Methyl-Ligated Tin Silsesquioxane Catalyzed Reactions of Glucose

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Abstract

Tin-containing zeolite Beta (Sn-Beta) has been investigated as a catalyst for isomerizing aldohexoses into ketohexoses through a Lewis acid mediated hydride shift. Recent studies on the reactivities of Lewis base-doped and alkali-exchanged Sn-Beta samples have conclusively demonstrated that the “open” tin site performs the glucose isomerization reaction. With Lewis base doped Sn-Beta, glucose conversion is almost completely eliminated and product selectivity is shifted predominantly to mannose. These data suggest that glucose reactions may occur through pathways that do not involve the “open” site in Sn-Beta; albeit at significantly lower rates. To examine this possibility, reactions of glucose catalyzed by a homogeneous model of Sn-Beta that does not contain “open” sites, methyl-ligated tin silsesquioxane **1a**, is experimentally and theoretically examined. **1a** is an active glucose conversion catalyst selectively producing mannose, although the rates of reaction are far below those obtained from Sn-Beta. A hybrid quantum mechanical/molecular mechanics model is constructed, and the complete catalytic cycle is computationally examined, considering ring-opening, three distinct pathways for each hydride- and carbon-shift reaction, and ring-closing. The combined experimental and computational results

suggest that there could be reaction pathways that involve Si-O-Sn cleavage that give much slower reaction rates than the open tin site in Sn-Beta.

1. Introduction

Microporous solids containing Lewis acid sites have garnered considerable interest for their ability to selectively convert highly functionalized, carbonyl-containing molecules such as glucose [1–3]. Interest in carbonyl-based chemistry has been driven by the attractiveness of producing transportation fuels and fine chemicals from biomass-derived sources [4–6]. A tin-containing molecular sieve with the zeolite beta topology (Sn-Beta) has emerged as a useful solid Lewis acid catalyst to perform highly selective reactions with carbohydrates, such as the isomerization of glucose to fructose [7]. Sn-Beta, initially synthesized by Corma *et al.* [8,9], has been demonstrated to catalyze the Baeyer-Villiger oxidation of ketones to lactones [9,10], Meerwein-Ponndorf-Verley (MPV) reduction of aldehydes and ketones [11,12], epimerization of glucose [13–16], carbon-carbon bond coupling reactions [17,18], and Diels-Alder reactions [19].

The efficacy of Sn-Beta has stimulated research on resolving the active catalytic site and mechanism for the glucose isomerization reaction. Metal-containing zeolites like Sn-Beta, contain a distribution of “closed” sites (a $(\text{SiO})_4\text{Sn}$ center) and “open” sites (a $(\text{SiO})_3\text{SnOH}$ center with an adjacent silanol group) that occur when the framework is partially hydrolyzed [20]. In a recent study, Harris *et al.* demonstrated that the number of open and closed sites in Sn-Beta may be quantitatively determined utilizing Lewis bases as titrants [21]. In the same report, an inverse linear correlation between the initial rate of glucose isomerization with the amount of pyridine dosed was demonstrated, implying that isomerization activity should be fully suppressed when all open sites are titrated. Bermejo-

Deval *et al.* sodium-exchanged the silanol groups adjacent to the open tin site and observed a complete shift in selectivity from fructose to mannose, providing the first experimental evidence that the open site was the most active tin site, as well as emphasizing the significance of the silanol moiety in the reaction mechanism [16]. This work also revealed that titration of the open site with NH_3 (Sn-Beta- NH_3) attenuated the activity of the catalyst indicating that the open and closed sites do not interconvert under reaction conditions.

Several different reaction mechanisms involving a catalytically active open site have been proposed. Work from Li *et al.* [22] suggests that glucose first binds to the open site through coordination of the basic C_1 carbon hydroxyl, with subsequent transfer of the acidic proton to the framework lattice followed by a 1,2-intramolecular hydride shift. This results in a monodentately bound fructose stabilized by the adjacent silanol group through the O_1 oxygen. Yang *et al.* [23] consider a similar type of mechanism involving the closed site. Rai *et al.* [24] and Christianson *et al.* [25] propose similar pathways, however, their calculations involve the acidic C_2 hydroxyl proton transferring to the stannanol group, forming a water molecule. Rai *et al.* also demonstrated that in the absence of a silanol group adjacent to the tin center, the glucose binds to the tin bidentately and selectively produces mannose through a 1,2-intramolecular carbon shift. Experimental results support this prediction [16]. The Davis lab has also shown the effect of the silanol moiety in directing the selectivity of glucose conversion to either fructose or mannose using a pair of silsesquioxanes retaining an octahedral tin site with and without an adjacent silanol substituent [26].

