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ACYLATION OF METHYLFURAN WITH BRØNSTED AND LEWIS ACID ZEOLITES

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Graphical Abstract



Highlights

- Lewis and Bronsted acidic zeolites are compared for acylation of methylfuran and furan
- Bronsted acid zeolite beta shows the highest specific rates at low Si/Al=12.5
- [Sn]-zeolite beta shows the lowest activation energy
- Acylation rate is controlled by the dissociation of the C-O-C linkage of the anhydride for methylfuran
- [Sn]-beta catalytic pathway involves Brønsted acid catalysis by the silanol group of the hydrolyzed "open" site

ABSTRACT

The acylation of methylfuran has been investigated using Brønsted and Lewis acid zeolite catalysts. The highest reaction rate for acylation on a per gram basis is found on zeolite Beta with high aluminum content (Si/Al=23) and the highest turnover frequency on a per metal site basis is found on zeolite Beta with low aluminum content (Si/Al=138). Among Lewis acid zeolites, [Sn]-Beta shows higher turnover frequency than [Hf]-, [Zr]- or [Ti]-Beta. Similar apparent activation energies were found for [Al]-Beta with different Si/Al ratios and a lower apparent activation energy was found for [Sn]-Beta. Electronic structure calculations reveal that on both [Al]- and [Sn]-Beta the most favorable pathway follows the classic addition-elimination aromatic electrophilic substitution mechanism. The calculations also reveal that, on both [Al]- and [Sn]-Beta, the rate of methylfuran acylation is controlled by the dissociation of the C-O-C linkage of the anhydride while hydrogen elimination is the rate-determining step in the acylation of furan. The latter is in complete agreement with measured primary kinetic isotope effects. One remarkable and unexpected finding from our calculations is that the most favorable catalytic pathway in [Sn]-Beta involves Brønsted acid catalysis by the silanol group of the hydrolyzed "open" site and not Lewis acid catalysis by the Sn metal center.

Keywords: acylation; furan; acid catalysis; DFT modeling; flow reactor kinetics; isotopic labeling

1. INTRODUCTION

The first examples of Friedel-Crafts acylation were carried out using homogenous Lewis acid catalysts such as aluminum chloride.^[1] Brønsted acid zeolites were subsequently found to catalyze this chemistry and had advantages over the classical Lewis acid catalysts in terms of separation, isomer selectivity and true catalysis; less than stoichiometric amount of catalyst is used.^[2-4] The acylation of furans with Brønsted acid zeolites is a particularly efficient and selective means of forming C-C bonds and adding functionality to these bio-derived compounds.^[5-8] In contrast to Brønsted acid zeolites—substituted with trivalent metals like aluminum—solid Lewis acid zeolites are isomorphously substituted with tetravalent metals that act as isolated framework Lewis acid sites. These materials have shown remarkable improvement in activity and selectivity over Brønsted acid zeolites for transformations of biomass, like glucose isomerization and reduction and etherification of hydroxymethylfurfural,^[9-11] but they have yet to be investigated for acylation. Thus, it is of interest to determine how Brønsted and Lewis acid zeolites compare in Friedel-Crafts acylation of bio-derived furans.

Brønsted and Lewis acid zeolites with the Beta framework are the focus of this work. For Brønsted acidic zeolites, H-[Al]-Beta results in higher conversion of methylfuran to 2-acetyl-5methylfuran (2A5MF) compared to H-[Al]-Y or H-[Al]-ZSM-5.^[8] Beta has been shown to be superior for the acylation of other reactants with acetic anhydride^[12-14] and with other acylation agents.^[15] This zeolite framework has been the subject of many other acylation studies, where other zeolite structures are not explicitly compared.^[5, 6, 16-21] Moreover, there is an array of Lewis acid zeolites formed from the substitution of various metals (Ti, Zr, Sn, Hf) into the Beta framework, which can be compared to the Brønsted acid form of [Al]-Beta. In this report, the rate and mechanism of methylfuran acylation with acetic anhydride, to form 2-acetyl-5-methylfuran

(2A5MF) and acetic acid (Scheme 1), are compared for a number of Brønsted and Lewis acid Beta zeolites.

The value of this reaction in the production of biomass-derived commodity chemicals has been demonstrated as a key step in the production of *para* aromatic species;^[8] and with fatty anhydrides this chemistry can be applied to the production of surfactants.^[22] Methylfuran may be produced by hydrodeoxygenation of furfural, which is produced industrially from hemicellulosic feedstocks.^[23] Acetic anhydride is used as the acylating agent as it requires much lower temperatures for reaction than acetic acid. Much of the previous literature on zeolite-catalyzed acylation with acetic anhydride in the liquid phase focuses on toluene or anisole on H-[Al]-Beta. These studies found that competitive adsorption between reactants and products contributes to deactivation and lower reaction rates,^[14, 18, 24] and that an acylium ion, rather than ketene, is the acylating intermediate.^[20] Similarly, the mechanism of electrophilic aromatic substitution with homogeneous Lewis acids is known to proceed via the formation of an acylium ion from the interaction of the acylating agent and the Lewis acid catalyst. Solid Lewis acid catalysts have not yet been investigated for this chemistry and thus the mechanism remains to be determined. While the mechanism is known to include the acylium ion in Friedel-Crafts acylation with acetic anhydride,^[20] the rate-determining step depends on the specific electrophile and nucleophile involved and can be probed with kinetic isotope effects (KIE). Here the rate-determining step was probed experimentally with a kinetic isotope effect study of furan acylation on Brønsted and Lewis acid zeolite and supplemented with density functional theory (DFT) calculations to investigate various catalytic pathways on H-[Al]-Beta and [Sn]-Beta.

An additional issue for Lewis acid zeolites is characterization of the true active site. While the tetravalent metal may exist with four bonds coordinated to the framework as a "closed" site, it

has also been found that one of these bonds may hydrolyze to create an "open" site with one hydroxyl group bound to the metal and a corresponding silanol group, as depicted in Scheme 2. Baeyer-Villiger oxidation, Meerwein-Ponndorf-Verley reduction and glucose isomerization have all been shown to be catalyzed by an open [Sn]-Beta site,^[25, 26] which involves a Lewis-acidic tin but also a Brønsted-acidic silanol (Si-OH). Here, experiments and modeling were used to determine the role of the open site for methylfuran acylation on [Sn]-Beta. X-ray absorption spectroscopy experiments were also conducted to better understand the active site of [Sn]-Beta materials.

In this study, Brønsted and Lewis acid Beta zeolites were screened using batch reactors. Brønsted acidic H-[Al]-Beta and Lewis acidic [Sn]-Beta were also studied in a flow system under differential conditions. Kinetic isotope effect experiments of furan acylation were used to compare the rate-determining step. DFT calculations of methylfuran acylation on H-[Al]-Beta and [Sn]-Beta were performed to probe the reaction mechanism on these materials.

