

# Metalloenzyme-like catalyzed isomerizations of sugars by Lewis acid zeolites

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**Isomerization of sugars is used in a variety of industrially relevant processes and in glycolysis. Here, we show that hydrophobic zeolite beta with framework tin or titanium Lewis acid centers isomerizes sugars, e.g., glucose, via reaction pathways that are analogous to those of metalloenzymes. Specifically, experimental and theoretical investigations reveal that glucose partitions into the zeolite in the pyranose form, ring opens to the acyclic form in the presence of the Lewis acid center, isomerizes into the acyclic form of fructose, and finally ring closes to yield the furanose product. The zeolite catalysts provide processing advantages over metalloenzymes such as an ability to work at higher temperatures and in acidic conditions that allow for the isomerization reaction to be coupled with other important conversions.**

glucose isomerization | heterogeneous catalysis | reaction mechanism

There is a growing interest in the use of renewable carbon sources for the production of chemicals, polymers, and fuels. Numerous chemical transformations of biomass into a wide variety of products are currently being explored. We have recently focused on the isomerizations of sugars, and in particular, the isomerization of glucose to fructose (Scheme 1) (1–3), as a key reaction that could be incorporated into a large number of pathways to convert biomass into useful products (4, 5). For example, oligomeric carbohydrates can be depolymerized into glucose monomers that can then be converted to the chemical platform molecule 5-hydroxymethylfurfural (HMF) (4, 5), via the fructose intermediate (3). Analogously, xylose has been converted to furfural via the xylulose intermediate (6). Additionally, the isomerization of glucose to fructose could be a step in creating synthetic glycolysis pathways (7).

We have shown that the isomerization of glucose to fructose can be catalyzed in aqueous media by hydrophobic zeolites that contain Lewis acids (1–3). Specifically, pure-silica zeolites with the zeolite beta structure containing small amounts of framework Ti<sup>4+</sup> or Sn<sup>4+</sup> (denoted as Ti-Beta and Sn-Beta, respectively) were able to isomerize glucose to fructose in high yield at relatively low temperatures (383–413 K). The Sn-Beta sample had superior activity to the Ti-Beta material, and could even convert solutions that contained 45 wt% glucose (1). We demonstrated that the reaction mechanism in aqueous media was a true Lewis acid-mediated intramolecular hydride shift (2). Additionally, it was shown that catalyst activity was maintained in aqueous media saturated with sodium chloride and acidic pH. This allowed for the “one pot” conversion of starch to HMF through a cascade reaction sequence involving the homogeneous acid-catalyzed depolymerization of starch to glucose, a heterogeneous Lewis acid-catalyzed isomerization of glucose to fructose, and a homogeneous acid-catalyzed dehydration of fructose to HMF (3).

The activation of molecules containing carbonyl groups, specifically sugars, by solids containing Lewis acid centers is a new area of heterogeneous catalysis. In addition to the isomerization of glucose in aqueous media (1–3), the isomerization of triose

sugars in methanol or water (8) and the conversion of sugars to lactic acid derivatives in methanol have been reported using Sn-containing porous solids (9). Activation of carbonyl-containing molecules with solid acids has recently been reviewed, and includes the limited data on solid Lewis acid catalysis (especially in aqueous media) (10).

The conversion of glucose to fructose (used for the production of high-fructose corn syrups) is accomplished commercially by immobilized enzyme catalysts, such as D-xylose isomerase XI. The reaction mechanisms for XI-mediated isomerizations have been investigated because of their relevance to glycolysis and industrial biocatalysis (11). It is well established that the aldose to ketose interconversion occurs by a three-stage mechanism after binding of the cyclic form of glucose takes place. These steps are: (i) aldose ring opening to form the acyclic form of the sugar, (ii) aldose to ketose isomerization of the linear sugar at C-1 and C-2 via a metal-assisted hydride transfer, and (iii) ring closure to release the cyclic form of the ketose (see Scheme 1). Similarly, it has been shown that this metalloenzyme requires two divalent metal ions (M1 and M2) for the enzyme to be active. The preferred metal ions are Mg<sup>2+</sup> or Mn<sup>2+</sup>. Only recently, complementary X-ray and neutron diffraction techniques aimed at probing the location and dynamics of H/D atoms in XI crystal structures have been exploited to reveal important details of the enzyme reaction mechanism (12). Three important new features were elucidated: (i) the primary role of M1 (in conjunction with specific amino acid residues) is to destabilize the pyranose structure and promote the ring opening of the sugar, (ii) M2 binds and stabilizes O1 and O2 on the acyclic sugar, promoting the hydride shift from C2 to C1, and (iii) a hydroxyl group bound to M2 is responsible for the deprotonation/protonation sequences that shuttle protons involved in the interconversion of aldehydes and hydroxyl groups between O2 and O1.

