A Periodic-DFT Study of Retro-Aldol Fragmentation of Fructose on MoO₃

Evangelos Miliordos¹, Stavros Caratzoulas^{1*}, and Dionisios G. Vlachos^{1,2}

¹Catalysis Center for Energy Innovation, University of Delaware, Newark, DE 19716

²Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, DE 19716

Abstract

We use Density-Functional Theory calculations to investigate the mechanism of the retro-aldol fragmentation of fructose to glyceraldehyde (GLA) and dihydroxyacetone (DHA) on MoO₃. We find that the reaction follows the classic mechanism of C-C bond activation by proton abstraction from the β-OH group of the sugar and stabilization of the transition state and resulting enolate intermediate by charge delocalization through coordination of the sugar's carbonyl group to a Lewis acidic Mo atom. The deprotonation of fructose and the C-C bond scission take place in a concerted fashion. On MoO₃, fructose can also undergo epimerization to D-hamamelose through a 1,2-carbon shift along a pathway that is as probable kinetically as the one that leads to retro-aldol fragmentation but is somewhat more favourable thermodynamically. We see that hamamelose formation does not have an adverse effect on the overall yield of alkyl lactates, because hamamelose can itself undergo retro-aldol fragmentation to GLA, which can further be converted to alkyl lactates through a cascade of thermodynamically favorable reactions involving isomerization via 1,2-hydrogen shift, dehydration and ketalization, all catalyzed by the Lewis acidic zeolite Sn-MFI.

Keywords: Retro-Aldol fragmentation; Density-Functional theory; fructose; alkyl lactates; molybdenum oxide; heterogeneous catalysis.

* Corresponding author: cstavros@udel.edu

1. INTRODUCTION

Utilization of lignocellulosic biomass as a renewable chemical feedstock is a promising path to a more sustainable chemical industry. Orazov and Davis recently succeeded in converting different sugars to alkyl lactates at moderate temperatures (100°C), employing tandem catalysis over MoO₃ and the Lewis acidic zeolite Sn-MFI in alcoholic solutions.[1] The importance of this achievement for the production of platform chemicals from biomass cannot be overstated, as lactic acid is used in a broad range of industrial processes, which include: it is the precursor of polylactic acid, a biodegradable thermoplastic;[2-4] it is used to increase the solubility and adjust the acidity of pharmaceutical products and cosmetics;[5, 6] and its anti-bacterial properties make it ideal for household cleaning products.[6]

Orazov and Davis demonstrated that MoO₃ can catalyze the retro-aldol fragmentation of aldoses and ketoses, which occurs by C-C bond cleaving at the α,β -position relative to the carbonyl group. In the case of fructose, the Davis group has reported yields of 75% in the trioses dihydroxyacetone (DHA) and glyceraldehyde (GLA) (Figure 1). The presence of Sn-MFI is crucial as without it the yield drops to 15%. The small pores of Sn-MFI preclude the isomerization or epimerization of the bigger C5 and C6 aldoses or ketoses to a number of side-products. The authors reported that in aqueous MoO₃ solution fructose can undergo epimerization to hamamelose in addition to retro-aldol reaction to DHA and GLA, which is in agreement with earlier experimental observations.[7] The overall reaction network is depicted in Figure 1. Along the same lines, Murillo et al. recently produced a mixture of several lactic acid derivatives from sugars by employing only zeolitic imidazolate frameworks.[8]

In this work, we present catalytic pathways obtained from Density-Functional theory calculations for the retro-aldol fragmentation and epimerization of fructose over MoO₃. We also discuss the thermodynamics of the overall conversion of fructose to alkyl lactates and the important role of the Lewis acidic zeolite Sn-MFI in driving this tandem synthetic scheme by catalyzing the isomerization and dehydration of the fragmentation products.