2. METHODS

2.1 Experimental

2.1.1 Materials. The aluminum Brønsted acid forms of zeolite Beta were purchased from Zeolyst. Specifically, for a low Al content H-Beta the hydrogen form of zeolite Beta (Zeolyst, CP811C, Si/Al=150) was used as received and is designated as H-[Al]-Beta-150. For a high Al content H-Beta the ammonium form of zeolite Beta (Zeolyst, CP814E, Si/Al=12.5) was calcined as follows: ramp 1 K min⁻¹ to 823 K, hold 12 hours. This sample is designated as H-[Al]-Beta-12.5. [Si]-Beta, [Sn]-Beta, [Zr]-Beta and [Hf]-Beta were synthesized hydrothermally as reported previously.^[27] [Sn]-Beta prepared via this method is designated as [Sn]-Beta-HT. Another [Sn]-Beta was prepared via solid-state ion exchange (SSIE) as described in literature,^[28] by grinding

dealuminated H-BEA with tin (II) acetate (Aldrich) and calcining in air. This sample was designated as [Sn]-Beta-SSIE. For control experiments, bulk SnO₂ was obtained from Sigma Aldrich and was used without further treatment. Al₂O₃ (99.97%, Alfa Aesar, γ -phase) was tested as a control as well. Prior to use, Al₂O₃ was calcined at 873 K (ramp 10 K min-1, hold 2 h).

Si/Al ratios of the commercial zeolites were determined by X-Ray fluorescence (XRF) with a Rigaku Supermini200 and the Si/Al for H-[Al]-Beta-12.5 was similar to the value advertised by the manufacturer but the Si/Al for H-[Al]-Beta-150 was not. For H-[Al]-Beta-150, n-propylamine adsorption was performed in order to ensure the Al content was as advertised. In this experiment, Brønsted acid site density was measured via n-propylamine decomposition into propylene and ammonia using a flow reactor with an on-line Agilent 7890A gas chromatograph (GC) equipped with an HP-PLOT Q column. This was accomplished using a microreactor system where all gas lines between the location of n-propylamine introduction and the GC were heat traced with temperature maintained at or above 348 K. Approximately 50 mg of H-[A1]-Beta-150 was loaded into a quartz tube in the reactor and was heated to 773 K at a rate of 10 K/min in flowing He (100 mL/min) and held at 773 K for 45 min. Then, the sample was cooled to 373 K and exposed to flowing He saturated with n-propylamine for 15 min via a bubbler. The sample was subsequently heated to 473 K and held for 90 min to desorb excess n-propylamine and ensure a 1:1 ratio of adsorbed n-propylamine to Brønsted acid sites. Finally, the temperature was increased to 773 K at a rate of 30 K/min. The GC sampling loop was immersed in liquid nitrogen to collect the desorbed reaction products, which were subsequently quantified via a thermal conductivity detector (TCD).

For Lewis acid zeolites (Sn,-Zr-,Hf-Beta), Si/Metal ratio was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) performed by Galbraith Laboratories (Knoxville, TN). [Ti]-Beta was synthesized as described previously.^[9] Si/Ti was determined by

XRF with a Rigaku Supermini200. Micropore volume for all samples was determined with nitrogen physisorption in a Micromeritics 3Flex system using the t-plot method. Samples were degassed overnight at 523 K and backfilled with nitrogen prior to analysis. X-ray diffraction (XRD) patterns were collected using a Bruker D8 diffractometer with Cu K α radiation. The pattern was collected for 0.5 seconds at each increment of 0.02 degrees between 5 and 50 degrees. Scanning electron microscopy (SEM) images were recorded on a JEOL JSM 7400F at 10 μ A.

Na-exchanged [Sn]-Beta was prepared following a procedure adapted from literature.^[26] Specifically, 300 mg of [Sn]-Beta was mixed with 45 mL of 1 M NaNO₃ (Sigma-Aldrich, \geq 99%) in distilled water for 24 hours at room temperature. The catalyst was recovered by filtration over a ceramic filter (Chemglass, CG-1402-16) and washed 3 times with 1 M NaNO₃ (50 mL solution for each wash). Then the material was calcined at 853 K for 5 hours (5 K/min ramp).

Thermogravimetric analysis (TGA) on spent catalysts was collected on a Mettler Toledo TGA/DSC Thermal Gravimetric Analyzer with STARe software. Samples were heated at a rate of 5 K/min under 80 mL/min of air flow. The first derivative (dTGA) of the TGA curves was calculated numerically using Origin. The differential curves were smoothed with an FFT filter with 100 points.

Extraction of retained organics on spent catalysts was performed as previously described^[29]: 30 mg of spent catalyst was dissolved in 1 g HF (Acros, 48%) and 2.6 g DI water and allowed to react for 1 hour at room temperature. The organic species in the mixture were extracted with methylene chloride and analyzed with a GC-MS (Shimadzu QP2010 Plus, HP-Innowax column). Because the concentrations of these samples were so low, the extracted mixture was placed in a hood overnight to allow some methylene chloride to evaporate before GC-MS analysis. Therefore, concentrations of the retained organics were not determined.

2.1.2 Batch Reaction Experiments. For batch reaction experiments, 5 mL of 2-methylfuran (Sigma Aldrich, 99%, BHT-stabilized) and 15 mL of acetic anhydride (Sigma-Aldrich, \geq 99%) were loaded into a 45 mL 4714 Parr reactor with 50 mg of catalyst and a magnetic stir bar for mixing. The reactor was pressurized with nitrogen to 14 bar, placed in an oil bath at a temperature of 383 K, and quenched with an ice bath after the desired reaction time. The reaction product was filtered from the catalyst with a 0.2 micron syringe filter (Corning). Product samples were analyzed by gas chromatography (Agilent 7890A) equipped with a flame ionization detector. An HP-Innowax column (Agilent) was used with the following temperature program: hold at 313 K for 4.5 min, 10 K min⁻¹ ramp to 523 K and a final hold for 3 minutes. Reaction side products were identified with a GC-MS (Shimadzu QP2010 Plus) equipped with an HP-Innowax column following the same temperature program.

For kinetic isotope effect experiments, the specified amount of 1 g furan (Aldrich, 99%) or 1.06 g furan-d₄ (Aldrich, 98% D atom) and 3.2 g acetic anhydride (Sigma-Aldrich, \geq 99%) were loaded into a 10 mL with 50 mg catalyst and a magnetic stir bar and sealed with crimp seal septum (Chemglass, CG-4920-10). The vial was then placed in a reactor block with oil at 393 K. After 20 minutes, the catalyst was filtered from the reaction product and analyzed as described above.

2.1.3 Flow Reaction Experiments. A flow reactor previously described^[27] was used to study the reaction under continuous flow conditions. Gamma-valerolactone (GVL) (Sigma-Aldrich, \geq 99%) was used as solvent to reduce the concentration of acetic anhydride. This was necessary because the back pressure regulator (Equilibar, EB1ULF1) diaphragm (Polyimide-5) and o-ring (Viton) is sensitive to acetic anhydride concentrations in excess of 50% v/v. A few experiments carried out without the addition of GVL were performed with a stainless steel diaphragm and Kalrez o-ring. Typically, a solution comprised of 45.5 g methylfuran, 150 mL acetic anhydride

and 200 mL GVL was supplied at 4 mL/min with an HPLC pump (Alltech). 14 bar pressure was applied with the back pressure regulator. The reactor consists of a ¹/₄ inch (6.4 mm) stainless steel tube between two VCR fittings. 50 mg of uniformly sized catalyst pellets (80-120 U.S. mesh, 125-180 µm) was held by a VCR gasket (Swagelok, SS-4-VCR-2-10M) on the bottom, and glass wool was used to hold the catalyst in place, filling the space up to the top VCR gasket. Unless otherwise stated, the reactor was submerged in the oil bath and heated under GVL flow until the desired temperature was reached; at that point, flow of the desired reaction mixture was started. For reactions at a flow rate of 4 mL/min, the first sample was taken after 15 min of time-on-stream and then periodically for the next 75 minutes. Experiments with H-[Al]-Beta-150 were run at 2 mL/min, and the initial sample was taken after 30 minutes and the periodically for the next 150 minutes. At each time point, 2 mL of sample was collected at the outlet and analyzed offline via gas chromatography (Agilent 7890A) equipped with a flame ionization detector. An HP-1 column (Agilent) was used with the following temperature program: hold at 313 K for 4 min, 15 K min⁻¹ ramp to 473 K and a final hold for 1 minute. The carbon balance in all runs was between 97.1-103.6%.

