Published in final edited form as:

Energy Environ Sci. 2012 September 20; 5(10): 8990–8997. doi:10.1039/C2EE22486K.

Acid-Catalyzed Conversion of Furfuryl Alcohol to Ethyl Levulinate in Liquid Ethanol

Gretchen M. González Maldonado¹, Rajeev S. Assary^{2,3}, James Dumesic^{1,*}, and Larry A. Curtiss^{2,4}

¹Department of Chemical and Biological Engineering, University of Wisconsin-Madison, 1415 Engineering Drive, Madison, Wisconsin 53706, United States

²Materials Science Division, Argonne National Laboratory, Argonne, Illinois 60439

³Chemical & Biological Engineering, Northwestern University, Evanston, Illinois 60208

⁴Center for Nanoscale Materials, Argonne National Laboratory, Argonne, Illinois 60439

Abstract

Reaction pathways for the acid-catalyzed conversion of furfuryl alcohol (FAL) to ethyl levulinate (EL) in ethanol were investigated using liquid chromatography-mass spectrometry (LC-MS), 1D and 2D nuclear magnetic resonance (NMR) spectroscopy, and *ab initio* high-level quantum chemical (G4MP2) calculations. Our combined studies show that the production of EL at high yields from FAL is not accompanied by stoichiometric production of diethyl ether (DEE), indicating that ethoxymethyl furan (EMF) is not an intermediate in the major reaction pathway. Several intermediates were observed using an LC-MS system, and three of these intermediates were isolated and subjected to reaction conditions. The structures of two intermediates were elucidated using 1D and 2D NMR techniques. One of these intermediates is EMF, which forms EL and DEE in a secondary reaction pathway. The second intermediate identified is 4,5,5-triethoxypentan-2-one, which is analogous to one of the intermediates observed in the conversion of FAL to LA in water (i.e. 4,5,5-trihydroxypentan-2-one). Furthermore, conversion of this intermediate to EL again involves the formation of DEE, indicating that it is also part of a secondary pathway. The primary pathway for production of EL involves solvent-assisted transfer of a water molecule from the partially detached protonated hydroxyl group of FAL to a ring carbon, followed by intra-molecular hydrogen shift, where the apparent reaction barrier for the hydrogen shift is relatively smaller in ethanol (21.1 kcal/mol) than that in water (26.6 kcal/mol).

1 INTRODUCTION

Ethyl levulinate (EL) is a value-added chemical that can be converted to levulinic acid (LA), which is considered to be one of the top ten biomass-derived platform chemicals that can potentially replace petroleum-derived precursors to produce industrial chemicals and

transportation fuels^{1–6}. Additionally, EL can be used as a flavoring agent⁷, fuel oxygenate additive⁸, and it is a precursor⁹ to γ -valerolactone (GVL), another chemical that can be converted to liquid alkanes and transportation fuels^{10, 11}. Production of LA and EL takes place by acid-catalyzed hydrolysis¹² and ethanolysis¹³, respectively, of furfuryl alcohol (FAL), which is itself obtained from the hydrogenation of biomass-derived furfural^{2, 13} (see scheme 1). Ethanolysis is advantageous compared to hydrolysis because it reduces the polymerization of FAL, which allows for high yields of EL, and also because the product EL can be converted to GVL using heterogeneous catalysts⁹. In aqueous medium an increased rate of polymerization¹⁴ of FAL leads to a decrease in production of LA, and the reactivity of the carboxylate functional group was shown to poison the heterogeneous catalysts for subsequent reactions^{2, 9}. Thus, it is desirable to explore the reaction mechanism of FAL to EL in ethanol due to the increased yields compared to aqueous media.

Recently, we have developed a molecular-level understanding of the formation of LA from FAL in aqueous medium using both experimental and theoretical approaches¹². Multiple pathways for the formation of LA from FAL were identified, and detailed reaction mechanisms were proposed based on experimentally observed intermediates. In the present paper, we explore a similar molecular level understanding of ethanolysis of FAL to EL and possible parallel reactions.

Recently, Zhang *et al.* have identified alkoxymethylfuran as the key intermediate in the conversion of furfuryl alcohol (FAL) to alkyl levulinate in alcohols¹⁵. Therefore, in ethanol, the transformation from ethoxymethylfuran (EMF) to EL would require the production of diethyl ether (DEE) in a stoichiometry 1:1 with EL. In the present investigation, we have found that the amount of DEE formed during the conversion of FAL is less than half the amount of EL formed, regardless of the catalyst (homogeneous or heterogeneous) and/or reaction conditions. This result indicates that there might be multiple pathways to EL, other than the pathway through EMF. Accordingly, we have carried out a combined experimental and theoretical study of pathways for the conversion of FAL to EL, using liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance spectroscopy (NMR), combined with high-level quantum chemical calculations (G4MP2).