Sn-Beta and Ti-Beta reveal a number of analogous reaction patterns to metalloenzymes when isomerizing glucose. In addition to having high activity and selectivity similar to the metalloenzyme (1), Sn-Beta was demonstrated to perform the isomerization via a metal-assisted intramolecular hydride shift (2). Given the potential significance of this emerging area of heterogeneous catalysis and the possibilities of drawing analogies between enzyme and heterogeneous catalysis, it is important to understand the molecular details of the reaction pathways using these solids. Here, we investigate the glucose isomerization reac-

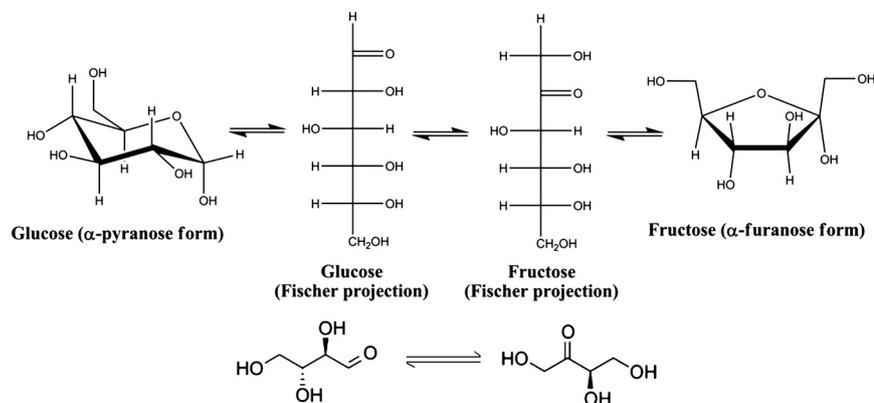
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**Scheme 1.** Schematic representations of the isomerization of glucose to fructose (*Top*) and erythrose to erythrose (*Bottom*).

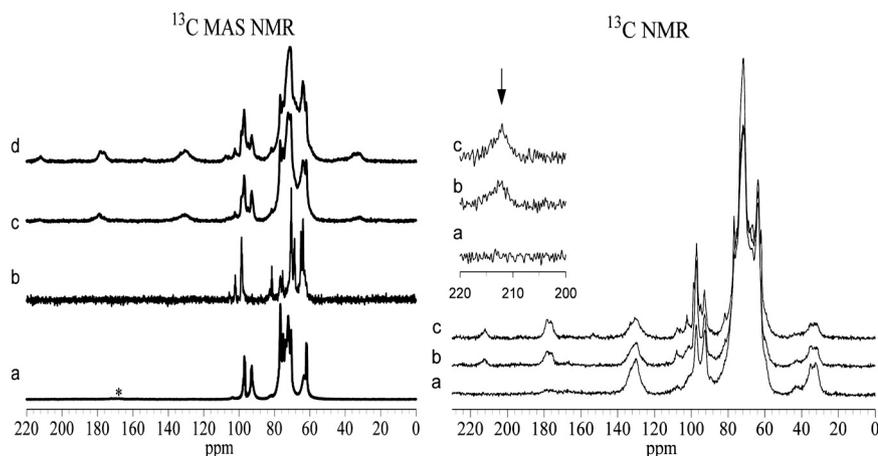
tion catalyzed by hydrophobic zeolites that contain Lewis acid centers using a number of experimental and theoretical techniques. The goal is to clarify the sequence of bond breaking and bond forming events in the reaction pathway by using a combination of experimental and theoretical methods, and to determine if there are further similarities between the heterogeneous, Lewis acid catalysts, and the metalloenzyme pathways.