2.1.4 X-ray absorption spectroscopy. X-ray absorption spectroscopy experiments were performed at beamline 5BM-D (DND-CAT). Spectra were recorded in transmission at the Sn K edge (29200 eV), using sealed ionization chambers (Danfysik). A Sn foil was used for energy calibration. Zeolite samples and a SnO₂ standard were pressed into pellets in stainless steel six-well sample holders ("shooters"), for a total absorption equal to 2 at the Sn K edge. The sample holder was then placed in a quartz tube (25.4 mm OD), which was in turn sealed with stainless steel fittings equipped with Kapton windows and welded ball valves. Nitrogen (Airgas 5.0) was flowed through the sample using a rotameter at 100 ml/min and the temperature was raised at 2

K/min to 923 K while recording spectra. The spectra were processed using the Demeter suite, using the Athena software for spectra normalization and the Artemis software for fitting. The fitting was performed using data from k = 2.5 to 13 Å⁻¹ for R = 1 to 2.3 Å. The amplitude reduction factor (S₀) was calibrated using SnO₂.

2.2 Computational

2.2.1 Zeolite Model. In the computational studies of the catalytic pathways, the H-[Al]-Beta and [Sn]-Beta zeolites were modeled with clusters that were treated quantum mechanically. For H-[Al]-Beta, the active site was created at the T2 crystallographic site by substituting an Al atom for a Si atom and neutralizing with a proton.^[30-32] In the case of [Sn]-Beta, the exact location of Sn in the framework is difficult to ascertain and also dependent on the synthesis method, and so still a matter of debate and vigorous experimental work.^[32-34] In this work we have opted for the T2 site. For [Sn]-Beta, we modelled both the closed (unhydrolysed) and open (hydrolysed) active sites (Scheme 2).

The cluster models were hewn out of the zeolite crystals using the "multi-centered distance cutoffs" approach of Migues, et al.^[35] Using geometries of the reactants in a very large cluster of the zeolite pre-optimized at a low-theory-level, the zeolite cluster is subsequently trimmed down by keeping only framework atoms within 5 Å of any atom of the 4T active site and of any atom of the guest molecules (reactants). To build well-connected clusters, framework atoms that lie outside the cutoff boundary but are bonded to atoms inside the boundary are also included in the cluster model. The cutoff radius of 5 Å has been determined by Migues *et al.* to be a reliable compromise between convergence and computational efficiency. The cluster is terminated at Si atoms whose dangling bonds are subsequently capped with H atoms; the terminal Si-H bonds are 1.47 Å long and in the direction of the corresponding Si-O crystallographic bond. The final clusters consisted

of 39T atoms and a total of 142 atoms for [Al]-Beta and 141 atoms for [Sn]-Beta; and incorporated the 12-membered ring of the channel along [100] and the 4- and 5-membered rings around the active site (see Figure 1).

2.2.2 Electronic Structure Calculations. All calculations were performed with the Gaussian 09 package.^[36] The Al, C, O and non-terminal H atoms were modeled at the M06-2X/6-31G(d,p) theory level; the capping H atoms were modelled at the M06-2X/3-21G level. The Si and Sn atoms were modelled at the M06-2X/LANL2DZ level. All the atoms were allowed to relax, except the capping H atoms, which were kept frozen. The transition states (TS) were characterized by vibrational frequency analyses and intrinsic reaction coordination (IRC) calculations. Population analysis was performed using the Natural Bond Orbital (NBO) theory, implemented in the NBO 6.0 program.^[37]

Unless otherwise specified, Gibbs free energies were computed at 393.15 K using the quasi rigid-rotor harmonic oscillator (qRRHO) approximation of Grimme^[38] and of Li et al.^[31] In addition, adsorbed species were considered as mobile and entropic contributions associated with the two-dimensional translational motion in the pore were added to the adsorbates. Details can be found in the SI (Section S1).

Binding energies (E_{BE}) were calculated by the equation

$$E_{BE} = E_{ads} + E_{zeo} - E_{ads+zeo},$$

where E_{ads} is the gas phase adsorbate energy, E_{zeo} is the energy of the bare zeolite and $E_{ads+zeo}$ is the total energy of the adsorbate in the zeolite.

2.2.3 *Microkinetic Modeling*. The calculated free energies profiles were used to parametrize a microkinetic model which was used to compute apparent activation energies and to determine rate-determining steps by sensitivity analysis. Details are provided in the SI.

3. RESULTS

3.1 Catalyst Characterization

Two Brønsted acid Beta zeolites were investigated: one with high aluminum content, H-[Al]-Beta-12.5, and one with low aluminum content, H-[Al]-Beta-150. A series of Lewis acid Beta zeolites (Sn, Zr, Hf, Ti) were synthesized hydrothermally. A siliceous zeolite Beta (Si-Beta) was also synthesized hydrothermally and tested as a control. Finally, a post-synthetic [Sn]-Beta-SSIE was synthesized via solid-state ion exchange by grinding tin acetate with dealuminated H-[Al]-Beta-12.5. This technique allows a much higher incorporation of tin compared to what is possible via the hydrothermal technique. The [Sn]-Beta synthesized hydrothermally is referred to as [Sn]-Beta-HT to distinguish it from its solid-state ion exchange analog.

The Si/M (M=heteroatom) and micropore volume are reported in Table 1 for each material, including the dealuminated Beta that [Sn]-Beta-SSIE was synthesized from. Si/M ratios were determined by ICP-AES, unless otherwise noted. In the case of H-[Al]-Beta-150, which was purchased from Zeolyst, Si/Al=75 was determined from XRF which is twice as high as listed, and could be due to extraframework (non-Brønsted acidic) aluminum. To address this seeming inconsistency, we performed n-propylamine decomposition, which specifically probes Brønsted acid site concentration. 120 µmol Brønsted acid sites per gram was measured, which corresponds to Si/Al=138, similar to the Si/Al=150 reported by the manufacturer. Normalized rates for H-[Al]-Beta-150 were based on this 120 µmol/g concentration. Similarly, the Brønsted acid site density of the H-[Al]-Beta-12.5 sample was determined to be 690 µmol/g, using the n-propylamine decomposition test. This corresponds to Si/Al=22.9, consistent with the presence of extraframework Al.^[38]

The results of nitrogen physisorption analysis are summarized in Table 1, while XRD patterns and SEM images are reported in the SI (Section S2). Micropore volumes and XRD patterns were all consistent with the structure of zeolite Beta for all the materials investigated. [Sn]-Beta-SSIE shows additional peaks in the XRD pattern consistent with the formation of SnO₂ from the decomposition of excess tin acetate in the zeolite. Consistent with this, the micropore volume of [Sn]-Beta-SSIE was lower than that of the other zeolites, likely due to the presence of SnO₂ occluded in the zeolite pores.