The observation of some glucose activity despite poisoning (Sn-Beta- NH_3) implies that there may be other reaction pathways with rates slower than those catalyzed by the

open site in Sn-Beta. One possible pathway could involve the protonation of a framework Sn-O-Si bond by glucose to facilitate binding to the Lewis acidic site. To test this case, we synthesized a methyl-ligated tin silsesquioxane (**1a**), and investigated its glucose reaction pathways, both experimentally and theoretically. Compound **1a** contains a tin atom terdentately bound to a silsesquioxane ligand through three Sn-O-Si bridging bonds, as schematically shown in Figure 1. Here, we demonstrate that **1a** is an active catalyst (but with low rates of reaction) for the conversion of glucose to mannose and fructose *via* 1,2-intramolecular carbon and hydride shifts, respectively. Additionally, a hybrid quantum mechanics/molecular mechanics (QM/MM) electronic structure model is used to compare pathways in the production of fructose and mannose. The catalytic cycle model consists of three distinct operations: 1) deprotonation and ring-opening of glucose, 2) hydride- or carbon-shift (Bílik) reactions, and 3) ring-closing and reprotonation of the mannose or fructose products.

Figure 1. Schematic representation of the structure of **1a**. R = cyclohexyl.

2. Experimental Methods

All glassware was dried at 433 K prior to all syntheses, and purged with argon while cooling. All syntheses, purification procedures, and reaction tests were carried out under argon using standard air- and water-free techniques. Benzene (99.8%, anhydrous, Sigma-

Aldrich), hexane (95%, anhydrous, Sigma-Aldrich), tetrahydrofuran (THF, $\geq 99.9\%$, anhydrous, Sigma-Aldrich), dimethyl sulfoxide (DMSO, $\geq 99.9\%$, anhydrous, Sigma-Aldrich) and acetonitrile (99.8%, anhydrous, Sigma-Aldrich) were used as received. Triethylamine (99.5%, Sigma-Aldrich) was distilled from 3A molecular sieves. Methyltin trichloride (97%, Sigma-Aldrich) was used without further purification. Heptacyclohexyl trisilanol silsesquioxane (**1**) was obtained from Hybrid Plastics and recrystallized by slow diffusion of acetonitrile into a concentrated THF solution of; its purity was confirmed by ^1H , ^{13}C , and ^{29}Si NMR [27].

2.1 Synthesis of **1a**

1a was synthesized by the reaction of methyltin trichloride with the incompletely condensed trisilanol silsesquioxane **1**, as reported by Feher *et al.* [27] To ensure that all triethylamine (used as a scavenger base, and reported to be a highly selective catalyst in the conversion of glucose to fructose [28]) was removed from the product, acetonitrile was layered onto a concentrated solution of **1a** in benzene. The resultant white powder was filtered and dried for 12 hours under a dynamic vacuum of <50 mTorr.

2.2 Material Characterization

Nuclear magnetic resonance (NMR) spectra of **1a** were collected either on a Varian Inova 500 (^1H , 499.7; ^{13}C , 125.7 MHz) equipped with a broadband probe or on a Varian Inova 400 (^{29}Si , 79.4; ^{119}Sn , 149.1 MHz). ^{29}Si and ^{119}Sn NMR were referenced to SiMe_4 and SnMe_4 , respectively. Chromium(III) acetylacetonate ($\text{Cr}(\text{acac})_3$) was added to samples for ^{29}Si and ^{119}Sn NMR characterization as a shiftless relaxation agent.

^1H NMR (500 MHz, CDCl_3 , 298 K): 1.60-1.90 (vbr m, 35 H, CH_2), 1.10-1.33 (vbr m, 35 H, CH_2), 0.94 (s, 3 H, CH_3), 0.65-0.81 (vbr m, 7 H, CH). ^{13}C NMR (125.7 MHz, CDCl_3 , 298 K):

27.70, 27.56, 27.18, 26.95, 26.73, 26.67 (s, CH₂); 24.35, 23.44, 23.24 (s, 3:3:1 for CH); -3.13 (s, CH₃). ²⁹Si NMR (79.4 MHz, CDCl₃, 298 K, 0.02 M Cr(acac)₃): -65.01, -68.24, -69.55 (s, 3:1:3). ¹¹⁹Sn NMR (149.1 MHz, CDCl₃, 298 K, 0.02 M Cr(acac)₃): -247.60.