2 METHODS AND ANALYSIS TECHNIQUES

2.1 Isolation and Purification of Intermediates

The conversion of FAL to EL was studied at an initial concentration of 0.25 wt% FAL (Aldrich, 98%) in ethanol (Sigma-Aldrich, 99.5%) at several temperatures, using 0.033 g of acid resin catalyst (AmberlystTM 15, hydrogen form; dry, moisture 1.5%, Sigma-Aldrich) per gram of feed. These reactions were performed in 10 mL glass batch reactors, continuously stirred at 700 rpm with a magnetic stirrer, using 1.5 g of feed. After cooling, the product was filtered and analyzed using an LC-MS equipped with an Agilent Eclipse XDB-C18 reverse phase column (4.6 mm ID $\times$ 250 mm (5 μ m) 80Å). The column was eluted in gradient mode. Solvent A was 20 mM ammonium acetate (Sigma Ultra, minimum 98%) in Milli-Q water. Solvent B was methanol (LC-MS CHROMASOLV® 99.99%, Sigma-Aldrich). The gradient was as follows: 5–80% B (0–10 min); 80% B (10–13 min);

80–5% B (13–13.25 min); 5% B (13.25–30 min). The HPLC was coupled to an Ion Trap with an Atmospheric Pressure Chemical Ionization (APCI) ion source described below.

The optimum reaction conditions to isolate the intermediates were found to be an initial concentration of 1.0 wt% reacted over 0.033 grams of Amberlyst™ 15 per gram of feed (1.5 g of 1.0 wt% FAL in ethanol) at 318 K for 10 minutes. The intermediates were isolated by fraction collection over 100 h (100 runs with a 25 µL injection per run) by eluting them from the HPLC column previously described. The intermediates were extracted from the mobile phase with chloroform (chloroform 99.8%, Fluka) in a ratio of approximately 1.5:1 extractant to mobile phase. After extraction the organic phase was evaporated at low pressure and ambient temperature. The resulting product was dissolved in deuterated chloroform (“100%”, 99.96% atom D, Sigma-Aldrich) in preparation for analysis by NMR spectroscopy.

2.2 Liquid Chromatography Mass Spectroscopy (LCMS)

An Agilent 1200 series LC system coupled to an Agilent APCI ion source and an Agilent 6320 Ion Trap was used for acquiring the mass spectra of the compounds of interest. The vaporization and drying gas was N₂ (refrigerated liquid, Airgas) at 623 K, the nebulizer pressure was 60 psi, and the dry gas flow was 5 L/min. In the positive APCI mode, the corona current was set to +3000 nA, capillary voltage to –1000 V, and the end-plate offset to –500 V. In the negative mode the corona current was set to –15,000 nA, and the capillary voltage to +1000 V. Helium (UHP, Airgas) served as a collision gas for MS(n) fragmentation. The mass-to-charge ratio reported for all compounds under study has an accuracy of ± 0.2 amu.

2.3 Nuclear Magnetic Resonance Analysis

One-dimensional and two-dimensional nuclear magnetic resonance experiments were carried out to acquire structural information about intermediates in the conversion of FAL to EL. The compounds under study were analyzed at frequencies from 500 to 750 MHz using Bruker Avance III 500, 600, 700, and 750 spectrometers. In addition to standard ¹H NMR and ¹³C NMR experiments, 2D NMR experiments were also used. The 2D NMR experiments include Total Correlation Spectroscopy (TOCSY), Correlation Spectroscopy (COSY), and Heteronuclear Single Quantum Correlation Spectroscopy (HSQC).

2.4 Reaction studies to monitor evolution of diethyl ether (DEE)

Experiments were carried out in a stainless steel pressure vessel at 363 K pressurized to 200 psi with helium. The solvent was 80% heptane (chosen for its inertness), and 20% ethanol by volume. To prevent ethanol from reacting over the acid catalyst before the FAL was fed, 16 mL of heptane with 1.3 g of Amberlyst™ 15 was pressurized to 200 psi, and warmed to 363 K. Afterwards, 4 mL of 4.44 wt% FAL in ethanol solution was fed to the reactor to give a final concentration of 1 wt% FAL, and this solution was reacted for 1.5 h. After cooling to room temperature, a gas sample was taken using a gas bag and analyzed via GC-FID (Agilent 6890, J&W Scientific GS-Q column 30 m $\times$ 0.32 mm). Liquid samples were analyzed by GC-FID (Shimadzu GC2010, DB-5MS column 30 m $\times$ 0.25 mm $\times$ 0.25 µm). DEE was quantified in both the liquid and gas phase. A control reaction was run to

determine how much DEE was formed from ethanol itself. In total, the following reaction conditions were studied (all of them at 363 K and 200 psi He):