A series of X-ray absorption experiments were performed to understand the local coordination environment of [Sn]-Beta zeolites (Table 2). At room temperature, the tin in asprepared [Sn]-Beta-HT zeolite is bound to six O atoms. Compared to values reported in the literature,^[39,40] the optimized Debye-Waller factor (σ^2) is significantly higher, indicating greater uncertainty in the measurement. This reflects the fact that the Sn-O distances are longer for the Sn-OH₂ bond to adsorbed water, compared to the Sn-OH and framework Sn-O bonds. Upon heating under inert gas, the coordination numbers, bond distances and Debye-Waller factors decrease, as initially the coordinating water is lost at temperatures lower than 120 °C (Figure 2). Following that, the condensation of adjacent silanol and stannanol groups results in the closing of the open sites and the reduction of the coordination number to 4.

In contrast, [Sn]-Beta-SSIE shows a much higher coordination number, both at room temperature and after treatment with inert gas at high temperature. At room temperature, the coordination number is 7.15 ± 0.37 , while after dehydration, it is equal to 5.81 ± 0.47 . This suggests that most (~90%) of the Sn in the sample is present as SnO₂, which has a coordination number of 6. The average bond distance of 2.029 Å is also closer to the Sn-O bond distance in SnO₂ (2.044)

Å and 2.061 Å for axial and equatorial O atoms, respectively) than to the Sn-O distance in the zeolite framework.

3.2 Batch Reactions

The results of acylation of methylfuran with acetic anhydride to form 2A5MF (Scheme 1) over various zeolite Beta catalysts at 383 K using a batch reactor are shown in Table 3. Turnover frequency (TOF) is normalized by metal content of the catalyst as determined by XRF or ICP-AES. Brønsted acidic H-[Al]-Beta-12.5 (row 1) exhibited the highest rate on a per gram basis. The high and low concentration H-[Al]-Beta catalysts (row 1 and 2) exhibited very similar TOF normalized by metal content, higher than any of the Lewis acid materials. The extraframework aluminum in these materials does not contribute significantly to the acylation activity as evidenced by row 9. The difference in TOF in the case of the [Sn]-Beta materials (row 3 and 7) is certainly affected by the presence of SnO₂ (observed via XRD and EXAFS) in [Sn]-Beta-SSIE, since the rate is normalized by total metal content and SnO_2 is inactive for this reaction (row 8). Despite the inactivity of most of the tin in [Sn]-Beta-SSIE, the specific reaction rate is significantly better than [Sn]-Beta-HT. The other hydrothermally synthesized Lewis acid zeolites had comparatively low reactivity, less than half the TOF measured on [Sn]-Beta (rows 4-6). [Ti]-Beta showed the least activity, similar to previous comparisons of Lewis acid Beta zeolites for Meerwein-Ponndorf-Verley reduction, where [Sn], [Zr] and [Hf]-Beta reaction rates are significantly faster than Ti.^{[41,} ^{42]} Control experiments with siliceous Beta or with no catalyst (rows 10-11) produced no acylated product. While [Sn]-Beta-HT had a TOF slightly higher than H-[Al]-Beta-12.5, its TOF was much lower than that of H-[Al]-Beta-150 which has a similar heteroatom concentration. While it is clear the Brønsted acid material is superior for this acylation chemistry, the [Al]- and [Sn]-Beta

materials were next investigated in a flow reactor under differential conditions to better understand their reactivity.

3.3 Flow Reactions

3.3.1 Activation energy. Since the [Al]-and [Sn]-Beta catalysts exhibited the highest turnover under batch conditions, they were investigated in a flow reactor to quantify the activation energy. All catalysts exhibited deactivation with time on stream as shown in Figure 3. To determine the initial rate, the product was sampled over time and the rate was extrapolated to t=0 with an exponential fit. Catalyst lifetimes were compared by determining the half-life of the catalyst (the time at which half of the rate at t=0 is observed, see Table 4). Arrhenius plots based on initial rates were used to determine the apparent activation energy of the reaction (Figure 4 and Table 4). Given the low activation energy on Sn compared to Al and the large crystal size of [Sn]-Beta-HT (Figure S2c), the possibility of mass transfer limitations was considered. However, the crystal size of [Sn]-Beta-SSIE prepared via solid-state ion exchange was much smaller (Figure S2g) and comparable to that of the H-[A1]-Beta-12.5 (Figure S2a) from which it was synthesized. Since a very similar activation energy was measured on two tin catalysts with very different crystal sizes, it is unlikely that mass transfer is affecting the apparent activation energy. Additionally, the Weisz-Prater criterion was estimated and falls below the limit where pore diffusion is limiting (SI Section 3).

3.3.2 TGA of spent catalysts. All catalysts deactivated with time on stream. Among the catalysts investigated, the half-life of the catalysts was in the range of 18-32 minutes (total length of experiments was 180 minutes for H-[Al]-Beta-150 and 90 minutes for all others). The spent catalyst obtained from the lowest-temperature measurement of each catalyst was analyzed using

TGA (Figure 5). H-[Al]-Beta-12.5 exhibited the largest weight loss (43%), followed by [Sn]-Beta (37%). H-[Al]-Beta-150 and [Sn]-Beta-SSIE had smallest weight loss (21% and 19%, respectively). Since the catalysts were only dried under nitrogen flow at room temperature, and the boiling points of the reactants and products are high, a portion of this weight loss is from reactants or products left inside and outside of the catalyst pores. The boiling points of the reactants and products in this system are: 336 K (methylfuran), 414 K (acetic anhydride), 373 K (2A5MF), 391 K (acetic acid), and 480 K (GVL). The differential of the TGA traces is shown in Figure S3, but even from Figure 5 it is clear that there is significant weight loss on H-[Al]-Beta-12.5 and [Sn]-Beta-HT between 380-400 K that is not observed on the other two catalysts. Based on boiling points, the weight loss in this region seems consistent with loss of either acetic acid or anhydride.

While weight loss in the TGA could be from reactants and products left in the intracrystalline voids of the samples, the TGA analysis also revealed some weight loss at higher temperatures that might be due to the occlusion of large byproducts in the pores. Spent catalyst from the flow reactions were dissolved with HF, and the organics were extracted and analyzed with GC-MS (Table 5) to identify the retained molecules. GVL was found retained on all the catalysts, which is likely due to its high boiling point since the catalyst is "dried" under nitrogen flow at room temperature. Acetic acid was detected in the extracted organic phase for H-[A1]-Beta-12.5, it is also possible that acetic acid and acetic anhydride were retained on the other catalysts, but stayed in the aqueous HF phase due to their polarity. Products with a higher molecular weight than the desired 2A5MF product (MW=124) were found on some of the catalysts, indicating some deactivation from pore blockage by these large molecules. The MW=206 product detected on H-[A1]-Beta-12.5 could be derived from the condensation of hydrated methylfuran (1,4-

pentanedione) with 2-acetyl-5-methylfuran. The MW=290 product detected on [Sn]-Beta could be from acylation at both ends of the double bond in the 206 molecule. Despite deactivation, previous work has shown that H-[Al]-Beta zeolites run in batch reactions at high temperature (453 K) can be regenerated via calcination resulting in minimal loss in conversion (<5%) and selectivity (<1%).^[8]