2. METHODS

All calculations were performed using the spin-polarized PBE exchange-correlation functional[9] as implemented in the CP2K suite of codes.[10-12] Coquet and Willock have carried out DFT+U calculations for MoO₃ with U-J = 6.3 eV and concluded that the +U

correction is only needed for reduced MoO₃, [13]; thus the +U correction was not applied in our study. In our calculations, the core electrons were represented by norm-conserving pseudopotentials,[14, 15] while valence electrons were described by a double- ζ Gaussian basis set. An auxiliary plane wave basis set of 300 Ry energy cutoff was also used.[16] To account for dispersion effects, we considered the D3 correction proposed by Grimme *et al.*[17] The climbing image nudged-elastic-band (CI-NEB) method with 8 images was used to locate transition states.[18, 19] The CI-NEB was optimized by means of molecular dynamics. Each replica was assigned an initial temperature of 10K and was annealed to 0K. The convergence criteria used for the maximum displacement and force are 2×10^{-4} and 4.5×10^{-4} a.u. The character of the transition state (1st-order saddle point) was verified by vibrational frequency analysis.

Owing to the weak interaction between adjacent bilayers of MoO₃ (see below), it has been demonstrated that a single bilayer can adequately capture the electronic structure of the oxide.[13]

We have modelled the (010) surface termination of the oxide. The size of the unit cell was first optimized for bulk α -MoO₃ ($15.795 \text{ \AA} \times 14.823 \text{ \AA} \times 13.953 \text{ \AA}$). Then a single bilayer was naturally isolated (see Figure 2) and the box was extended in the z-direction to 25 $\text{\AA}$ to build a Mo₃₂O₉₆ slab.

Harmonic vibrational frequencies were calculated numerically with a step size of 0.01 $\text{\AA}$. Thermal corrections at 100°C were calculated within the harmonic approximation.

All thermochemistry figures reported in this work are at the M062X/aug-cc-pVTZ theory level and the calculations were performed in Gaussian 09.[20] Bader analysis was performed to obtain atomic charges.[21] The charge densities were obtained at the structures obtained with CP2K using VASP[22, 23] and analyzed using the Henkelman code.[24-27]

3. RESULTS

3.1 MoO₃ Structure. MoO₃ is a layered oxide where a two-dimensional bilayer, *xy*-plane, is repeated along the *z*-axis (Figure 2). Two adjacent bilayers are kept together through dispersion forces. All Mo atoms are equivalent and connected to three types of oxygen atoms, which we label O_t, O_a and O_s in Figure 3. The terminal oxygen O_t is linked to only one molybdenum atom, the O_a atoms bridge two Mo atoms each and form Mo-O bonds of unequal lengths, while the O_s atoms form two equivalent Mo-O bonds with two Mo atoms each and interact with a third

molybdenum atom, at a longer distance, via van der Waals forces. The bond lengths of the bulk material and of the two-dimensional slab are given in Table 1; for the bulk material we also provide values from experimental and past computational work. All of the covalent Mo-O bond lengths (R_1 , R_3 , R_4) are in excellent agreement with experimental values, within a few hundredths of an Å. The weaker, dispersion bonds are also in good agreement with experiment, within a few tenths of an Å.

To further understand the nature of the chemical bonds in MoO_3 we have performed gas-phase calculations on the chemical unit MoO_3 . It features three Mo-O double bonds of length 1.72 Å at the PBE-D3 theory level. In the $\text{Mo}(\text{OH})_3$ molecule, the single Mo-O bond length is 1.90 Å. These figures indicate that the Mo- O_t bond in the MoO_3 crystal has a π character ($R_1 = 1.68$ Å), in agreement with the bond order analysis undertaken by Tokarz-Sobieraj et al.,[28] who reported a bond order of 1.7. Judging by their lengths, one of the Mo- O_a bonds, $R_4 = 1.75$ Å, is closer to a double bond, while the two Mo- O_s bonds ($R_3 = 1.96$ Å) are rather single bonds. The remaining two bonds, $R_2 = 2.44$ Å and $R_5 = 2.21$ Å, are weaker interactions.