## Results and Discussion

**Reaction Pathways for Glucose Isomerization on Sn-Beta. Ring opening step.** The initial step in the enzymatic isomerization of glucose to fructose involves the ring opening of a glucose molecule at M1 (12). To determine if a similar pathway is followed by Sn-Beta, the adsorption of  $^{13}\text{C}$  labeled glucose and fructose into Sn-Beta and Si-Beta (pure-silica zeolite without Lewis acid active sites: used as control) was investigated using  $^{13}\text{C}$  NMR (see Fig. 1). Spectra obtained from glucose and fructose adsorbed into Si-Beta show that the sugars are in their cyclic configurations (resonances between 100 and 90 ppm are assigned to the alpha and beta anomers of the pyranose and furanose rings). No new resonances are observed when compared to the spectra of pure glucose or fructose solutions. Conversely, upon adsorption of these sugars in Sn-Beta, new resonances at ca. 30, 130, 180, and 214 ppm appear. The resonance at 214 ppm is at the chemical shift reported for the keto carbonyl carbon of the acyclic form of fructose (13). Cross polarization (CP) experiments with variable contact times are consistent with an assignment of a keto group for the 214 ppm resonance (Fig. 1). The CP method is based on  $^1\text{H}$ - $^{13}\text{C}$  heteronuclear dipolar coupling so the  $^{13}\text{C}$  signal strongly depends on their internuclear distance. Appearance of the 214 ppm resonance only at longer contact times (0.1 and 1.0 ms) rules out the possibility of the carbonyl carbon having a C-H bond as in an aldehyde. Quantitative NMR measurements performed on adsorbed fructose samples reveal that the amount of the acyclic form is on the same order of magnitude as the amount of Sn pre-

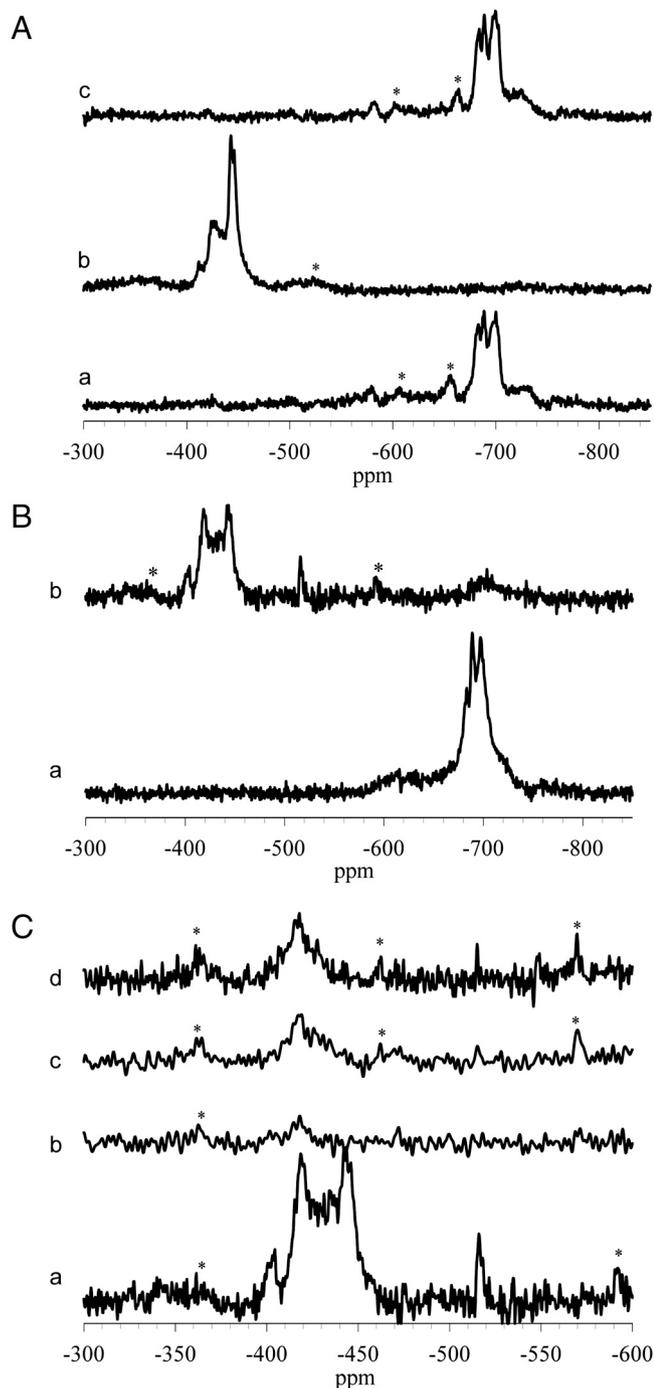
sent in the sample. Because of the errors in the elemental analyses and NMR experiments, greater precision on the estimate of the amount of the acyclic form is not possible. These measurements indicate that ca. 5% of the fructose inside of the zeolite is in the acyclic form, approximately an order of magnitude larger than in solution. Additionally, when fructose is adsorbed in Sn-Beta (but not in Si-Beta), IR measurements reveal the presence of a carbonyl band at ca.  $1728\text{ cm}^{-1}$  that has been assigned previously to the keto carbonyl of the acyclic form of fructose (14) (*SI Appendix, Fig. S1*). Altogether, these data provide direct evidence for the presence of ring opened fructose molecules in Sn-Beta, show that Sn is necessary to observe the acyclic form of fructose, and also suggest that Sn plays an important role in stabilizing the acyclic form of fructose.