3.3.3 Effect of GVL. GVL was used as solvent to minimize acetic anhydride and acetic acid concentration in the effluent and minimize potential damage to the back-pressure regulator. Acetonitrile was also investigated as a solvent, but resulted in the same or lower rates on H-[Al]-Beta-12.5 and [Sn]-Beta-HT, respectively (Figures S4 and S5). Extraction and analysis of the organics on spent catalyst from these experiments revealed the presence of both 2A5MF and GVL retained in the catalyst. It is possible that methylfuran is hydrated by residual water, forming an unstable 1,4-pentanedione that then isomerizes to GVL. There are no products corresponding to the molecular weight of 5,5-bismethylfuran-2-pentanone, formed from the reaction of two methylfuran molecules with 1,4-pentanedione, as described by Corma et al.^[42] The observation of 2A5MF in the spent catalyst in acetonitrile but not in GVL indicates that GVL may have a promoting effect in removing the 2A5MF product from the active site, resulting in the higher rates observed for [Sn]-Beta with GVL as solvent. Consequently, a backpressure regulator configuration compatible with acetic anhydride was used to investigate the reaction without solvent on H-[A1]-Beta-150. This resulted in a dramatic decrease in the rate (no GVL in Figure 6) compared to when GVL was used (with GVL in Figure 6), which further reveals the positive effect of GVL solvent on this reaction. Additionally, when the bed was heated under GVL flow but then only supplied with methylfuran and acetic anhydride once the desired temperature was reached (heat with GVL

in Figure 6), the initial rate was improved over heating under acetic anhydride flow, but still reached a regime of no product evolution after about two hours of time on stream.

3.3.4 Co-feeding of products. The retention of acylation products can contribute to deactivation observed in acylation reactions.^[14, 16, 18, 24] To this end, acetic acid and 2A5MF products were co-fed to determine their effect on the reaction rate on the catalyst with the highest turnover, H-[A1]-Beta-150. As shown in Figure 7, co-feeding just a small amount (5 mol% based on methylfuran) of acetic acid resulted in a reduced reaction rate. Similarly, co-feeding 5 mol% of 2A5MF decreased the initial rate, though not as severely as 5 mol% of acetic acid. A further increase of 10 mol% 2A5MF in the feed reduced the initial rate more. The co-feeding of 2A5MF also slowed the rate of deactivation and the catalyst half-life was increased from 32 to 44 minutes. The reduced reaction rate upon co-feeding of products indicates product inhibition is contributing to deactivation similar to what is reported in other acylation studies.

3.4 Mechanistic Studies

3.4.1 Kinetic isotope effect. The acylation mechanism over zeolites was probed with labeled furan-d4. A significant primary isotope effect of 2.5 and 1.8 was found for both H-[Al]-Beta-150 and [Sn]-Beta-HT, respectively. For deuterated aromatics, a concerted, single-step substitution of the acetyl group should result in a primary kinetic isotope effect (KIE). In contrast, the absence of a primary KIE would suggest a two-step mechanism, involving the formation of a Wheland intermediate followed by deprotonation (see Scheme 3).^[42] This Wheland complex is the origin of the positional selectivity observed in electrophilic aromatic substitution (EAS) reactions; a late Wheland complex transition state leads to high positional selectivity. This complex is also

stabilized by electron donating groups, which accounts for the acceleration of EAS reactions by electron donating substituents on the aromatic. Whether the formation of this intermediate is the rate-determining step has been found to be dependent on the strength of the electrophile and nucleophile. In the case of strong electrophiles or strong nucleophiles, the highest energy transition state resembles the starting aromatic (early transition state) and the formation of the Wheland intermediate is rate determining. In the case of weak electrophiles or weakly basic aromatics, the highest energy transition state resembles the Wheland intermediate (late transition state) and the deprotonation of this intermediate is rate determining.^[1, 43, 44] If formation of the Wheland complex is rate determining, only a small secondary inverse KIE would be expected due to change from sp² to sp³ of the carbon on the aromatic.^[45] If deprotonation of the Wheland complex is rate determining, or if the mechanism is concerted, a significant primary KIE would be expected due to C-H bond breaking during hydrogen elimination.^[45] Based on these considerations, the measured KIE in the case of furan-d4 indicate that deprotonation (either in a concerted or stepwise manner) is the rate-determining step. This is also supported by the computational modeling discussed in the next section. We should note that strong primary KIE of 3.25 and 2.25 have been observed for toluene and benzene acylation, respectively, with acetyl fluoride catalyzed by antimony pentafluoride.^[46] However, for the acylation of *p*-xylene with isobutyl chloride catalyzed by aluminum chloride, the lack of primary KIE has ruled out deprotonation as the rate-determining step.^[47] As explained by Effenberger, the magnitude of the KIE is a function of the Wheland complex formation and deprotonation rates.^[48]

Since methylfuran is a stronger nucleophile than furan, on account of the electron-donating methyl group—and strong nucleophiles are not associated with primary KIE and an earlier rate-determining step—it might be that the rate-determining step could be different for methylfuran

compared to furan. Indeed, calculations and microkinetic analysis (see next section) indicate a change in the rate-limiting step in the case of 2-methylfuran. That was unexpected considering that a primary KIE for both toluene and benzene with the same acylating agent (as discussed earlier) indicates that the additional methyl group is not enough to change the rate-determining step.

3.4.2 Na-exchanged [Sn]-Beta. To determine whether the active site for acylation on [Sn]-Beta is open or closed, a [Sn]-Beta-HT sample was exchanged with sodium to replace the hydroxyl groups at the open site, as reported in Bermejo-Deval *et al.*^[26] When the exchanged sample was tested under the same conditions as described for the experiments in Table 3, no 2A5MF was formed, that is, sodium exchanged with an open site and prevented the reaction from occurring, that is, the open site is the active site. There is still uncertainty in the quantification of open and closed sites in these materials, particularly under reaction conditions. Currently the active site concentration is estimated to be the same as the metal content, however, if only a fraction of Sn is in an open configuration, this would result in an underestimate of the true turnover frequency. Since recent work has shown that less than half of Sn atoms in [Sn]-Beta samples are open sites,^[49] the TOFs reported here are probably underestimated.

An additional consideration arising from the identification of the Sn open site as the active site is the possibility of Brønsted acid catalysis at this site. Recent computational modeling of [Sn]-Beta open sites revealed the silanol coordinated to the Sn of the open site to be more Brønsted acidic than typical framework defect silanols and comparable in binding strength to the Lewis-acidic Sn center for strong bases like ammonia and pyridine.^[50] Given that this chemistry can clearly be catalyzed by either Brønsted or Lewis acids, it is possible that the reaction occurring at the open Sn site is actually catalyzed by the Brønsted-acidic silanol and not the Lewis-acidic Sn

atom. The reaction was investigated computationally to address this question and to compare the mechanisms on [Al]- and [Sn]-Beta.

3.5 Computational Modeling of Acylation on H-[Al]-Beta and [Sn]-Beta

3.5.1 H-[Al]-Beta. Acetic anhydride binds more strongly than methylfuran to H-[Al]-Beta by 11.8 kcal/mol (Figure 8). The binding energy of acetic anhydride is 12.7 kcal/mol and binding takes place through a carbonyl oxygen, O₁, forming a hydrogen bond (1.39Å) with the proton of the active site (Figure 8a). NBO analysis shows weakening of the O₅-H bond at the Brønsted site; the occupancy of the anti-bonding orbital $\sigma^*(O_5-H)$ is 0.14 compared to 0.02 prior to binding. The occupancy of the bonding orbital $\sigma(O_5-H)$, however, is unaffected: 1.99 prior to and 1.98 after binding.