2.3 Reaction Procedures

Reactions of D-glucose (Sigma-Aldrich, anhydrous, ≥99.5%) were conducted under anhydrous conditions in 10 mL thick-walled glass reactors (VWR) that were heated in a temperature-controlled oil bath placed on top of a digital stirring hot plate (Fisher Scientific). Both glucose and **1a** were separately dried under vacuum (<50 mTorr) for at least 12 hours prior to the addition of anhydrous DMSO and benzene solvents, respectively. Glass reactors (with their stir bars) were dried for at least 3 hours at 433 K, capped with Teflon septa, and purged with argon while cooling. In a typical reaction, the dried reactors were charged with 6 mL of a 1:1 volumetric ratio of the catalyst and glucose stock solutions, resulting in a 2% (w/w) initial glucose solution, with a glucose:Sn molar ratio of 75. Reactors were placed in the oil bath at a predetermined temperature, and approximately 125 mg aliquots were extracted at regular time intervals. These reaction aliquots were mixed with 125 mg of a 2% (w/w) aqueous D-mannitol (Sigma-Aldrich, ≥98%) solution, which was used as an internal standard for quantification. To ensure thorough catalyst removal from the aliquot solution prior to quantification, 0.3 mL of H₂O was added, and the solution was filtered using a 0.2 μm PTFE syringe filter.

Reaction aliquots were analyzed by high performance liquid chromatography (HPLC) using an Agilent 1200 system (Agilent) equipped with refractive index (RI) and evaporative light scattering (ELS) detectors. The glucose, fructose, mannose, and mannitol fractions were separated with a Hi-Plex Ca column (6.5 x 300 mm, 8 μm particle size,

Agilent) held at 353 K. Ultrapure water was used as the mobile phase at a flow rate of 0.6 mL min⁻¹.

Glucose conversion and product yields were calculated by

$$X_{Gluc}(t) = \frac{n_{Gluc}(t = 0) - n_{Gluc}(t)}{n_{Gluc}(t = 0)} \times 100 \text{ [\%]}$$

$$Y_i(t) = \frac{n_i(t)}{n_{Gluc}(t = 0)} \times 100 \text{ [\%]}$$

where $X_{gluc}(t)$ is the glucose conversion at time t ; $Y_i(t)$ is the yield of product i at time t ; $n_{gluc}(t = 0)$ is the initial moles of glucose in the reactor; and $n_i(t)$ is the moles of product i at time t .

Reactions using singly- and doubly-labeled glucose at the C₁ position (1-¹³C glucose, 98-99%, Cambridge Isotope Laboratories; 2-²H; 1-¹³C glucose, 99% ¹³C, 98% ²H, Omicron Biochemicals) were performed utilizing the same conditions outlined for D-glucose, but were quenched in cold water after a set duration. To separate the catalyst from the reaction solution, approximately 6 mL of ultrapure water was added and the resultant biphasic solution was filtered. Solvent was removed from the catalyst-free fraction by rotary evaporation; the recovered solids were dissolved in D₂O and analyzed by ¹H and ¹³C NMR. These NMR spectra were referenced to 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS).

2.4 Computational Methods

Hybrid quantum mechanics/molecular mechanics (QM/MM) electronic structure calculations were used to examine the interactions between the sugars and the catalyst and also to compute various reaction pathways for glucose isomerization and epimerization. All 167 atoms of the catalyst/sugar complex were included in all of the calculations. Within the

framework of the ONIOM approach to QM/MM calculations [29,30], the M062X functional [31] was implemented to model the quantum mechanical domain of the system. Specifically, the cyclohexyl ligands terminating the Si corners of **1a** were parameterized using the universal molecular mechanics force field (UFF). The complexing sugar, methyl substituent, and the silicon and oxygen atoms of the complex were modeled with the 6-31G(d,p) basis set, while the Sn atom was described using the LANL2DZ effective core basis set [32]. All calculations were performed in the gas phase using Gaussian 09 version A.09 [33].