The acyclic form of glucose contains an aldehyde with a chemical shift around 205 ppm (15). This resonance is not observed in the glucose adsorption experiments. Certainly, if the acyclic forms of glucose and fructose were present in similar proportions as measured in solution, acyclic glucose would be about a hundred times lower in concentration than acyclic fructose and could not be detected by solid-state NMR (16). Note that the 214 ppm resonance is present in the sample where glucose is adsorbed into Sn-Beta in an amount that corresponds to approximately 30% of the amount observed in the fructose adsorption experiment (*SI Appendix, Fig. S2*). The existence of this resonance implies that some of the glucose has ring opened and isomerized to the ring open form of fructose. In fact, when this sample was reanalyzed after several months of storage at room temperature, the reaction proceeded further. These NMR data strongly support the ring opening reaction pathway illustrated in Scheme 1. While there is an IR assignment of the keto carbonyl of the acyclic form of fructose, no assignment for the acyclic aldehyde carbonyl of glucose has been reported. However, when glucose is adsorbed on Sn-Beta, (but not Si-Beta) there is a broad band at ca.  $1730$ – $1720\text{ cm}^{-1}$  that is reasonable to assign to the combination of



**Fig. 1.**  $^{13}\text{C}$  Solid State NMR of sugars adsorbed in zeolites. (*Left*) (A) glucose adsorbed into Si-Beta, (B) fructose adsorbed into Si-Beta, (C) glucose adsorbed into Sn-Beta, (D) fructose adsorbed into Sn-Beta. (*Right*) spectra from fructose adsorbed into Sn-Beta, (A) cross polarization contact time of 0.1 ms, (B) cross polarization contact time of 1.0 ms, and (C) no cross polarization.