The electronic structure, density of states, and vacancy formation energies of MoO_3 have been extensively studied in the literature.[13, 28-30] The Mo atoms have partial charge of $+2.23e$ (Mulliken analysis), while the three oxygen sites, O_t , O_a and O_s , carry partial charges of -0.48, -0.74 and -0.99 e , respectively.[28]

3.2 Fructose Ring Opening. The fructofuranose molecule binds to the surface of the oxide via electrostatic interactions and hydrogen bonding. By Bader analysis, we see that the Mo surface atoms carry partial charges of $+2.36e$ and electrostatically interact with the fructofuranose O2 atom, which has a partial charge of -1.15 e . At the same time, the C2-OH is a H-bond donor to an O_t surface atom, which itself carries a charge of -0.6 e .

Formally, the fructose ring opening entails deletion of the H atom in the O2 position and addition of an H atom in the O5 position (ring O). Mechanistically, following binding to the catalyst, the transformation follows a stepwise proton transfer from O2 to O5 (Figure 4). The proton transfer is mediated by a proton acceptor at the surface of the catalyst (oxide O_t atom) and stabilization of the resulting intermediate by delocalization of the excess charge on the proton donor (fructose O2 atom) via a Lewis acid centre (Mo atom). The furanose ring opens and the formyl group at C2 forms upon back-donation of the proton from the surface O_t to fructose O5.

We have identified two mechanistically similar pathways which, however, differ in their binding geometries, specifically in the number of Mo atoms bridged by the fructose O2 atom. One of them involves monodentate binding to the Mo atom directly bonded to the O_t atom that accepts the proton from O2 (Figure 4, upper pathway). The other pathway proceeds through bidentate binding of the O2 atom to the surface (Figure 4, lower pathway). In this case, the requisite charge delocalization described earlier takes place via a second Mo atom, neighbouring the one directly bonded to the protonated O_t. The two Mo atoms are part of an oxide Mo-O_s-Mo bridge and in the course of the reaction one of the two Mo-O_s bonds elongates from 2.09 Å to 2.72 Å while the other one shortens from 2.09 Å to 1.76 Å. This indicates that the Mo atoms tend to retain six covalent bonds at all times.

The energy profiles for both pathways are shown in Figure 5. We can see that the opening of the ring is kinetically controlled by the activation energy required for the initial proton transfer from O2 to O_t. Moreover, with an intrinsic energy barrier of 19.5 kcal/mol, the bidentate, ring-opening pathway is kinetically more probable than the monodentate one, which has an intrinsic barrier of 46.4 kcal/mol. Considering thermal corrections within the harmonic approximation with frozen surface, the free energy barriers are 13.9 and 41.0 kcal/mol, respectively. The reason the bidentate pathway is energetically more favourable is that the proton transfer transition state is less strained. In the monodentate mode, a significant energy penalty is incurred as the Mo=O_t bond bends to make it possible for the deprotonated O2 atom of the sugar to coordinate to the Mo atom. In contrast, by engaging a neighbouring Mo atom, the bidentate geometry allows for efficient Lewis acid catalysis, namely, stabilization of the transition state via charge delocalization.

3.3 Fructose Retro-Aldol Fragmentation. The open-chain fructose molecule can undergo retro-aldol fragmentation at the α - β position. Our calculations show that on MoO₃ the reaction follows the classic mechanism: The molecule is initially activated by deprotonation of the β -OH group. The ensuing electron density re-distribution effects the C-C bond scission that results in the formation of glyceraldehyde and an enolate intermediate which is stabilized by coordinating to a Lewis acid centre (Mo atom). Proton uptake by the enolate and formation of the dihydroxyacetone fragment complete the reaction (Figure 6). Overall, the retro-aldol fragmentation of fructose is endergonic: $\Delta G_{\text{retro}}=10.7$ kcal/mol at the PBE level, but a more