3. Results and Discussion

3.1 Catalytic Behavior of **1a**

Conversion and yield data for glucose reactions catalyzed by **1a** are given in Figure 2 and Figure 3, respectively. Reaction profiles were collected between 363 – 393 K at 10 K intervals. As with Sn-Beta-NH₃, **1a** converts glucose more selectively to mannose than fructose. Fructose is detected as a primary product. As the reaction temperature is increased, formation of by-products becomes increasingly significant, as indicated by the deterioration in carbon balance (Supporting Information: Figure S.1). An initial investigation into identifying these products indicates that numerous retro-aldol and aldol products are formed. Retro-aldol and aldol reactions have been reported to be catalyzed by tin-containing molecular sieves, although under different reaction conditions, e.g., at high temperatures (>433 K) and through the use of tandem catalysts [34,35].

Figure 2 Glucose conversion as a function of time from the reaction of 2% (w/w) glucose in 1:1 DMSO:benzene solution with **1a** (1:75 Sn/glucose molar ratio) at 363 K (●), 373 K (◆), 383 K (■), 393 K (▲).

Figure 3. Mannose (A) and fructose (B) yields as a function of time from the reaction of 2% (w/w) glucose in 1:1 DMSO:benzene solution with **1a** (1:75 Sn/glucose molar ratio) at 363 K (●), 373 K (◆), 383 K (■), 393 K (▲).

Table 1 summarizes the initial rate data for as-made and modified Sn-Beta, **1a**, and for two other tin silsesquioxanes capable of binding glucose without necessarily protonating the Sn-O-Si bond [26]. These silsesquioxanes retain octahedrally coordinated tin sites with an adjacent siloxy group capped by either a proton (**2a**), analogous to the open site in Sn-Beta, or a trimethylsilyl substituent (**2b**), representative of sodium-exchanged zeolite Beta (Na-Sn-Beta) (structures for **2a** and **2b** are given in Figure 4).

Figure 4. Schematic representation of the structures of **2a** and **2b**. “R” denotes a cyclohexyl ligand.

From these data, **1a** and Sn-Beta-NH₃ have the lowest initial rates, approximately an order of magnitude slower than Sn-Beta. The decreased activity for Sn-Beta titrated with NH₃ (to effectively block the open framework site), in conjunction with that for **1a**, corroborates the hypothesis that reactions at closed sites are slow and selective to mannose. An alternative hypothesis consistent with the experimental data is that the “open” sites remain active for NH₃-Sn-Beta, while the modification reduces their activity and fructose selectivity. However, limited activity of the closed site is a simpler explanation: it does not require assuming the coincidence of two distinct modifications similarly affecting both rate

and selectivity of the open site.

Table 1. Initial rate data for as-made and modified Sn-Beta, as well as tin silsesquioxanes considered here and in other work [16,26]. All initial rate data were calculated from reactions performed at 353 K unless otherwise noted. All heterogeneous reactions were performed in methanol. ^aAt 363K. ^bInitial rates at 353 K determined from activation energy data. Heterogeneous materials were normalized by total tin content, which may underestimate the actual initial rates at the open site in Sn-Beta.

Initial Rate, mol/(s-L-total mol Sn)	Catalytic Material						
	1a ^a	1a ^b	2a	2b	Sn-Beta	Na-Sn-Beta	Sn-Beta-NH ₃
Glucose Consumption	2.69 x 10 ⁻¹	1.02 x 10 ⁻¹	1.42	8.23 x 10 ⁻¹	2.10	1.64	2.99 x 10 ⁻¹
Mannose Production	1.01 x 10 ⁻¹	4.43 x 10 ⁻²	5.49 x 10 ⁻¹	3.80 x 10 ⁻¹	3.52 x 10 ⁻¹	1.04	1.89 x 10 ⁻¹
Fructose Production	6.28 x 10 ⁻²	2.55 x 10 ⁻²	7.56 x 10 ⁻¹	1.34 x 10 ⁻¹	9.30 x 10 ⁻¹	0	0

Apparent activation energies for the simultaneous production of mannose and fructose by **1a** are calculated from the data shown in Figure 5 (Arrhenius plots are given in Supporting Information: Figures S.2-S.3, and the calculated rate constants are listed in Supporting Information: Table S.1). The concentrations of the mannose and fructose products were used to calculate the values of apparent first-order rate constants, k . High conversion values, wherein catalyst deactivation and equilibrium effects become significant, were ignored in the analysis. The epimerization of glucose to mannose has a calculated apparent activation energy of 87.9 kJ·mol⁻¹, while the isomerization of glucose to fructose has a modestly higher apparent activation energy of 96.1 kJ·mol⁻¹. For Sn-Beta, an experimentally determined apparent activation energy of 93 ± 15 kJ·mol⁻¹ has been reported for fructose production in H₂O, and 70 ± 14 kJ·mol⁻¹ for mannose production in CH₃OH [14]. The similarity of these activation energies, however, does not take into account any variations in non-rate-limiting, pre-equilibrium step energies that may be responsible for the observed differences in activity between **1a** and Sn-Beta.