1. 1wt% FAL using pure ethanol and HPLC grade heptane over Amberlyst™ 15
2. 1wt% FAL using anhydrous ethanol and anhydrous heptane (prepared in a glove box) over Amberlyst™ 15.
3. 1wt% FAL using anhydrous ethanol (prepared in a glove box) over benzenesulfonic acid (homogeneous catalyst)
4. 1wt% FAL in 90/10 and 50/50 ethanol water over Amberlyst™ 15

2.4 Computational Details

In previous work¹², we employed CCSD(T)-based G4MP2¹⁶ level of theory to investigate the reaction mechanism and to understand the thermodynamic landscape of the conversion of FAL to LA in aqueous medium. A similar approach is taken in the present investigation. The geometries, zero-point energies, and temperature corrections for this method are evaluated at the B3LYP/6-31G(2df,p) level of theory. To account for the solvation from ethanol medium, calculations were also performed in ethanol dielectric ($\epsilon=24.85$) using the SMD¹⁷ solvation model at the B3LYP level of theory with the same basis set used for the geometry evaluations. The proton solvation energy in ethanol is taken as -261.2 kcal/mol to compute the energies of protonated species¹⁸. The association and dissociation processes in the gas phase lead to significant changes in entropic contributions. These changes are expected to be far less in solution. Therefore, to simplify the entropic effects on calculated Gibbs free energies, the free energy due to the translational entropy of ethanol molecules is excluded in all calculations. Explicit solvent (ethanol) molecules were included during the calculations of selected reaction barriers. The calculations for this investigation were carried out using Gaussian 09¹⁹

3 RESULTS AND DISCUSSION

3.1 Identification of Intermediates Using LCMS

Ethanol was chosen as the solvent for the conversion of FAL because high yields of EL are achieved in this medium over an ion exchange resin²⁰. From LC-MS analysis, several species were observed to increase with time in parallel with ethyl levulinate, and other species were observed to be formed and later consumed in the interval of time where EL was increasing, suggesting an intermediate behavior. Only three species were isolated for further analysis with NMR. These species will be referred to, in order of retention time in the LCMS configuration described above, as Intermediate 1, Intermediate 2, and Intermediate 3. Intermediates 1 and 2, which exhibit intermediate behavior, were selected based on their molecular weight, which suggest reaction of an ethanol molecule and FAL. Intermediate 3 was chosen because of its analogy to an intermediate in FAL conversion in aqueous medium. Formation of this latter intermediate indicates that FAL has reacted with several ethanol molecules, which is directly comparable with our previous work, where FAL reacted with several water molecules to form 4,5,5-trihydroxypentan-2-one, an intermediate in the formation of levulinic acid¹².

Plots depicting qualitative reaction trends were made using peak areas from extracted ion chromatograms (EIC). Fig. 1 shows EIC trends for FAL and EL with respect to the reaction time, and Fig. 2 shows the EIC trends of the three intermediates compared to EL with respect to time. Intermediate 3 was formed at a faster initial rate than EL (see Figure 2), and was seen to be increasing at the same time that the concentration of EL was increasing.

Most of the LC-MS analyses were carried out in the positive ionization mode (see Figures 3 to 5). According to the fragmentation of intermediate 1, shown in the supplemental information, it can be said that an ethanol molecule reacted with a FAL ring through the hydroxyl group to give intermediate 1, shown as a protonated species with an m/z of 127 in Figure 3. A possible structure for intermediate 2 is shown in scheme 3 as species B-2. Note that the fragmentation of intermediate 2, shown in the Supplemental Information has similar MS(2), MS(3), and MS(4) fragments to those of levulinic acid¹². Proposed fragmentation patterns for intermediate 1, 2, and 3 are shown in the supplemental information.

According to the m/z of intermediate 3, it seems that the FAL ring-opened and reacted with two ethanol molecules; however, further analysis using NMR (see below) reveals that FAL has reacted with three ethanol molecules to form intermediate 3.

3.2 Structure Elucidation of Intermediate 1 and 3 using NMR

We were able to isolate three of the species identified in the LC-MS and carry out NMR analyses for two of the intermediates isolated. Intermediate 2 was not sufficiently stable to perform NMR analysis. The ¹H NMR spectrum for intermediate 1 is as follows: ¹H NMR (700.13 MHz, CDCl₃) δ 1.229 (t, J = 7 Hz, 3H), 3.538 (q, J = 7 Hz, 2H), 4.444 (s, 2H), 6.332 (m, 2H), 7.405 (m, 1H), and the spectrum can be found in the supplemental information. There are chemical shifts of intermediate 1 that match those of FAL, i.e. δ 4.444 (s, 2H), 6.332 (m, 2H), 7.405 (m, 1H); therefore, it can be said that intermediate 1 has a furfuryl ring. The quartet and triplet upfield correspond to an ethyl group. Based on these assignments, this species was determined to be ethoxymethylfuran (EMF).