We have identified two acylation pathways on H-[Al]-Beta (Scheme 4). Both follow the classic, two-stage, addition-elimination mechanism of electrophilic aromatic substitution which involves formation of a stable addition intermediate (σ -complex). The two pathways differ, however, in one respect. In the first, (H1), the active-site-bound anhydride dissociates upon protonation to form acetic acid and an acyl cation, which is stabilized by covalent bonding to a framework oxygen atom. The first phase of the reaction is completed by electrophilic attack on methyfuran in the C₅ position by the acyl cation. The electrophilic substitution is completed by proton elimination from the intermediate (σ -complex) back to the conjugate base of the active site. In contrast, in the second pathway (H2), the protonation of the anhydride, its dissociation and formation of the acyl cation and the electrophilic attack by the latter occur in a single step.

The free energy profiles for the two pathways are shown in Figure 9. In H1, the dissociation of the protonated anhydride (INT1^H to INT1^{H1}) has an intrinsic barrier (ΔG^{\ddagger}) of 24.3 kcal/mol.

NBO analysis confirms a covalent bond between the acyl group and a framework oxygen atom (INT1^{H1}). This is consistent with work by Kresnawahjuesa *et al.*, who have reported dissociation of acetic anhydride over H-[A1]-ZSM-5.^[51] Then the acyl group detaches from the zeolite to form a surface acyl cation (INT2^{H1}, $\Delta G^{\ddagger} = 10.7$ kcal/mol), which easily adds to the C₅ of methylfuran ($\Delta G^{\ddagger} = 3.7$ kcal/mol). The proton back-donation to the conjugate base of the Brønsted site requires $\Delta G^{\ddagger} = 12.5$ kcal/mol. In the H2 mechanism, the concerted formation of the acyl cation and its addition to methylfuran (INT1^H to INT2^H) has $\Delta G^{\ddagger} = 37.0$ kcal/mol, significantly higher than in H1. The geometry of the transition state (TS^{H2}) shows that the proton of the active site has already migrated to the acetic anhydride while the acyl cation is in close proximity to the C₅ of methylfuran. All of these factors indicate a late transition state, characteristic of an endergonic process and in accord with Hammond's postulate.^[51] As can be seen from Figure 9, the two pathways, H1 and H2, share the intermediate INT2^H and all the intermediates that follow on from it.

Clearly, the stepwise pathway H1 is energetically more favorable for the acylation of methylfuran over H-[A1]-Beta. Although the free energy profile in Figure 9 suggests that the hydrogen elimination is the rate-determining step, microkinetic modelling (*vide infra*) reveals that the rate of acylation of methyfuran is controlled by the breaking of the C-O-C linkage in the anhydride and the acyl formation. The rate of acylation of furan, however, is controlled by the hydrogen elimination step (presented in Section 8 of the SI), which is consistent with the observed KIE reported above from kinetic isotope effect experiments.

3.5.2 [Sn]-Beta. Both the closed and open [Sn]-Beta sites were modeled; the mechanism on the closed site was found to be slower than on the open site. Given that the sodium exchange experiments also support the open active site, only the open site calculations are discussed here,

but a discussion of the mechanism on the closed site is available in the SI (Section S6). Owing to the moderate acidity of the silanol proton of the [Sn]-Beta open site, which has been demonstrated in previous DFT studies,^[50, 53] the silanol could be deprotonated by acetic anhydride and catalyze the reaction following pathways similar to those described above for H-[A1]-Beta. At the same time, the metal Sn center may also participate in the reaction as a Lewis acid. This interplay between Brønsted and Lewis acidity complicates the elucidation of mechanisms for the open-Sn site. In the following, we present three competing reaction pathways for the acylation of methylfuran (Scheme 5). Below, two of them will be classified as Brønsted acid catalysis (denoted by D1 and D2), as they only involve the moderately acidic silanol group and are very similar to those identified in the H-[A1]-Beta case. The third pathway (denoted by D3) engages both the Lewis-acidic metal center and the neighboring silanol group.

Two modes of binding of acetic anhydride to the active site were considered, shown in Figure 10. In the first mode (Figure 10a), one of the two carbonyl groups of the anhydride is coordinated to the Sn atom, while the other carbonyl interacts with the silanol, with a total binding energy of 4.4 kcal/mol. In this binding geometry, Sn assumes octahedral coordination. Alternatively, as shown in Figure 10b, both carbonyl groups of the anhydride may interact with the silanol proton, while the Sn atom remains pentacoordinated. This results in a more stable geometry, with a binding energy of 9.4 kcal/mol and is consistent with the XAS data presented above. NBO analysis shows that stabilization largely comes from hydrogen bonding while the lone pairs of both carbonyl oxygen atoms donate electron density to the antibonding orbital of the silanol OH. In all three identified reaction pathways presented in Scheme 4, the reaction proceeds through the latter binding mode (Figure 10b).

Free energy profiles for the three mechanisms are shown in Figure 11 and Figure 12. The mechanisms D1 and D2 (Figure 11) are essentially the same as H1 and H2 in H-[A1]-Beta (Figure 9), respectively, and overall, the pathway D1 is energetically more favorable than D2. In the D1 pathway, the dissociation of the anhydride and the formation of the acyl cation requires $\Delta G^{\ddagger} = 24.7$ kcal/mol compared to 24.3 kcal/mol for the H1 case in H-[A1]-Beta, indicating similar Brønsted acid strengths.

In the mechanism D3, which engages the Sn center, the reaction proceeds with donation of the silanol proton to the bridging oxygen of the anhydride, producing acetic acid and an acylium cation, and requires $\Delta G^{\ddagger} = 25.7$ kcal/mol. The subsequent electrophilic attack of the furan ring by the acyl cation (INT2^{D3}) is practically non-activated, as it requires a mere 1.7 kcal/mol to climb up the barrier. The geometries of TS1^{D3} and INT2^{D3} in Figure 12 show the Sn atom in a 6-fold coordinated state, which is evidence of the engagement of the Sn atom. Interestingly, the proton elimination after the acyl addition is different from the mechanisms described so far. In pathway D3, the proton back-donation to the active site is still the rate-controlling step, but it does not take place in a direct fashion. Rather, it is mediated by the carboxyl group of acetic acid. The intrinsic free energy barrier for the hydrogen elimination is calculated to be 17.9 kcal/mol (TS3^{D3}), which is 5.4 kcal/mol higher than in pathway D1. Clearly, the participation of the Lewis-acidic Sn center does not facilitate the reaction.