Figure 5. Arrhenius plot for the first-order epimerization and isomerization of glucose catalyzed by **1a**.

3.2 Glucose Reaction Pathways

Scheme 1 depicts possible routes to fructose and mannose from glucose. A C₂ to C₁ hydride transfer converts glucose into fructose (F1), and a secondary hydride transfer from C₁ to C₂ transforms fructose (F1) to mannose (M1). A 1,2-intramolecular carbon shift directly transforms glucose into mannose (M2). A subsequent hydride transfer also produces fructose (F2). The formation of these products may be distinguished through the use of isotopically labeled starting compounds.

Scheme 1. Possible reaction pathways involving hydride and carbon shifts at C₁ and C₂. Sugars are depicted using Fischer projections. Abbreviations F1, M1, M2, and F2 indicate

location of ^{13}C on first or second carbon of sugar, when C_1 of glucose reactant is labeled. $\text{R} = \text{C}_4\text{H}_9\text{O}_4$.

3.2.1 ^{13}C - and ^2H -labeling experiments

To investigate the reaction pathways promoted by **1a**, 10% (w/w) glucose enriched with ^{13}C at the C_1 position ($1\text{-}^{13}\text{C}$ glucose) or with ^{13}C at the C_1 position and ^2H at the C_2 position ($2\text{-}^2\text{H}$; $1\text{-}^{13}\text{C}$ glucose) solutions were reacted for 60 minutes at 373 K in 1:1 DMSO:benzene, maintaining a glucose:Sn molar ratio of 75. ^{13}C spectra (Figure 6) show strong resonances at $\delta = 98.7$ and 94.8 , corresponding to the β - and α -glucopyranose starting material labeled with ^{13}C at the C_1 position, respectively. Additionally, both spectra have resonances at $\delta = 74.0$ and 73.5 , corresponding to β - and α -mannopyranose labeled with ^{13}C at the C_2 position, respectively (M2 in Scheme 1). These results, coupled with the reaction data, suggest that **1a** preferentially catalyzes the 1,2-intramolecular carbon shift of glucose to mannose, analogous to the Bílik reaction [36].

Figure 6. ^{13}C NMR spectra for reactant and products with **1a** (1:75 Sn/glucose molar ratio) in a 10% (w/w) at 373 K for 60 minutes with: (A) 1- ^{13}C glucose and (B) 2- ^2H ; 1- ^{13}C glucose in a 1:1 DMSO:benzene solvent system.

In addition to the formation of mannose, fructose is produced in lower yields. For the singly labeled 1- ^{13}C glucose experiment, two ^{13}C resonances at $\delta = 66.7$ and 65.5 are observed, corresponding to the β and α forms of fructofuranose, respectively. These resonances are not observed in the spectra obtained from 2- ^2H ; 1- ^{13}C glucose. This result is likely a consequence of a 1,2-intramolecular hydride shift that negates the nuclear Overhauser enhancement (NOE), an effect that amplifies ^{13}C resonances for directly bonded ^{13}C - ^1H pairs; no such amplification occurs for ^{13}C - ^2H pairs, resulting in substantial attenuation of the ^{13}C resonances and the subsequent production of triplets from coupling to ^2H (spin 1) [37]. The low intensity triplets that would be expected in ^{13}C spectra for ^{13}C - ^2H pairs are not observable in Figure 6, reflecting the low yield of fructose as a consequence of the kinetic isotope effect. The ^1H NMR spectra from the reaction of 2- ^2H ; 1- ^{13}C glucose, shown in Figure 7, may also be used to confirm that the 1,2-intramolecular hydride shift is the prevailing fructose-forming mechanism. As discussed by Román-Leshkov *et al.*, the base-catalyzed conversion of 2- ^2H glucose to fructose results in scrambling of the deuterons between the glucose and solvent system, resulting in unlabeled glucose exhibiting a peak corresponding to a proton in the C_2 position at $\delta = 3.2$ [38]. The spectra shown in Figure 7 do not demonstrate this behavior, indicating the glucose remains deuterated at the C_2 position, further suggesting that the 1,2-intramolecular hydride shift mechanism occurs. Moreover, this spectrum exhibits no C_1 position mannose proton at $\delta = 5.17$, indicating the deuteron shifts from the C_2 to C_1 position during the intramolecular carbon shift reaction, and that the F1 to M1 hydride

shift does not occur in significant yield. In general, the mannose to fructose hydride shift is not detectable under the reaction conditions utilized. These reaction pathways are analogous to what has been observed with Sn-Beta [16,38].

