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Highly Efficient Chemical Process To Convert Mucic Acid into Adipic Acid and DFT Studies of the Mechanism of the Rhenium-Catalyzed Deoxydehydration**

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Abstract: *The production of bulk chemicals and fuels from renewable bio-based feedstocks is of significant importance for the sustainability of human society. Adipic acid, as one of the most-demanded drop-in chemicals from a bioresource, is used primarily for the large-volume production of nylon-6,6 polyamide. It is highly desirable to develop sustainable and environmentally friendly processes for the production of adipic acid from renewable feedstocks. However, currently there is no suitable bio-adipic acid synthesis process. Demonstrated herein is the highly efficient synthetic protocol for the conversion of mucic acid into adipic acid through the oxorhenium-complex-catalyzed deoxydehydration (DODH) reaction and subsequent Pt/C-catalyzed transfer hydrogenation. Quantitative yields (99%) were achieved for the conversion of mucic acid into muconic acid and adipic acid either in separate sequences or in a one-step process.*

The production of bulk chemicals and fuels from renewable bio-based feedstocks is of significant importance for the sustainability of human society.[1] Adipic acid (hexanedioic acid), as one of the most demanded drop in chemicals from a bioresource, is used primarily for the large-volume production of nylon-6,6 polyamide.[2] Currently, the commercial adipic acid is mainly produced through the petroleum-based cyclohexane route which involves a nitric acid oxidation process.[3] Besides the nonrenewable feedstock source of cyclohexane for this route, the emission of large amounts of nitrous oxides (N_2O, NO, and NO_2) during the oxidation process is also a major environmental concern.[4] It is highly desirable to develop a sustainable and environmentally friendly process for the production of adipic acid from renewable feedstocks.[5]

Combined biocatalytic and chemocatalytic pathways have been used to produce adipic acid from renewable precursors, with *cis,cis*-muconic acid as the key intermediate.[6] In the reported biocatalytic conversions of glucose into muconic acid, the multiple-step fermentation processes invoke several different kinds of enzymes, but the product yield and the production efficiency are very low.[7,8] In contrast, the conversion of muconic acid into adipic acid is rather straightforward by using a hydrogenation reaction.[9] Adipic acid preparations by chemocatalytic hydrogenations of furan-2,5-dicarboxylic acid (FDCA)[10] and glucaric acid[11] have been reported in patents. However, drastic reaction conditions such as strong halogen acids and high pressure (more than 50 bar) of H_2 were employed. The step by step hydrogenolysis of 5-hydroxymethylfurfural (HMF) can produce 1,6-hexanediol (a potential precursor for adipic acid) with high selectivity, albeit with low HMF conversion.[12] The harsh reaction conditions and low efficiency of these methods make them unlikely to be industrialized.

The key challenge for the conversion of oxygen-rich biocompounds (sugar, sugar acids, and sugar alcohols) into industrial bulk chemicals is to develop highly efficient catalytic deoxygenation systems which can selectively convert a bioresource into the target chemicals. Recently, the well-known deoxydehydration (DODH) reaction has been successfully applied to the conversion of polyols, including sugar alcohols, into conjugated alkenes.[13] Although the reaction conditions for DODH reactions are rather mild, the substrate scope is limited to polyols and the product selectivity is not high enough.[13] Very recently, Shiramizu and Toste reported the conversion of mucic acid into adipic acid ester, by using a DODH and hydrogenation reaction, in moderate yields.[14] In the present work, we report the highly efficient conversion of mucic acid (**1**) into muconic acid (**2**) through a DODH reaction catalyzed by an oxorhenium complex. Remarkably, excellent yield (99%) is achieved for the DODH reaction of this sugar acid substrate. By combining DODH with a transfer-hydrogenation reaction, **1** is successfully converted into adipic acid (**3**) with excellent yield in either one or two steps (see Scheme S1 in the Supporting Information).

Mucic acid (**1**) is a C_6 sugar acid which can be produced from galactose on large scale by an established method.[15] In our work, **1** was tested under typical DODH reaction conditions with methyltrioxorhenium (MTO) as a catalyst.[13] In the initial trial, **1** was heated in 3-octanol at 180°C for 2 hours. The reaction went very slowly and the selectivity was low. The majority of **1** remained an insoluble solid throughout the reaction. With 3-pentanol as the solvent at 120°C, the reaction was still slow in the initial stage, probably because of