What endows the silanol with stronger than usual acidity is its proximity to the Sn framework atom—the oxygen of SiOH is not formally bonded to the Sn framework, but it is, nevertheless, within the first coordination sphere of the latter (see Figure 13a). As a result, the OH moiety of the silanol is polarized, becoming a good proton donor. We have compared the relative

acidities of the open [Sn]-Beta silanol and the bridging hydroxyl in H-[Al]-Beta by computing the deprotonation energies the respective deprotonation energies (DPE):

$$DPE = E_{Zeo-M^-} - E_{Zeo[M]}$$
 ,

where E_{Zeo-M^-} and $E_{Zeo[M]}$ are the electronic energies (zero-point energy corrected) of the deprotonated and initial metasubstituted zeolites, respectively. The smaller the DPE, the easier to remove the proton, and the stronger the acidity of the catalyst. The DPE of the open [Sn]-Beta silanol is 293 kcal/mol, which is only 5 kcal/mol higher than that of H-[A1]-Beta (288 kcal/mol). It is also worth pointing out that upon deprotonation of the silanol, the conjugate base is stabilized by restoring the former Sn-O covalent bond with the framework, which effectively delocalizes the negative charge (Figure 13b). Thus, even though we do not see effective Lewis acid catalysis by the Sn metal center, the catalytic ability of the silanol must be attributed to the presence of the metal atom. One would have expected that [Zr]-Beta and [Hf]-Beta would be as active as [Sn]-Beta as the DPEs of the respective open sites are equal to 292 and 290 kcal/mol, practically the same as that of [Sn]-Beta. It is certainly curious and unclear why [Zr]-Beta and [Hf]-Beta turned out to be quite inactive when tested for this reaction—a matter that warrants further investigation.

3.5.7 Microkinetic model. We have utilized the free energy profiles presented above to look into the microkinetics of the reaction. The model and its parameterization are presented in detail in Section S7 of the SI. By solving the model at different temperatures and constructing Arrhenius plots, we have computed apparent activation energies of 22 kcal/mol in H-[Al]-Beta and 25.4 kcal/mol in [Sn]-Beta. In the case of H-[Al]-Beta, the agreement with the experimental values of 16.9 kcal/mol for H-[Al]-Beta-12.5 and 20.9 kcal/mol for H-[Al]-Beta-150 is quite satisfactory (Table 4). In the case of [Sn]-Beta, there is a discrepancy of about 16 kcal/mol between the model and the experimental value. A plausible explanation for this discrepancy is that the ONIOM model

for [Sn]-Beta possibly overestimates the enthalpy of binding of the anhydride to the active site, overpredicting the coverage in anhydride. Such overbinding does *not* affect the calculated intrinsic activation energies (primarily owing to error cancellation), but it can affect the predicted apparent activation energies, as the latter are determined by both the intrinsic barriers and heats of adsorption; the stronger the binding, the higher the coverage and the closer the apparent activation energy is to the intrinsic energy span.

Sensitivity analysis of the rate of the acylation of 2-methylfuran (Figure 14) has revealed that on both H-[Al]-Beta and [Sn]-Beta the reaction is controlled not by the deprotonation of the Wheland intermediate but rather by the dissociation of the anhydride and the formation of the framework bound acyl group. In contrast, the acylation of furan is controlled by the last step of the reaction, namely the hydrogen elimination that follows the addition of the acyl group to the furan ring (Figures S9 and S10 in Section S8 of the SI). This is in complete agreement with the KIE experiments presented earlier in Section 3.4.1. Our calculations with furan on H-[Al]-Beta also show that its acylation is considerably slower than that of 2-methylfuran, with an apparent activation energy of 31.7 kcal/mol, consistent with the fact that electron donating groups enhance the nucleophilic character of the furan ring, accelerating the electrophilic aromatic substitution.

4. CONCLUSIONS

A comparison of Brønsted and Lewis acid zeolite Beta catalysts for methylfuran acylation reveals that H-[Al]-Beta with a low Si/Al ratio exhibits the highest specific reaction rates. When turnover is normalized on a per site basis, H-[Al]-Beta exhibits higher turnover frequency compared to all Lewis-acid zeolite Beta materials investigated. The difference in rates and activation energies on [Al]- and [Sn]-Beta is interesting, since the apparent activation energy is

lower on [Sn]-Beta despite it having a lower rate. It is possible that the intrinsic activation energy is higher for [Sn]-Beta and a more exothermic adsorption makes it appear lower, however this is not supported by the lower binding energy computed for [Sn]-Beta compared to H-[Al]-Beta. There could be a large compensation in the rate through entropic effects on H-[Al]-Beta that result in a higher pre-exponential factor and higher rate despite a higher activation energy. However, the rate on [Sn]-Beta may be underestimated because we were unable to unequivocally determine the relative number of Sn open sites. This report demonstrates that commercially available Brønsted acid zeolites exhibit excellent activity and selectivity for this reaction. Although all the catalysts deactivate with time on stream, GVL has a promotional effect on the rate, which may be helpful for scale up purposes.

Computational modeling of the acylation of methylfuran reveals that the reaction follows classic addition-elimination (i.e., stepwise) aromatic electrophilic substitution mechanisms in both [Al]- and [Sn]-Beta, and that the rate-determining step is the hydrogen elimination from the Wheland intermediate in the case of furan but the dissociation of the acetic anhydride in the case of methylfuran. The former is supported experimentally by the observation of a primary KIE on both catalysts. One remarkable and unexpected finding from our calculations is that the most favorable catalytic pathway in [Sn]-Beta involves Brønsted acid catalysis by the silanol group of the open site and not Lewis acid catalysis by the Sn metal center.

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Figure 1: [M]-Beta zeolite cluster model (M=Al, Sn). The active site is highlighted in blue. Atoms shown: H (white), O (red), Al (purple), Si (gray).



Figure 2: TPD-EXAFS of [Sn]-Beta-HT. Conditions: 2 K/min to 923 K, 100 ml/min N2 flow





Figure 3: Rate with time on stream for methylfuran acylation with acetic anhydride. Inset is natural log of rate to show exponential fit used to extrapolate time on stream rate data to initial rate. Conditions: 14 bar, 0.05 g catalyst, 393K, 45.5g MF, 150 mL acetic anhydride, 200 mL GVL, 4 ml/min (2ml/min for H-[Al]-Beta-150).





Figure 4: Arrhenius plot for methylfuran acylation with acetic anhydride. Conditions: 14 bar, 45.5g MF, 150 mL acetic anhydride, 200 mL GVL, 4 ml/min (2 ml/min for H-[Al]-Beta-150), 0.05 g catalyst



Figure 5: TGA of spent catalyst from flow experiments at temperature indicated in parentheses and same conditions as Figure 3.



Figure 6: Methylfuran acylation with acetic anhydride. Conditions: 14 bar, 403 K, 2 ml/min, 0.05 g H-[Al]-Beta-150. With GVL: 45.5g MF, 150 mL acetic anhydride, 200 mL GVL and heated under GVL flow. Heat with GVL: 45.5 g MF, 350 mL acetic anhydride and heated under GVL flow. No GVL: 45.5 g MF, 350 mL acetic anhydride and heated under GVL flow.



Figure 7: Methylfuran acylation with acetic anhydride and co-fed products. Conditions: 14 bar, 393 K, 2 ml/min, 0.05 g H-[Al]-Beta-150, 45.5g MF, 150 mL acetic anhydride, 200 mL GVL and specified mol % (with respect to methylfuran) of product.





Figure 8: Binding of (a) acetic anhydride and (b) methylfuran to the active site. For clarity, only the active site of the catalyst is shown here. Atoms shown: H (white), C (black), O (red), Al (purple).