Figure 7. ¹H NMR spectra for: (A) unreacted 2-²H; 1-¹³C glucose, and (B) reactant and products with **1a** (1:75 Sn/glucose molar ratio) in a 10% (w/w) at 373 K for 60 minutes with 2-²H; 1-¹³C glucose in a 1:1 DMSO:benzene solvent system.

3.3 Identification of the Catalytic Species

Experiments were performed to confirm that the observed catalysis was due solely to **1a**, and not a consequence of starting reagents or leached tin species formed by degradation of the catalyst under reaction conditions. Control experiments were performed with **1** exposed to all synthesis procedures, but without the addition of CH₃SnCl₃. In this instance, no glucose conversion was observed. A solution of CH₃SnCl₃ in

benzene catalyzed formation of fructose, but in yields lower than that observed with **1a**; no mannose formation was observed.

To examine the structural integrity of **1a** post reaction, the catalyst was separated from a reaction performed at 393 K for 1 hour, utilizing the same parameters and procedures outlined previously. These conditions were chosen to ensure a large excess of glucose relative to **1a**, so that statistically all Lewis acid sites should participate in the catalysis. In order to separate the catalyst from the crude reaction solution, an excess of hexane was added to the mixture while the reaction vessel was maintained at 393 K. This resulted in the formation of an immiscible two-phase system, consisting of the dense polar DMSO phase containing the carbohydrates and the less dense non-polar catalyst-containing phase. The two phases were separated, and the hexane solution was allowed to cool, then washed with an excess of acetonitrile. The hexane phase was again separated, the volatiles were removed, and the resultant white powder was dried under vacuum for 12 hours. NMR analysis of this material (Supporting Information: Figures S.4-S.7) is in very good agreement with spectra obtained of the material prior to reaction, and data presented in the literature [27]. Taken together, these results suggest that the structure of **1a** likely remains intact over the course of the reaction, and is the origin of the catalytically active species.

3.3.1 Computational Chemistry

For Sn-Beta, the open site has been postulated to be the active catalytic site, whereby a stannanol group facilitates the initial binding step of the glucose molecule to the Lewis acid site [15,23,24,38]. This reaction mechanism is not possible for **1a**, however, due to the absence of the stannanol. In order for **1a** to catalyze the conversion of glucose, we

hypothesize that the Sn-O-Si bridging bonds must be involved to allow the glucose C₁ hydroxy proton to transfer to one of the three Si-O-Sn bridging bonds, analogous to pathways proposed by Li *et al.* [22] and Yang *et al.* [23] In a very recent study, Beletskiy *et al.* provide evidence that this type of proton shift may occur for 2-propanol (adsorbed as 2-propoxide) on silica-immobilized tin silsesquioxane complexes [39]. Similar lattice protonation mechanisms have been proposed for metal-containing zeolites [17,40]. This proton transfer results in the formation of an adjacent silanol group to the tin site, as well as glucose bound to the tin site. *In situ* NMR spectroscopy characterization was attempted by exposing the catalyst to reaction conditions and collecting spectra at 373 K; unfortunately, no evidence for proton transfer to one of the Sn-O-Si bond was obtained. In order to garner further insight into the glucose reaction mechanisms for **1a**, a theoretical approach was taken.

Figure 8 depicts the previously described proposed glucose ring-opening mechanism on **1a** and compares the relative gas-phase free energies. The calculations estimate that deprotonation and ring-opening are endothermic, with intrinsic free energy barriers of 41.3 and 66.6 kJ·mol⁻¹, respectively. Bermejo-Deval *et al.* [41] report an activation energy of 37.3 kJ·mol⁻¹ for ring-opening at an open site. Work by Yang *et al.* [23] also suggests that the initial glucose deprotonation step at the open site is thermodynamically more stable than at the closed site. These data suggest that binding to and performing ring opening at a site without a hydroxyl moiety present (as with **1a** and the closed site in Sn-Beta) is less favorable. As considered by Li *et al.* [22], this variation and subsequent difference in energies is likely a function of geometric distortion and deviations in Lewis acidity between the two sites.