**Fig. 2.**  $^{119}\text{Sn}$  Solid State NMR spectra of Sn-Beta. **A:**  $^{119}\text{Sn}$  Solid State NMR spectra of Sn-Beta after different treatments. (a) calcined, (b) dehydrated after calcination, (c) rehydrated after step (b). The spinning rate was 14 kHz and spinning sidebands are marked by \*. **B:**  $^{119}\text{Sn}$  MAS NMR spectra of Sn-Beta as a function of hydration. (a) Sample was calcined with more humid conditions and exposed to ambient conditions, and (b) sample shown in (a) after vacuum drying at 393 K. The spinning rate was 14 kHz and spinning sidebands are marked by \*. **C:**  $^{119}\text{Sn}$  MAS (a) and CPMAS NMR (b–d) spectra for dehydrated Sn-Beta. The cross polarization contact times from  $^1\text{H}$  to  $^{119}\text{Sn}$  were varied: b) 0.2 ms, c) 1.0 ms, d) 2.0 ms. The spinning rate was 14 kHz for the MAS spectrum and 10 kHz for the CPMAS spectra, and spinning sidebands are marked by \*.

the ring-closed (pyranose) form, and that the ring-closed form is too large to diffuse into TS-1. Since TS-1 is active for the isomerization of erythrose, this reaction can be used to test whether or not exchanging the proton on the adjacent silanol group of the Ti

center with  $\text{Na}^+$  affects the isomerization activity like it did with the oxidation reaction.

Following the work by Khouw and Davis, TS-1, Ti-Beta, and Sn-Beta were exchanged with  $\text{Na}^+$  to identify which type of Sn or Ti center is active for the isomerization reactions. The presence of the sodium atom was confirmed by IR spectroscopy (21). TS-1 catalyzed the isomerization of erythrose to erythrulose independent of whether or not the adjacent silanol group of the Ti center was exchanged with  $\text{Na}^+$  [unlike the oxidation reaction (21)]. Ti-Beta and Sn-Beta were also active for the isomerization of erythrose reaction. Additionally, Ti-Beta and Sn-Beta were also active for the isomerization of both erythrose and glucose before and after  $\text{Na}^+$  exchange. In order to rule out the possibility that the  $\text{Na}^+$  was being removed from the adjacent silanol group during the reactions in pure water solvent [the oxidation reaction with TS-1 was conducted in a mixed methanol/water solvent (21)], the glucose isomerization reaction was performed in saturated NaCl solutions. We have shown previously that the glucose isomerization reaction can proceed at these conditions (3). After reaction, the IR spectrum of the Sn-Beta shows that the adjacent silanol group remained populated with  $\text{Na}^+$ . These reaction data, when taken in total, do not allow us to distinguish whether the open site or the closed site (or both) is the active center. It is possible that the open site is an active site, but the adjacent silanol group, whether in the proton or sodium form, does not significantly alter the reaction rate (unlike the case with TS-1 and the oxidation reaction).

To further investigate the nature of the active Sn site, Sn-containing zeolite beta was prepared using trichloromethyltin as the Sn source (*SI Appendix*, denoted as  $\text{CH}_3\text{Sn-Beta}$ , powder X-ray diffraction pattern in Fig. S4). Successful preparation of zeolite beta with framework tin in this case gives tin centers that exclusively have three bonds via oxygen atoms to framework silicon atoms. The SDA in this sample is removed by acid extraction rather than calcination to preserve the Sn- $\text{CH}_3$  bond.  $^{13}\text{C}$  MAS NMR and thermogravimetric analyses before and after extraction can be used to demonstrate that the extracted  $\text{CH}_3\text{Sn-Beta}$  sample does not contain a significant amount of SDA. In addition,  $\text{N}_2$  adsorption experiments performed on the extracted  $\text{CH}_3\text{Sn-Beta}$  and on a calcined pure-silica Beta (Si-Beta) samples show that both materials have nearly identical adsorption isotherms and equivalent micropore volumes, thus further confirming that there is little to no SDA occluded within the pores after the acid treatment (*SI Appendix*, Fig. S5). Glucose isomerization reactions performed in the presence of the extracted  $\text{CH}_3\text{Sn-Beta}$  give negligible glucose conversion after 45 min at 110 °C (*SI Appendix*, Fig. S6). In contrast, reactions performed with Sn-Beta show nearly 50% conversion at the same reaction conditions. Calcination of  $\text{CH}_3\text{Sn-Beta}$  provides an active glucose isomerization catalyst that was no different from the Sn-Beta samples prepared from tin tetrachloride (*SI Appendix*, Fig. S6). The similar reactivity of these two samples suggests that the amounts of both the open and closed sites are predominantly a function of the high temperature calcination conditions (upon loss of the methyl group the tin center would have an OH group that could then condense with the adjacent silanol group to give a closed site for some of the tin centers in  $\text{CH}_3\text{Sn-Beta}$ ).