The ¹H and ¹³C NMR spectra for intermediate 3 are as follows: ¹H NMR (700.13 MHz, CDCl₃) δ 1.15 (t, J = 7 Hz, 3H), 1.21 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 2.09 (s, 3H), 2.68 (d, J = 7 Hz, 2H), 3.59 (m, J = 7 Hz, 3H), 3.72 (m, J = 7 Hz, 3H), 3.84 (m, 1H), 4.41 (d, J = 7, 1H); ¹³C NMR (176.05 MHz, CDCl₃) δ 15.036, 15.146, 15.333, 31.010, 43.961, 64.076, 64.090, 66.612, 76.156, 103.353, 208.278. Both spectra are presented in the supplemental information. Correlation spectroscopy (COSY) was also used to determine the correlations of the protons in intermediate 3. The presence of three sets of quartet-triplets, i.e. three quartets coupled to three triplets, implies that there are three ethoxy groups that form part of the molecule. According to the COSY NMR data in the supplemental information, four groups of resonances are observed to couple to each other; these are: δ 2.09 (s, 3H), 2.68 (d, J = 7 Hz, 2H), 3.84 (m, 1H), 4.41 (d, J = 7, 1H). These groups account for 7 protons that are part of the main body of the molecule (not including the ethyl groups – see Figure 8). The multiplets correlate with the three triplets up field. The ethoxy groups should have a quartet, accounting for the CH₂ group, and a triplet accounting for the CH₃ group. Detailed analysis of the multiplets revealed that there are several overlapping quartets that correspond to the CH₂ functional groups in the three ethoxy groups. Combining this

information with data from the HSQC experiments it can be said that the four correlating proton groups account for four carbon atoms with the following chemical ^{13}C NMR chemical shifts: δ 31.0 ppm, 43.9 ppm, 73.2 ppm, and 103.0 ppm respectively. As there were five carbon atoms donated from FAL, the remaining carbon must be present as a carbonyl with a ^{13}C NMR chemical shift of 208 ppm. The HSQC NMR is shown on Figure S12 of the supplemental information.

The ^{13}C NMR chemical shifts for intermediate 3 were compared with one of the intermediates in Horvat's mechanistic study of FAL conversion to methyl levulinate²¹. In Horvat's proposed mechanism, one of the key intermediates is the result of the reaction between FAL and three methanol molecules, which is 4,5,5-trimethoxypentan-2-one. The chemical shifts of this species and intermediate 3 using ^{13}C NMR are compared and presented in Table 1.

Results from Table 1 suggest that intermediate 3 (in ethanol) is analogous to Horvat's intermediate in methanol. Note that the second, third, and fourth rows are slightly different. This difference in shifts is likely a result of the difference between the ethyl groups in intermediate 3 and the methyl groups in the intermediate proposed in the literature. The possibility of having two ethyl groups, as suggested by the mass spectrum, was disregarded because three ethyl groups were reproducibly observed via NMR. Thus, it is concluded that intermediate 3 must undergo cleavage of one of the acetal ethoxy groups before detection in the LC-MS in order to give a 173 m/z. Also, having a hemiacetal instead of an acetal would shift the doublet at 4.4 ppm downfield closer to 5 ppm due to the polarity of the hydroxyl group, but this is not observed. Scheme 2 below shows the structures of intermediate 1 and intermediate 3. The intermediates 1, 2, and 3 were isolated and subjected to reaction in ethanol at 333 K over AmberlystTM 15. It was found that intermediate 1 reacts to form intermediate 2 and then intermediate 3, and it produces small quantities of EL. Intermediate 2 was seen to be in equilibrium with intermediate 1, and it reacts to form intermediate 3 and EL. Finally intermediate 3 was seen to react to EL and other products as well.

3.3 Monitoring Diethyl Ether (DEE) Concentration

If the conversion of FAL to EL passes mainly through EMF (intermediate 1), intermediate 2 (structure as yet undetermined), and 4,5,5-triethoxypentan-2-one (intermediate 3) as suggested by the results presented above, then DEE must be present in the product in a stoichiometric amount. In order to probe this effect, experiments were carried out in stainless steel pressure vessels that allow gas-phase products to be collected. The results of these experiments are shown in Table 2.