accurate calculation at the M062X/aug-cc-pVTZ level gives $\Delta G_{\text{retro}}=16.7$ kcal/mol. The initial proton abstraction by the O_t atom of the oxide and the attendant C-C scission take place in a concerted fashion through a transition state with monodentate coordination of O2 to the Mo atom. The intrinsic energy barrier of this step is 31.3 kcal/mol (Figure 7). The protonation of the enolate intermediate turns out to be slower, with an intrinsic energy barrier of 36.1 kcal/mol. With thermal corrections, the respective intrinsic free energy barriers are 22.8 and 21.5 kcal/mol. Under equilibrium conditions, the apparent activation energy (Gibbs free energy relative to isolated reactants) is 21.5 kcal/mol. We should note that we were not able to find a bidentate mechanism similar to that described above for the ring-opening. Although we identified geometries in which the substrate is bound to the surface of the catalyst in a bidentate configuration, NEB calculations for the identification of a bidentate transition state failed to converge to physically or chemically meaningful structures; the substrate molecule incurred a number of bond scissions, indicating that the NEB minimum energy pathway explored high-energy regions of the potential energy surface.

The catalytic activity of the $\text{Mo}=\text{O}_t$ surface group has also been demonstrated in calculations of the catalytic dehydrogenation of alcohols by $(\text{MoO}_3)_3$ clusters.[31] In our work, we have seen that the catalytic process entails coordination of the carbonyl group to the positively charged Mo atom, which facilitates the delocalization of excess charge on the substrate molecule as a result of a proton transfer from a neighbouring hydroxyl group to the O_t surface atom. In Figure 8, we show the Bader partial charges on select substrate and active site atoms before and after binding. The large positive charge on Mo ($+2.36 e$) induces an electron flux from the side carbon chains of fructose (R_1 and R_2 in Figure 8) towards the carbonyl group. The charge of the carbonyl oxygen atom changes from -1.02 to $-1.06 e$ and that of the carbon atom from $+0.97$ to $+0.91 e$. Similarly, the positive charge of the hydroxyl H atom that participates in H-bonding with the surface O_t induces an increase in the negative charge on O_t , from -0.60 to $-0.66 e$. The net effect of this charge polarization is to increase the tendency of the carbonyl and O_t oxygen atoms to donate electronic density to Mo and H, respectively. As a result, both the carbonyl and the $\text{Mo}=\text{O}_t$ double bonds are pre-activated. The activation of the carbonyl is also evident in the structure of the density of states.

In Figures 9, we plot the density of states (DOS) of clean MoO_3 (Figures 9(a) and 9(b)), isolated fructose (Figure 9(c)), and of the surface-adsorbate system (Figure 9(d)). The Fermi

level of MoO₃ is at -5.41 eV, and the valence and conduction bands are 1.77 eV apart, in agreement with the 1.79 eV value reported by Getsoian and Bell[29] at the same level of theory. The Fermi level of the surface-adsorbate system is at -3.74 eV (Figure 9(d)). In Figure 9(c) we plot the DOS of isolated fructose and its projection on the carbonyl oxygen's *p*-orbitals. The peak at -2.5 eV corresponds to the fructose LUMO, which is mostly the $\pi^*(\text{C}=\text{O})$ orbital. Upon adsorption, this peak shifts almost entirely below the Fermi level, resulting in partial occupancy of the anti-bonding $\pi^*(\text{C}=\text{O})$ and in the weakening of the carbonyl double bond.