In an attempt to alter the distribution of the Sn sites, the  $\text{CH}_3\text{Sn-Beta}$  was first exchanged into the sodium form and then calcined (attempt to limit condensation by reducing the number of available silanol groups adjacent to the open Sn center). The reaction rates for this sample were virtually identical to those obtained with the non-exchanged sample. Based upon these results alone, it cannot be established which site is the active site or whether both sites are active. These results strongly suggest that the calcination and initial exposure to the reaction environment interconverts the distribution of the tin centers between the open and closed sites, bringing them to an equilibrated state dictated by the reactions conditions. Alternatively, the reactivity of the two

types of sites could be the same, but this situation is highly unlikely. This hypothesis implies that the distribution of open and closed sites is dynamic at reaction conditions, requiring the development of an in-situ method for determining site distributions. Such a characterization technique is currently not available to us, and thus theoretical studies were used to gain further insights into the structure and reactivity of the active site.

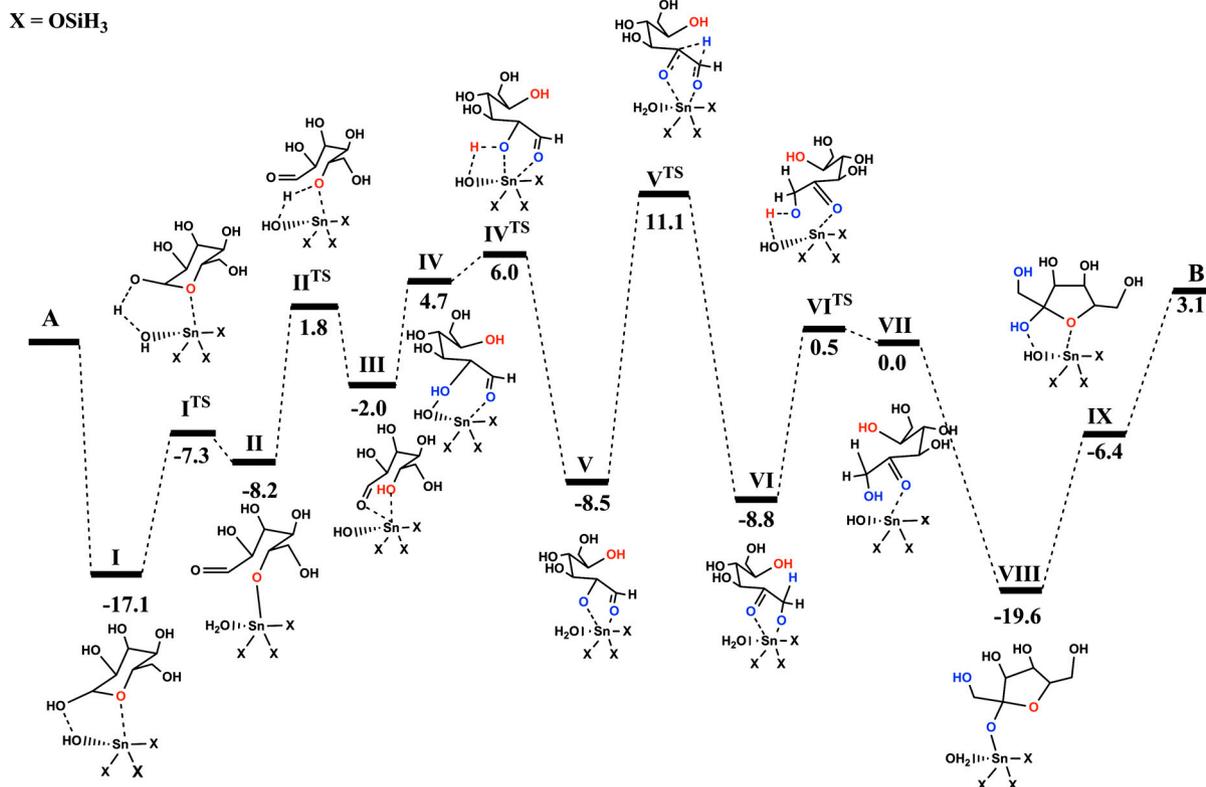
**Computational Studies for Glucose–Fructose Isomerization.** Quantum chemical studies were performed to gain further molecular-level understanding of the glucose–fructose isomerization pathways and to compare with experimental kinetics of both Sn-Beta and Ti-Beta. The structures and energies of intermediates and transition states were determined (*SI Appendix, Text S2*). Based on previous experimental and theoretical studies, it has been suggested that the open site in Sn-Beta, TS-1, and Ti-Beta is the active site for reactions other than the glucose isomerization (18, 19, 21, 22). The enthalpy profile (Fig. 3) and the free energy profile (*SI Appendix, Fig. S7 and Text S3*) for glucose–fructose isomerization catalyzed by the Sn-Beta open site indicate that, similarly to enzymatic systems, the process can be described as a sequence of ring opening (I to IV), hydride shift (V to VI), and ring closing (VI to IX) events. The initial adsorption of cyclic glucose and ring opening does not require any apparent reaction barriers. The process requiring significant activation is the intra molecular hydride shift (V to VI) via a transition state ( $V^{TS}$ ), and is consistent with experimental results showing a kinetic isotope effect when the glucose is labeled with deuterium at the C2 position.