From Table 2, the yield of EL increases slightly when using anhydrous solvents, as does the DEE:EL molar ratio. Importantly, however, the DEE:EL molar ratio is always less than 1. To eliminate the possibility of DEE being adsorbed on the catalyst surface, benzenesulfonic acid (95.0 %, Aldrich Purum) was used as a homogeneous analogue to AmberlystTM 15. As shown in Table 4, the yield to EL increased when using benzenesulfonic acid, but the DEE:EL ratio decreased in comparison to the anhydrous 80% heptane 20% ethanol experiment, which indicates that DEE is not being adsorbed onto the solid catalyst surface when using AmberlystTM 15. Experiments were also carried out to study the effect of adding

water to the reaction solvent at different compositions to probe the possibility of water being an important part of the mechanism to ethyl levulinate. The addition of water decreases the yield of EL resulting from the competitive formation of LA.

The role of intermediate 3 in the pathways for production of EL was studied further by conducting experiments for longer times. For example, when the reaction of FAL was carried out for 1.5 h in ethanol, the EL yield was 85% and intermediate 3 was still present in the reaction product, indicating it would still be possible to produce additional DEE even at such high yields. After reaction for 2.5 h, a slightly higher yield (89%) of EL was achieved and intermediate 3 was no longer observed in the reaction product. Accordingly, it appears that the formation of EL does not occur solely via formation of EMF, since EMF mainly reacts to intermediate 3, which is stable and even at high yields of EL, it is still present in solution.

In summary, the results from Table 2 show that DEE is not formed in a 1:1 ratio with EL, indicating that more than one pathway exists for the production of EL, and the main pathway does not involve the formation DEE. In addition, water does not participate in the mechanism for conversion of FAL to EL, as indicated by the decrease in EL yield with the addition of water.

3.5 Computational Study and Proposed Mechanism

We have computed the free energy required to protonate various positions of FAL in ethanol medium. Since the proton solvation energy of ethanol (-261.2 kcal/mol) is similar to that of water (-262.4 kcal/mol²²), the protonation energy of various positions of FAL is similar to our previous study¹², i.e. 4 to 17 kcal/mol at 298 K. The protonation of the hydroxyl group requires 11 kcal/mol in terms of Gibbs free energy (at 298 K). Solvent addition reactions to FAL are more likely when the species is positively charged than in its neutral form. Also, calculations suggest that formation of EL (-38.6 kcal/mol) in ethanol is thermodynamically more favorable than the formation of LA (-33.2 kcal/mol) in aqueous solution from FAL^{23, 24}. This larger driving force in ethanol further supports the use of alcohols as solvents for the reaction rather than reaction in water; the latter causing a high degree of polymerization in addition to the rehydration¹⁴. Having understood the nature of intermediate 1 and intermediate 3 using experimental studies, we have computed likely reaction pathways that include these intermediates for the conversion of FAL to EL. A proposed scheme is shown in Scheme 3, including the calculated free energies of all the species. These free energies are with respect to that of FAL, and they are computed at the G4MP2 level of theory at 298 K in ethanol dielectric.

Three different pathways are presented in Scheme 3; denoted as A, B, and C. The initial step of all the pathways is the protonation of the hydroxyl group. At 298 K, the initial protonation of FAL to form A1 is thermodynamically uphill by 11 kcal/mol. In pathway A, the oxygen atom of the hydroxyl group is retained and transforms to the ketone oxygen of EL. The next step in pathway A is the formation of species A2 (4.0 kcal/mol). This process involves solvent-assisted binding of a water molecule from the partially detached protonated hydroxyl group of A1 alcohol to a ring carbon. The schematic representation of this transformation and the energies of the likely intermediates are shown in Scheme 4. This

process (A1 to A2) occurs through two transition states denoted by A1_1 (+ 22.9 kcal/mol) and A1_3 (14.6 kcal/mol). In contrast, a complete detachment of water from A1 leads to formation of species C1 (11.5 kcal/mol, Scheme 3). This species C1 undergoes addition of one ethanol molecule to form intermediate 1 (after deprotonation). This process is exothermic and intermediate 1 has a relative free energy of -5.2 kcal/mol (See Scheme S2 in the supporting information for details). Alternatively A1 transforms to species B2 through addition of one ethanol molecule assisted by the solvent, as shown in Scheme 4. If EMF (intermediate 1) is the reactant, then protonation and rearrangement would result in the formation of intermediate B2. The transition state, where the rearrangement occurs is B1_1, and the free energy of activation required is 17.6 kcal/mol, comparatively smaller than the binding of water (A1_1, +22.9 kcal/mol). This difference is due to stabilization of positive charge by electron donating CH₃-CH₂-group compared to hydrogen. The species B2 can undergo further reaction with ethanol to form A2 or subsequent addition reactions with ethanol (See Scheme S2 in the Supporting Information). From our detailed experimental studies by monitoring the concentration of DEE, it is evident that formation of EL through EMF is not a major pathway.