3.4 Fructose Epimerization. Orazov and Davis reported also small amounts of D-hamamelose when fructose was reacted with molybdate. The reaction follows a 1,2-carbon shift and is analogous to that previously reported for molybdate- and nickel(II) diamine-catalyzed reactions of aldoses (also known as Bilik reaction). For the epimerization to happen, the fructose molecule needs to bind through the carbonyl oxygen and the C3-OH instead of the C4-OH group. Our calculations show that this binding mode is less favourable by ca. 8 kcal/mol, and that the fructose-hamamelose epimerization is thermodynamically reversible with $\Delta G_{\text{epim}}=8.2$ kcal/mol (M062X/aug-cc-pVTZ). Nevertheless, fructose epimerization is thermodynamically more favourable than retro-aldol fragmentation by ca. 9 kcal/mol. Mechanistically (Figure 10), a proton transfer from C4-OH to the surface O_t atom activates the fructose molecule and the C3-to-C2 carbon-shift ensues in a concerted fashion. The resulting intermediate is D-hamamelose in a deprotonated state. Proton back-donation from the surface Mo-O_t-H to the substrate completes the reaction. The energy profile along this catalytic pathway is shown in Figure 11. An energy barrier of 19.8 kcal/mol must be overcome for the concerted proton transfer and 1,2-carbon shift to occur. A similar energy barrier, 20.5 kcal/mol, is associated with the proton back-donation. Considering thermal corrections, the proton back-donation transition state lies higher than the 1,2-carbon shift transition state and, in this sense, it determines the apparent activation energy (Gibbs free energy) of the epimerization, which is equal to ca. 20.8 kcal/mol—practically the same as the retro-aldol apparent activation energy.

Hamamelose can itself undergo retro-aldol fragmentation by the same mechanism described earlier for fructose (see Figure 6 with R₁=HOCH₂CH(OH), leading to the formation of two GLA molecules). According to our calculations, the transition state **3d** (rate-limiting) lies 28.8 kcal/mol above the energy of isolated reactants, about 8 kcal/mol lower than that of the fructose

retro-aldol pathway. By including thermal corrections at 100 °C, the Gibbs free energy of the transition state lies 23.3 kcal/mol higher than the isolated reactants, compared with 21.5 kcal/mol in the case of fructose. This suggests that fructose and D-hamamelose undergo retro-aldol fragmentation at about the same rate, which is in agreement with the experimental observation, made by Orazov and Davis, that “*the rate of ethyl lactate from hamamelose is nearly identical to that of fructose*”[1].

4. DISCUSSION

Our calculations therefore suggest that fructose retro-aldol fragmentation to GLA and DHA is not kinetically preferred to epimerization and that, in fact, the thermodynamics favours the latter. However, hamamelose can itself undergo retro-aldol fragmentation to two GLA molecules or to formaldehyde and an aldopentose (Figure 1), the equilibria of which are unfavourable, with respective ΔG_{epim} equal to 12.9 and 3.9 kcal/mol (or 21.9 and 12.0 kcal/mol with respect to fructose) at the M062X/aug-cc-pVTZ level.

So, what drives the conversion of fructose to alkyl lactates is the downstream conversion of the retro-aldol products in a cascade of reactions in which the Lewis-acidic zeolite Sn-MFI plays a pivotal role, clearly demonstrated in the drop in the methyl lactate yield to 15% when fructose is reacted with MoO_3 alone. The fructose retro-aldol products, GLA and DHA, can undergo isomerization to each other and DHA—the most stable of the two isomers by 4.4 kcal/mol—can itself subsequently undergo dehydration to pyruvaldehyde, with $\Delta G_{\text{rxn}}=-7.2$ kcal/mol. In methanolic solution, the pyruvaldehyde can in turn react with methanol to yield a hemiacetal, which can undergo isomerization to methyl lactate, with overall $\Delta G_{\text{rxn}}=-20.2$ kcal/mol. So, according to our calculations, the fructose to methyl lactate equilibrium is very favourable, with $\Delta G_{\text{tot}}=-42.4$ kcal/mol. The isomerization reactions described above proceed via 1,2-hydrogen shift, which is readily catalyzed by the zeolite Sn-MFI; which is also capable of catalyzing the dehydration of DHA to the pyruvaldehyde. On the other hand, the aldopentose formed from the retro-aldol fragmentation of hamamelose does not undergo either 1,2-hydrogen or 1,2-carbon shift because it is too large to fit in the small pores of the Sn-MFI framework, which, however, can accommodate the smaller C2-C4 molecules.