The enthalpy profiles for glucose–fructose isomerization catalyzed by three open active site models with and without adjacent silanol groups were also calculated (*SI Appendix, Fig. S8, Text S4, and Table S1*), the activation enthalpy for the glucose–fructose isomerization process was computed to be 18.6, 22.1 and

17.3 kcal/mol for the Sn-Beta open site, the Sn-Beta open site with one silanol group, and Sn-Beta open site with two adjacent silanol groups, respectively. The calculated activation enthalpy for the Sn-Beta open site with one adjacent silanol group is found to be consistent with our experimental value of  $21.2 \pm 0.7$  kcal/mol, and supports the assignment of the catalytic activity to the open site of Sn-Beta for glucose–fructose isomerization. Overall, these calculations show relatively small energetic differences between the three open sites models, thus suggesting that the presence or absence of adjacent silanol groups does not drastically influence reaction rates. This is in agreement with our experimental results showing that catalysts with  $\text{Na}^+$  exchanged silanol groups had similar activity as the nonexchanged catalysts.

It was previously shown that the apparent activation energy for the hydride shift associated with the isomerization of glyceraldehyde to dihydroxy acetone is 10 kcal/mol higher for the Sn-Beta closed site than that of an open site (22). The glucose isomerization over the closed site would require the participation of a water molecule to allow for ring opening of the glucose. We have performed calculations on a closed site with the presence of an explicit water molecule and the computed apparent activation barrier is approximately 30 kcal/mol (*SI Appendix, Text S5 and Fig. S9*) and is therefore unlikely to be the primary reaction pathway for glucose isomerization over Sn-Beta. These results support the suggestion that the open site is a catalytically more active site for the glucose–fructose isomerization.