Addition of one and two ethanol molecule to species A2 leads to the formation of A3 (-7.0 kcal/mol) and A4 (-22.1 kcal/mol), respectively. Subsequent condensation of A4 (a hemi acetal) with an ethanol molecule leads to the formation of an acetal (A5, -27.5 kcal/mol) and a water molecule. Deprotonation of A5 results in the formation of Intermediate 3 (A6, -24.2 kcal/mol). It is noteworthy that intermediate 3 is analogous to the geminal diol intermediate observed in the conversion of FAL to LA in water. In terms of relative Gibbs free energy, the formation of this intermediate is significantly more downhill (by 10 kcal/mol) in ethanol than in the water media. Acid-catalyzed removal of ethanol from A6 leads to species A7 (-17.1 kcal/mol). Reaction with ethanol and species A7 produces DEE and species A8 (-11.9 kcal/mol). The ketoenol tautomerization of A8 results in the formation of EL (-38.6 kcal/mol). This pathway, similar to the pathway from EMF, leads to the formation of DEE. The formation of species such as A7, A8 is thermodynamically uphill from Intermediate 3, suggesting that the formation of EL from Intermediate 3 could be a slow process. This prediction is consistent with our experimental observations.

In parallel to the formation of species A4 from A3 in pathway A, species A3 can undergo a separate route to produce EL denoted as Pathway B in scheme 3. This reaction sequence is initiated through hydrogen shift from A3 to form B3 (-18.8 kcal/mol). This hydrogen shift requires an apparent activation free energy barrier of 21.1 kcal/mol. Species B3 undergoes tautomerization (no apparent activation is required) and deprotonation to give EL. It is important to note that pathway B does not involve the production of DEE.

Another pathway that we have computed is shown as Pathway C in Scheme 3. This pathway is initiated through formation of species C1 by removal of water or ethanol from FAL or EMF, respectively upon acid hydrolysis. The resulting cation C1 undergoes nucleophilic conjugate 1,4-addition of ethanol to form species C2 (-8.5 kcal/mol). A hydrogen shift from C2 results in the formation of C3 (-17.1 kcal/mol). This hydrogen shift requires an apparent free energy barrier of 17 kcal/mol. Addition of ethanol leads to the formation of C4 (-27.1 kcal/mol). Subsequent tautomerization (C5, -36.9 kcal/mol) and removal of CH₃CH₂-group

(by forming DEE in the presence of ethanol) results in the formation of EL. Both these processes are thermodynamically downhill and formation of DEE is essential to complete this process in the absence of water. We note that the water produced in the conversion of FAL to C1 (in pathway C) and A4 to A5 (Pathway C), can potentially react with diethyl ether in the presence of acid to produce ethanol. This reaction would decrease the concentration of DEE. This behavior is consistent with the experimental observation that the net production of diethyl ether is not detected when 10% and 50% water (Table 4) are added to reaction mixture.

A key step in the formation of EL from FAL without the formation of DEE in pathway B is hydrogen shift with a relatively large intrinsic activation barrier (28.1 kcal/mol, apparent barrier 21.1 kcal/mol). It is important to note that similar hydrogen shift in water requires an apparent activation barrier of 26.6 kcal/mol¹². Also, the hydrogen shift in ethanol is more downhill (−11.8 kcal/mol) than in aqueous media (−7.9 kcal/mol). The pathway B takes place in parallel to the formation of intermediate 3 by pathway A. Thus, the production of EL is parallel to the production of Intermediate 3 during the early part of the reaction, as observed experimentally. Independent of pathways A and B, the conversion of FAL to EL can take place by pathway C, leading to the formation of EMF, and the co-production of DEE. Accordingly, based on combined experimental and theoretical studies, we can conclude that multiple pathway are present during the conversion of FAL to EL, and the pathway through EMF in pathway C is a minor one compared to pathway B.

4 Summary and Conclusions

Mechanistic understanding of the conversion of furfuryl alcohol to ethyl levulinate was elucidated using LC-MS, 1D and 2D NMR, and G4MP2 *ab initio* methods. Two intermediates were identified using NMR and LC-MS: ethoxy-methyl-furan (intermediate 1, EMF) and 4,5,5-triethoxypentan-2-one (intermediate 3). According to the experimental and computational results presented in this paper, conversion of FAL to EL takes place by multiple pathways. Formation of 4,5,5-triethoxypentan-2-one takes place in parallel to the production of EL, and this intermediate can also be produced from EMF. Furthermore, this species reacts slowly to EL, and it was demonstrated that at 85% yield of EL, 4,5,5-triethoxypentan-2-one is still present in solution; therefore, this species is not part of the primary pathway to EL. Based on experimental and computational studies, it is concluded that the major reaction pathway does not occur through intermediate 1 or intermediate 3, but rather it occurs through a parallel pathway (shown as pathway B in Scheme 3), where diethyl ether is not formed during the production of ethyl levulinate from furfuryl alcohol.

