCIATED CONTENT

### Supporting Information

Mechanistic scheme for glucose isomerization and epimerization on Sn-Beta, catalyst characterization (X-ray diffractograms, $N_2$ adsorption isotherms, diffuse reflectance UV−visible spectra), kinetic studies of glucose reactions with Ti-Beta-F, product identification ($^1H$ and $^{13}C$ liquid NMR spectra), and H/D kinetic isotope effect estimates are provided. This material is available free of charge via the Internet at http://pubs.acs.org/.

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### Notes

The authors declare no competing financial interest.

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