Figure 8. Glucose ring-opening mechanism. Gas-phase free energies (in kJ·mol⁻¹) at 373 K for intermediates and transition states are reported relative to isolated glucose and catalyst. Intrinsic barriers reported in parentheses. GLUp: glucopyranose; DP: deprotonation; RO: ring opening; GLU: open-chain glucose.

After ring-opening, hydride transfer or Břilik reactions convert glucose into fructose or mannose, respectively. Generally, there are three possible pathways in converting glucose, which we categorize as “O₁ Binding,” “O₂ Binding,” and “Bidentate,” identified according to whether the open glucose binds to the Sn Lewis acid site *via* the O₁ position, O₂ position, or both during the reaction. The mechanistic details and energetics of these pathways are compared in Figures 9 and 10.

The bidentate mechanism involves: 1) coordination of both O₁ and O₂ to the Sn center in an octahedral geometry, 2) deprotonation, forming a silanol and binding O₂ to the Sn, 3) a H/C-shift with a chelate-like transition state, and 4) reprotonation in sequential steps. For both isomerization and epimerization, the bidentate pathway is predicted to be the most favorable, with intrinsic free energy barriers of 79.6 kJ·mol⁻¹ and 101.0 kJ·mol⁻¹, respectively.

The O₁ binding pathway begins by coordination of the aldehyde oxygen to the Sn, maintaining a hydrogen bonding interaction between O₂ and the Sn-O-Si bridge. The first step binds O₁ to the Sn during a concerted deprotonation of O₂ alongside the H/C-shift.

Intrinsic barriers for the H/C-shift are 115.5 kJ-mol⁻¹ and 110.9 kJ-mol⁻¹, respectively. Reprotonation of O₁ follows in a subsequent step.

The O₂ binding pathway starts with a deprotonation forming a silanol and binding O₂ to the Sn. This deprotonation is endothermic, with an intrinsic barrier of 50 kJ-mol⁻¹ and a free energy of reaction of 26.9 kJ-mol⁻¹. O₁ then forms a hydrogen bond with the silanol formed *in situ*, which subsequently reprotonates the sugar during the concerted H/C-shift reaction. Intrinsic barriers for the H/C-shift are 61.1 kJ-mol⁻¹ and 93.5 kJ-mol⁻¹, respectively.

To our knowledge, this is the first time a systematic approach has been considered for glucose isomerization and epimerization reaction mechanisms, which frequently consider only the bidentate [15,23–25,42,43], O₁ binding [15], or O₂ binding [23–25,43].

Bidentate

O1 Binding

O2 Binding

Figure 9. H-Shift Pathways. Three pathways are shown for transforming open-chain glucose (GLU) into open-chain fructose (F1), *via* deprotonation (DP), reprotonation (RP), and H-shift reactions. The bidentate transition state gives the lowest barrier for reaction, with a slightly more stable transition state than the O₂ binding pathway. Gas-phase free energies (in kJ·mol⁻¹) at 373 K for intermediates and transition states are reported relative to isolated glucose and catalyst, with intrinsic barriers reported in parentheses.

Bidentate 1

O1 Binding

O2 Binding

Bidentate 2

Figure 10. C-Shift Pathways. Open-chain glucose (GLU) transforms directly into open-chain mannose (M2) through deprotonation (DP), reprotonation (RP), and C-shift reactions. Four pathways are shown: three starting from the initial geometries of the H-shift reactions (bidentate, O₁ binding, and O₂ binding) and an additional bidentate pathway starting from a different geometry to facilitate O₃ hydroxyl interaction with **1a**. Gas-phase free energies (in kJ·mol⁻¹) at 373 K for intermediates and transition states are reported relative to isolated glucose and catalyst, with intrinsic barriers reported in parentheses.

To finish the catalytic cycle, the ring closing reactions of deprotonated fructose, open fructose, and open mannose were examined. Deprotonated open fructose ring-closes

to produce O₁-deprotonated fructofuranose. A slightly different pathway for open fructose ring closing produces O₂-deprotonated fructofuranose. Subsequent reprotonation regenerates the catalyst and produces fructofuranose. Similarly, open mannose ring-closes to form O₁-deprotonated mannopyranose, and subsequent reprotonation regenerates the catalyst and produces mannopyranose. These pathways have relatively low barriers compared to H/C-shift reactions, and their details are in the Supporting Information. Also included in the Supporting Information are the bidentate, O₁ binding, and O₂ binding pathways for interconverting fructose and mannose (F1 to M1), which have higher barriers than the competing fructose ring-closing pathways. Products M1 and F2 are not observed because ring-closing is facile relative to additional H/C-shift reactions.