Comparing these results (ethanolysis) with our previous work¹² (hydrolysis), we conclude that intermediate 3 in the conversion of FAL to EL is equivalent to the major intermediate observed (4,5,5-trihydroxypentan-2-one) in the conversion of FAL to LA. In the acid catalyzed conversion of FAL, the intermediate 4,5,5-trihydroxypentan-2-one is part of a major pathway in the formation of LA in water, whereas intermediate 3 is part of a slower pathway to EL in ethanol. Also, we conclude that FAL follows a similar ring-opening pathway in both water and ethanol, and further converts to the desired products, i.e. LA and EL respectively. Additionally, FAL undergoes condensation reaction in ethanol to produce

EMF, which is eventually transformed to intermediate 3 and EL, with the formation of DEE. Intermediate 3 is produced at early reactions times in parallel to EL, similar to the formation of 4,5,5-trihdropentane-2-one formation in the LA pathway in aqueous media. Therefore, the major observed difference between the reaction of FAL in water and in ethanol is the dominance of the pathway that leads to EL through hydrogen shift, where the apparent reaction barrier for the hydrogen shift is relatively smaller in ethanol (21.1 kcal/mol) than that in water (26.6 kcal/mol).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge Dr. Mark Anderson and the National Magnetic Resonance Facility at Madison for the NMR data acquisition time. This study made use of the National Magnetic Resonance Facility at Madison, which is supported by NIH grants P41RR02301 (BRT/NCRR) and P41GM66326 (NIGMS). Additional equipment was purchased with funds from the University of Wisconsin, the NIH (RR02781, RR08438), the NSF (DMB-8415048, OIA-9977486, BIR-9214394), and the USDA. This work was supported by the U.S. Department of Energy under Contract DE-AC0206CH11357. This material is based upon work supported as part of the Institute for Atom-efficient Chemical Transformations (IACT), an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, and Office of Basic Energy Sciences. We gratefully acknowledge grants of computer time from EMSL, a national scientific user facility located at Pacific Northwest National Laboratory, the ANL Laboratory Computing Resource Center (LCRC), and the ANL Center for Nanoscale Materials. This research used computational resources of the National Energy Research Scientific Computing Center (NERSC), which is supported by the Office of Sciences of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231. We also acknowledge Thomas J. Schwartz and Max Mellmer for their input during the preparation of this article.

References

1. Bozell JJ, Petersen GR. *Green Chem.* 2010; 12:539–554.
2. Lange JP, van der Heide E, van Buijtenen J, Price R. *Chemsuschem.* 2012; 5:150–166. [PubMed: 22213717]
3. Rackemann DW, Doherty WOS. *Biofuels, Bioprod Biorefin.* 2011; 5:198–214.
4. Lange JP, Price R, Ayoub PM, Louis J, Petrus L, Clarke L, Gosselink H. *Angew Chem Int Ed.* 2010; 49:4479–4483.
5. Chheda JN, Huber GW, Dumesic JA. *Angew Chem Int Ed.* 2007; 46:7164–7183.
6. Serrano-Ruiz JC, Wang D, Dumesic JA. *Green Chem.* 2010; 12:574–577.
7. Leonard RH. *Ind Eng Chem.* 1956; 48:1330–1341.
8. Hayes, DJ.; Fitzpatrick, S.; Hayes, MHB.; Ross, JRH. *Biorefineries-Industrial Processes and Products: Status Quo and Future Directions.* Wiley-VCH Verlag GmbH; Weinheim, Germany: 2008. The Biofine Process-Production of Levulinic Acid, Furfural, and Formic Acid from Lignocellulosic Feedstocks.
9. Chia M, Dumesic JA. *Chem Commun.* 2011; 47:12233–12235.
10. Bond JQ, Alonso DM, Wang D, West RM, Dumesic JA. *Science.* 2010; 327:1110–1114. [PubMed: 20185721]
11. Serrano-Ruiz JC, Dumesic JA. *Energy Environ Sci.* 2011; 4:83–99.
12. Gonzalez Maldonado GM, Assary RS, Dumesic J, Curtiss LA. *Energy Environ Sci.* 2012; 5:6981–6989.
13. Lange JP, van de Graaf WD, Haan RJ. *Chemsuschem.* 2009; 2:437–441. [PubMed: 19370740]
14. Kim T, Assary RS, Marshall CL, Gosztola DJ, Curtiss LA, Stair PC. *Chemcatchem.* 2011; 3:1451–1458.