The glucose–fructose isomerization using models of the open sites of Ti-Beta (*SI Appendix, Scheme S2*) was also investigated. The initial glucose absorption on the open Ti-Beta model site (with one silanol group) is much weaker, and the rate limiting hydride shift is 10 kcal/mol higher in barrier height (*SI Appendix, Figs. S9 and S10 and Text S6*) compared to that catalyzed by the open site of Sn-Beta with one adjacent silanol group. This trend is



**Fig. 3.** Computed enthalpy profile (MP2, 298 K in water dielectric) for glucose–fructose isomerization catalyzed by open site of Sn-Beta. The label A denotes the sum of the enthalpy of glucose and the active site model (*SI Appendix, Scheme S1a*) at infinite separation in aqueous medium, B denotes the same quantity for fructose. All energies are relative to the energy of A and are in kcal/mol. Note that the mode of binding of the acyclic glucose to the Sn site is slightly different in structures III and IV.

consistent with previously reported theoretical studies for aldose–ketose isomerization by Sn-Beta and Ti-Beta active site models (22). The computed activation enthalpy for glucose–fructose isomerization catalyzed by the open site of Ti-Beta, open site of Ti-Beta with one adjacent silanol, and the open site of Ti-Beta with two adjacent silanol groups are 28.0, 34.3, and 36.3 kcal/mol, respectively (*SI Appendix*, Table S1). The computed activation enthalpies of Ti-Beta with silanol group(s) are consistent with the experimentally measured activation enthalpy ( $37.1 \pm 1.0$  kcal/mol).

Computational results indicate that the acyclic forms of glucose and fructose are equally stabilized by Sn centers (Fig. 3, species V and VI). Gas phase calculations at the G4 level suggest that acyclic fructose is more stable than acyclic glucose by  $\sim 2$  kcal/mol (ketone groups have more intramolecular hydrogen bonding than the aldehyde) (23). Thus, at thermodynamic equilibrium, cyclic and acyclic species of both sugars (Fig. 3, species I, II, V, VI, VIII, and IX) are expected to be present within the zeolite pores. The enthalpy surfaces support the concept of having acyclic forms strongly coordinated with the Sn active site, which is consistent with the experimental observation of acyclic fructose species by NMR. Note that although the cyclic furanose form of fructose bound to the Sn center has a lower energy ( $-19$  kcal/mol; Fig. 3, species VIII) than the bound acyclic form ( $-9$  kcal/mol; Fig. 3, species VI), it is still possible to observe the bound acyclic form since a barrier of  $\sim 10$  kcal is required for the cyclization. A similar conclusion can be drawn for glucose.

## Conclusions

The metalloenzyme D-xylose isomerase can catalyze the isomerization of glucose to fructose. We previously have shown that Sn-Beta and Ti-Beta can also catalyze this reaction to give similar product distributions to the enzyme, and like the enzyme, Sn-Beta can convert up to 45 wt% aqueous solutions of glucose (1). With Sn-Beta (and to a great extent Ti-Beta), we have shown that the reaction mechanism is very similar to that of the enzyme. We have provided evidence to conclude that the glucose partitions into the zeolite in the cyclic form. In the presence of Sn (or Ti), direct NMR evidence of the acyclic fructose is observed. We infer that acyclic glucose must have first been bound to the Lewis acid center prior to being isomerized to obtain the acyclic fructose. The isomerization is clearly occurring via a Lewis acid-mediated, intramolecular hydride transfer mechanism (2). Here, both experimental

results (kinetic isotope effects) and theoretical calculations support the conclusion that the rate-determining step is the intramolecular hydride transfer, and that the open site is likely the active site responsible for isomerization activity. It is exciting to learn that the hydrophobic, Lewis acid containing zeolite catalysts can perform this type of reaction mechanism with glucose and presumably other sugars such as xylose (6) and erythrose. The fact that the zeolite catalysts are quite stable allows them to be used at processing conditions not possible with enzymes, e.g., low pH, high ionic strength, high temperature, and have provided ways of coupling the isomerization reaction to other types of reactions important to the production of chemicals and fuels from biomass (3, 6).

## Materials and Methods

Complete details of materials and methods are found in *SI Appendix*.

**Synthesis of Materials.** The synthesis of the zeolites is described in the *SI Appendix*.

**Characterization Methods.** Powder X-ray diffraction, solid state NMR, IR an adsorption methods are provided in the *SI Appendix*.

**Isomerization Reactions.** Details of the experimental methods for the isomerization reactions are given in the *SI Appendix*.

**Computational Methods.** The methods used for the computational studies are provided in the *SI Appendix*.

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