We analyzed the selectivity trends using the energy span model [44] (see Supporting Information). The gas-phase transition state free energies for the mannose (135.6 kJ·mol⁻¹) and fructose (123.7 kJ·mol⁻¹) pathways slightly favor fructose as the major product. In experiment, the difference in apparent activation energy is 8.2 kJ·mol⁻¹ in favor of mannose production – a difference too small to be expected to be resolved by QM/MM calculations which do not take into account the complex solvation environment of the experiments.

3.3.2 Electronic structure analysis of the H/C-shift reactions

The character of the H/C-shift reactions was also analyzed according to the Natural Bond Orbital (NBO) method (see Tables S.3 – S.8). In general, four overall mechanisms govern a hydride transfer: (a) electron-proton-electron pathway ($e^- - H^+ - e^-$); (b) electron-hydrogen atom transfer; (c) hydrogen atom-electron transfer; and (d) one-step hydride ion transfer [45]. Choudhary *et al.* analyzed the hydride transfer in the bidentate mechanism

for xylose to xylulose on the Sn-Beta zeolite [42]. They proposed that the H-shift mechanism involves the rate-limiting transfer of a neutral hydrogen atom from C₂ to C₁, concerted with a rapid electron transfer from O₂ to O₁. Following a similar methodology, we conclude that the bidentate mechanism for the H-shift on **1a** follows the same mechanism: a neutral hydrogen atom transfers from C₂ to C₁ concertedly with an adiabatic electron transfer from O₂ to O₁, facilitated by a C₂-O₂ and C₁-O₁ anti-bonding π system at the transition state. The O₁-binding H-shift is a test case for observing the H-shift reaction without the prior deprotonation of O₂. Without deprotonation prior to the hydride transfer, the H-C₂ bond is less polarized and thus charge separation comes at a higher energy cost. Comparison with the bidentate pathway shows how the sugar deprotonation step activates the C₂ donor fragment for the subsequent H-shift. The electronic structure of the bidentate C-shift was also analyzed. The results demonstrate that this pathway's electronic composition is remarkably analogous to that of the H-shift, including the C₂-O₂ and C₁-O₁ π system for transferring an electron and a neutral C₃ fragment as a transferring group. A detailed analysis may be found in the Supporting Information.

4. Conclusions

We have synthesized and tested methyl-ligated tin silsesquioxane as a catalyst for glucose reactivity to examine the activity and structure of tin species that are analogous to the closed tin site in Sn-Beta. The catalytic nature of **1a** suggests that there are glucose conversion pathways that involve the breaking of the Si-O-Sn linkage at some point in the reaction cycle and that such pathways may be possible from the closed sites in Sn-Beta. We have not conclusively proven this point here, and since the bond angles in **1a** are significantly different from Sn-Beta, these pathways may not occur in the latter. However, if

they do, they participate in catalyzing the reaction of glucose at a rate significantly slower than the open site. Isotopic labeling experiments demonstrate that these reactions occur *via* 1,2-intramolecular carbon and hydrogen shift pathways for mannose and fructose, respectively, yielding products that are indistinguishable from those obtained by catalysis at the open site. The full catalytic cycle has been theoretically investigated considering three distinct pathways for the hydride- and carbon-shift reaction reactions. It has been calculated that the most favorable pathway to produce both fructose and mannose over **1a** is by glucose binding bidentately to the tin center, deprotonation to one of the Sn-O-Si bridges, and performing either a hydride- or carbon-shift reaction. We propose that a similar mechanism occurs at the closed site in Sn-Beta.

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7. Acknowledgements

Research was supported as part of the Catalysis Center for Energy Innovation, an Energy Frontier Research Center funded by the U.S. Department of Energy (DOE), Office of Science, Basic Energy Sciences (BES), under Award number DE-SC0001004. S.K.B. wishes to acknowledge funding from the National Science Foundation Graduate Research Fellowship Program under Grant No. DGE-1144469. T.R.J. also wishes to acknowledge funding from the National Science Foundation Graduate Research Fellowship Program under Grant No. 0750966, as well as the George W. Laird Merit Fellowship. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation. The authors would like to thank Marat Orazov and Jeff Christianson for numerous useful conversations.

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Graphical Abstract

*Formed via
1,2-Intramolecular
Hydride Shift*

D-Fructose

"Open" Site

D-Glucose

"Closed" Site

*Formed via
1,2-Intramolecular
Carbon Shift*

D-Mannose