Figure 9: Free energy profiles at 393.15 K (in kcal/mol) for stepwise (H1, black) and concerted (H2, green) mechanisms in H-[A1]-Beta. The labeled states correspond to those shown in Scheme 4. $R^{H}(P^{H})$ represent infinitely separated reactants (products). For clarity, only the active site of the catalyst is shown. Atoms shown: H (white), C (black), O (red), Al (purple).



Figure 10: Two binding modes of acetic anhydride to the active site in open [Sn]-Beta: (a) binding to both the silanol and Sn; (b) binding to the silanol proton only. For clarity, only the active site of catalyst is shown here. Atoms shown: H (white), C (black), O (red), Sn (green), Si (gray).



Figure 11: Free energy profiles at 393.15 K (in kcal/mol) for Brønsted acid catalysis, pathways D1 (black) and D2 (green), on open [Sn]-Beta. The labeled states correspond to those shown in Scheme 5. R^{D} (P^{D}) denotes infinitely separated cluster and reactants (products), not shown in Scheme 5. For clarity, only the active site of catalyst is shown here. Atoms shown: H (white), C (black), O (red), Sn (green), Si (gray).



Figure 12: Free energy profile at 393.15 K (in kcal/mol) for pathway D3, engaging the Sn metal center of the open site. The labeled states correspond to those shown in Scheme 5. R^{D} (P^{D}) denotes infinitely separated cluster and reactants (products), which are not shown in Scheme 5. For clarity, only the active site of catalyst is shown here. Atoms shown: H (white), C (black), O (red), Sn (green), Si (gray).



Figure 13: Magnified view of (a) [Sn]-Beta open site and (b) deprotonated silanol in the [Sn]-Beta open site. Atoms shown: H (white), C (black), O (red), Sn (green), Si (gray).



Figure 14: Sensitivity analysis of the rate of acylation of 2-methylfuran by acetic anhydride. The normalized sensitivity coefficient is calculated by $\ln(TOF_{perturbed} - TOF_{unperturbed}) / \ln(k_{i,perturbed} - k_{i,unperturbed})$. The rate constant was perturbed by +1% at 120 °C. In the graph, reaction step 1 corresponds to the dissociation of the anhydride; step 2 corresponds to the deprotonation of the Wheland intermediate.

Scheme 1: Acylation of methylfuran with acetic anhydride to form 2-acetyl-5-methylfuran and acetic acid.

0 Ο + OH 2-Acetyl-5-Acetic acid Methylfuran Acetic anhydride methylfuran

Scheme 2: [Sn]-Beta open and closed sites.

'n Ņ Snillo н_{`0-Н} Sn 11111 Ĵ ŝ 1111 H

Fully Coordinated Closed Site

Hydrolyzed Open Site

Scheme 3: Acylation of methylfuran with acetic anhydride to form 2-acetyl-5-methylfuran and acetic acid from Wheland intermediate

Ο О Ο \cap Ή ЮH `H Wheland ter∽ 2-Acetyl-5-Methylfuran Acetic Acetic acid anhydride intermediate methylfuran

Scheme 4: Stepwise (H1) and concerted (H2) mechanisms for the acylation of methylfuran on H-[Al]-Beta





Scheme 5: Proposed mechanisms for the acylation of methylfuran on open [Sn]-Beta. D1 and D2 are Brønsted catalysis pathways, and D3 engages the Sn metal center.

Catalyst	Si/M	Micropore Volume [cc/g]
H-[A1]-Beta-12.5	22.9 (690 µmol Al/g)*	0.18
H-[A1]-Beta-150	138 (120 µmol Al/g)*	0.21
[Sn]-Beta-HT	110	0.22
[Zr]-Beta	173	0.20
[Hf]-Beta	147	0.21
[Ti]-Beta	58^{\dagger}	0.21
Si-Beta	n/a	0.20
Dealuminated H-[Al]-Beta	750 [†] (Si/Al)	0.17
[Sn]-Beta-SSIE	11.7	0.13

Table 1: Framework metal composition and micropore volume for zeolite catalysts. †Determined from XRF *Determined from n-propylamine decomposition

Table 2: Fitting of the	e Sn K EXAFS	region of the	Sn-substituted	Beta zeolite	s before	and after
dehydration						

[Sn]-Beta-HT-as received [Sn]-Beta-SSIE-as received	5.92 + 0.57			
[Sn]-Beta-SSIE-as received	5.85 ± 0.57	0.35 ± 1.33	1.976 ± 0.010	68 ± 13
	7.16 ± 0.37	7.54 ± 0.70	2.041 ± 0.005	54 ± 7
[Sn]-Beta-HT-dehydrated	3.82 ± 0.30	0.59 ± 1.22	1.898 ± 0.007	32 ± 10
[Sn]-Beta-SSIE-dehydrated	5.81 ± 0.47	4.87 ± 1.10	2.029 ± 0.009	82 ± 12

Table 3: Conversion, yield and TOF from batch reactions of 5 mL methylfuran and 15 mL acetic anhydride with 50 mg catalyst at 383 K, 14 bar. Numbers reported are averages and the standard deviation of two experiments.

	Catalyst	Time [h]	Conversion [%]	Yield [%]	TOF [mol 2A5MF/min/ mol metal]
1	H-[A1]-Beta-12.5	0.5	18.7±0.2	15.9±0.7	8.7±0.4
2	H-[Al]-Beta-150	1	6.8±0.5	5.3±0.2	9.2±0.3
3	[Sn]-Beta	1	5.2±0.7	4.6±0.4	5.7±0.4
4	[Zr]-Beta	3.5	4.6±1.1	3.0±0.1	1.7±0.1
5	[Hf]-Beta	3.5	5.7±0.9	3.6±0.3	1.8±0.2
6	[Ti]-Beta	1	1.6	0.1	0.08
7	[Sn]-Beta-SSIE	0.5	8.3±0.1	5.3±0.5	2.0±0.2
8	SnO ₂	1	3.9	0	0
9	Al ₂ O ₃	1	4.1	0	0
10	Si-Beta	1	2.2	0	0
11	No catalyst	1	0.4	0	0

Catalyst	Apparent Activation Energy [*] [kcal/mol]	Half-life [min]
H-[Al]-Beta-12.5	16.9±2.9	23-25
H-[Al]-Beta-150	20.9±4.0	26-32
[Sn]-Beta-HT	9.0±3.5	18-22
[Sn]-Beta-SSIE	8.8±3.9	19-23

Table 4: Apparent activation energies and half-life of catalysts tested under differential conditions with a flow reactor. ^{*}Error is 90% confidence interval.

Table 5:	Organics	extracted	from	spent	catalyst	run	at	temperature	specified	and	reaction
conditions	s as describ	oed in Figu	ire 3.								

Catalyst	Reaction Temperature [K]	Molecules Observed
H-[Al]-Beta-12.5	383	GVL, acetic acid, higher MW product (206)
H-[Al]-Beta-150	383	GVL
[Sn]-Beta-HT	393	GVL, higher MW product (290)
[Sn]-Beta-SSIE	393	GVL, 2A5MF

Table 6: Acylation of labeled and unlabeled furan with acetic anhydride. 1 g furan or 1.06 g furand₄, 3.2 g acetic anhydride, 393K, 0.05 g catalyst, 20 minutes.

	Yield [%]		
Catalyst	Unlabeled	Labolad furan	k _H /k _D
	furan	Labeled furan	
H-[Al]-Beta-150	13.3	5.3	2.5
[Sn]-Beta-HT	3.4	1.9	1.8