15. Zhang Z, Dong K, Zhao Z. *Chemsuschem*. 2011; 4:112–118. [PubMed: 21226220]
16. Curtiss LA, Redfern PC, Raghavachari K. *J Chem Phys*. 2007; 127:124105. [PubMed: 17902891]
17. Marenich AV, Cramer CJ, Truhlar DG. *J Phys Chemistry B*. 2009; 113:6378–6396.
18. Fawcett WR. *Langmuir*. 2008; 24:9868–9875. [PubMed: 18690731]
19. Frisch, MJ.; Trucks, GW.; Schlegel, HB.; Scuseria, GE.; Robb, MA.; Cheeseman, JR.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, GA.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, HP.; Izmaylov, AF.; Bloino, J.; Zheng, G.; Sonnenberg, JL.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, JA., Jr; Peralta, JE.; Ogliaro, F.; Bearpark, M.; Heyd, JJ.; Brothers, E.; Kudin, KN.; Staroverov, VN.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, JC.; Iyengar, SS.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, JM.; Klene, M.; Knox, JE.; Cross, JB.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, O.; Austin, AJ.; Cammi, R.; Pomelli, C.; Ochterski, JW.; Martin, RL.; Morokuma, K.; Zakrzewski, VG.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Dapprich, S.; Daniels, AD.; Farkas, Ö.; Foresman, JB.; Ortiz, JV.; Cioslowski, J.; Fox, DJ. *Gaussian 09*. Gaussian, Inc; Wallingford CT: 2009.
20. Lange J, van de Graaf W, Haan R. *Chemsuschem*. 2009; 2:437–441. [PubMed: 19370740]
21. Horvat J, Klaic B, Metelko B, Sunjic V. *Tetrahedron Lett*. 1985; 26:2111–2114.
22. Zhan CG, Dixon DA. *J Phys Chem A*. 2001; 105:11534–11540.
23. Assary RS, Redfern PC, Hammond JR, Greeley J, Curtiss LA. *J Phys Chem B*. 2010; 114:9002–9009. [PubMed: 20572641]
24. Assary RS, Redfern PC, Hammond JR, Greeley J, Curtiss LA. *Chem Phys Lett*. 2010; 497:123–128.

Fig. 1.
EIC trends of FAL and EL with reaction time. FAL (□) EL (●)

Fig. 2.
EIC trends of intermediates species and increasing species with respect to EL. EL (●),
Intermediate 1 (■), Intermediate 2 (△), Intermediate 3 (○)

Fig. 3.
EIC Mass spectrum of intermediate 1 (EMF)

Fig. 4.
Mass spectrum of intermediate 2

Fig. 5.
Mass spectrum of intermediate 3

Scheme 1.

Schematic representation of acid-catalyzed conversion of FAL to EL in ethanol medium and LA in aqueous medium

Scheme 2.

Interconversion among intermediate 1 (EMF), a hypothesized structure for intermediate 2, and intermediate 3 (4,5,5-triethoxypentan-2-one)

Scheme 3.

Computed reaction pathways (A to C) for the conversion of furfuryl alcohol to ethyl levulinate in ethanol dielectric media. The computed free energies at 298 K using the G4MP2 method are also shown. All free energies are reported in kcal/mol and w.r.t to FAL. [*] indicates that the transformation is not direct and detailed picture of these reaction is shown in Scheme 4. Notes:(a) computed apparent free energy barrier for hydride shift is 21.1 kcal/mol (b) no-barrier reaction; (c) computed apparent free energy barrier for hydride shift is 17 kcal/mol.

Scheme 4.

Likely reaction pathway for the formation of species A2 and B2 from A1 (scheme 3). The reaction from B1_2 to B2 is barrier less reaction. The free energies computed at the G4MP2 level of theory at 298 K are also given. All energies are reported in kcal/mol

Table 1

Comparison of Horvat's intermediate and intermediate 3. Note that the alkyl group chemical shifts are not included.

Intermediate 3 ¹³ C NMR	Horvat's Intermediate ¹³ C NMR	Carbon Type
208.0	208.0	CH ₂ -(C=O)-R
103.0	108.0	R-C-(OR) ₂
76.2	66.5	R-(COR)-R
43.9	39.9	H ₃ C-(C=O)-CH ₂ -C-(OR)-R
31.0	30.0	R-(C=O)-CH ₃

Table 2

The DEE to EL ratio in controlled experiments in various reaction conditions.

Solvents	Catalyst	Diethyl ether/Ethyl levulinate	Ethyl Levulinate Yield %
20% Ethanol 80% Heptane	Amberlyst 15	0.16	84.3
20% Ethanol, 80% Heptane (anhydrous)	Amberlyst 15	0.45	87.7
100 % Ethanol (anhydrous)	Benzene sulfonic acid	~0.20	92.5
90% Ethanol, 10% Water	Amberlyst 15	n/a	66.9
50 % Ethanol, 50% Water	Amberlyst 15	n/a	46.7