5. CONCLUSIONS

We have used Density-Functional Theory calculations to investigate the mechanism of the retro-aldol fragmentation of fructose to glyceraldehyde (GLA) and dihydroxyacetone (DHA) on MoO₃. We have found that the reaction follows the classic mechanism of C-C bond activation by proton abstraction from the β -OH group of the sugar and stabilization of the transition state and resulting enolate intermediate by charge delocalization via coordination of the sugar's carbonyl group to a Lewis acidic Mo atom. The activating deprotonation of fructose and the C-C bond scission take place in a concerted fashion. On MoO₃, fructose can also undergo epimerization to D-hamamelose through a 1,2-carbon shift along a pathway that is as probable kinetically as the one that leads to retro-aldol fragmentation but is somewhat more favorable thermodynamically. The formation of hamamelose, nevertheless, has no adverse effects on the overall yield of alkyl lactates, because hamamelose can itself undergo retro-aldol fragmentation to two GLA molecules at nearly the same rate as fructose. GLA and DHA are further converted to alkyl lactates through a cascade of thermodynamically favorable reactions involving isomerization via 1,2-hydrogen shift, dehydration and ketalization, all catalyzed by the Lewis acidic zeolite Sn-MFI.

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Table 1. Mo-O bond lengths (in Å) of bulk α -MoO₃ and of surface slab used in this work. Bond lengths are defined in Figure 2.

Method	R ₁	R ₂	R ₃	R ₄	R ₅
PBE-D3 ^a	1.68	2.44	1.96	1.75	2.21
PBE-D3 ^b	1.70	2.47	1.96	1.77	2.20
PBE+U ^c	1.70	2.34	1.97	1.75	2.29
optB88 ^d	1.70	2.39	1.96	1.78	2.19
Expt ^e	1.68	2.24	1.96	1.74	2.30
Expt ^f	1.67	2.33	1.95	1.73	2.25

^a This work. Optimized structure using a single slab of dimensions 15.795 Å $\times$ 14.823 Å

^b This work. Bulk MoO₃ (box dimensions 15.795 Å $\times$ 14.823 Å $\times$ 13.953 Å).

^c Ref. [13]

^d Ref. [32]

^e Ref. [33]

^f Ref. [34]

Figure 1. Fructose conversion to alkyl lactate over MoO_3 and Sn-MFI in tandem. (DHA = dihydroxyacetone, GLA = Glyceraldehyde.)

Figure 2. The layered structure of MoO_3 . The bilayer extending in the xy-plane is repeated along the z-axis.

Figure 3. The six Mo-O bonds around the Mo center.

Figure 4. Ring opening of fructose over MoO_3 following monodentate (upper) or bidentate (lower) binding pathways.

Figure 5. Fructose ring opening energy profiles for the monodentate (blue) and bidentate (red) binding pathways shown in Figure 4. States marked as in Figure 4.

Figure 6. Fructose retro-aldol fragmentation mechanism over MoO_3 . The initial proton abstraction from the substrate and the ensuing C-C bond scission take place in a concerted fashion. ($\text{R}_1 = \text{CHOHCH}_2\text{OH}$, $\text{R}_2 = \text{CH}_2\text{OH}$.)

Figure 7. Energy profile of catalytic pathway for fructose retro-aldol fragmentation over MoO_3 shown in Figure 6.

Figure 8. Bader partial charges before and after binding of fructose to the MoO_3 active site.

Figure 9. Density of states (DOS) of clean MoO₃ (a), and projected DOS of clean MoO₃ (b), isolated fructose (c), and surface-adsorbate system (d). Vertical black lines indicate the Fermi level.

Figure 10. Fructose epimerization reaction mechanism over MoO_3 . The initial proton abstraction from the substrate and the 1,2-carbon shift take place in a concerted manner. ($\text{R}_1 = \text{CHOHCHOHCH}_2\text{OH}$, $\text{R}_2 = \text{CH}_2\text{OH}$.)

Figure 11. Energy profile of catalytic pathway for fructose epimerization reaction over MoO_3 shown in Figure 10.

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