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the low solubility of **1**, but showed excellent selectivity. Kinetic studies showed that **1** was gradually converted into the conjugated double-bond products in boiling 3-pentanol (120 °C) with 5 mol% MTO (Figure 1 A). It was found that the products were the monoester **4** and diester **5**. The yield of **4** increased continuously and reached the maximum at 24 hours, and then decreased (Scheme 1). Meanwhile, the yield of **5** kept increasing even after 24 hours. It was clear that **1** was first converted into **4** and then further converted into **5**. The full conversion into **4** and **5** was observed after 24 hours. Compared with the DODH reactions of polyols,[13] the reaction temperature of this system is lower, and the reaction rate is also slower. This outcome could be due to the low solubility of **1** or the interference of carboxylic acid groups. In fact, higher reaction temperature led to lower selectivity, but the reaction was sluggish at lower reaction temperature (90 °C). To understand more about this reaction, the diethylmucate (**6**; Scheme 1) was prepared according to a reported method[16] and was used as the starting material for the DODH reaction. Under the same reaction conditions, full conversion of **6** into **5** (30%) and **7** (70%) were achieved at 20 hours (see Figure S1 in the Supporting Information). Apparently, the ester exchange reaction occurred and 65.0% of the ethyl groups were substituted by 3-pentanol. Despite the fact that **6** has much better solubility than **1** in hot alcohols,[16] the reaction of **6** proceeded only slightly faster than that of **1**. This result indicated that **1** was first subject to esterification before undergoing the DODH reaction. The reaction was generally conducted under N_2 or air flow (entry 3, Table S1). In contrast, a slower reaction was observed in the sealed system (entry 4, Table S1) and much faster reaction was achieved when a water separator was employed (entry 5, Table S1).

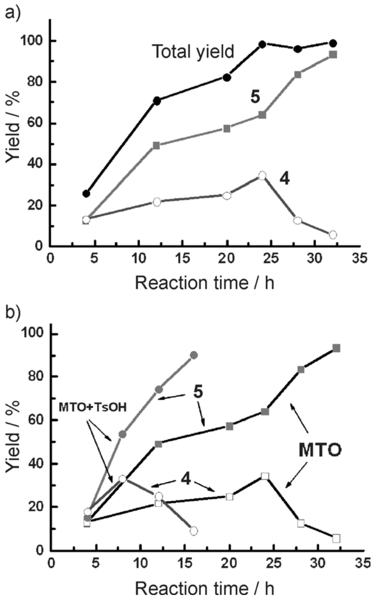
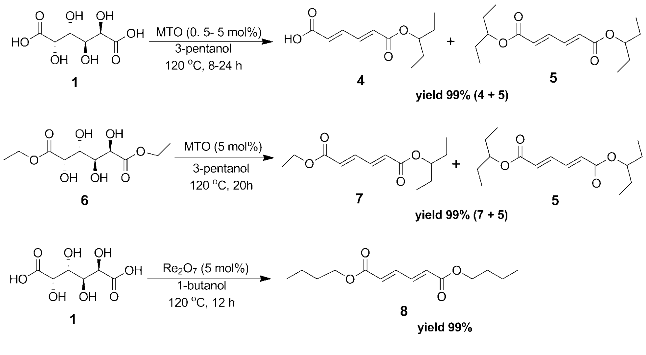


Figure 1. a) DODH of mucic acid with an MTO catalyst. b) DODH of mucic acid with MTO and TsOH catalysts. Reaction conditions: mucic acid (1.0 mmol), catalysts (5.0 mol%), 3-pentanol (20.0 mL), 120 °C.



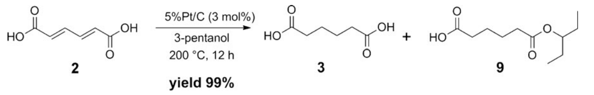
Scheme 1. DODH of **1** and mucic acid diethyl ester to muconates.

To accelerate the reaction, Brønsted acids were added as cocatalysts to promote the esterification step and enhance the solubility of the starting material. As shown in Figure 1 b, the addition of *para*-toluene sulfonic acid (TsOH) remarkably shortened the reaction time required to achieve full conversion, and the product distribution and the trends of products formation remained the same. Sulfuric acid also showed the similar promoting effect (entry 7, Table S1). In fact, the acid additives for the DODH reaction would assist olefin extrusion by protonation of the rhenium diolate intermediate,[17,18] and the extrusion of olefin from oxorhenium complex is the key step in DODH reaction.[13a,19] With the aid of an acid cocatalyst, the catalyst (MTO) loading can be reduced to as low as 0.5 mol% (entries 8–11, Table S1).

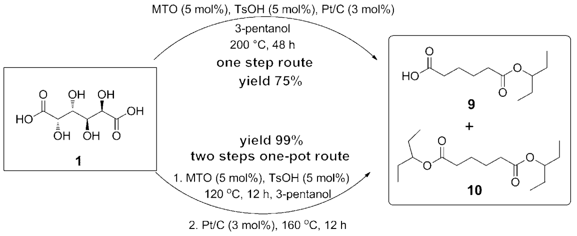
Various Re catalysts have also been tested for the reaction. $[Re_2(CO)_{10}]$ is efficient for the DODH reaction of a variety of vicinal diols.[13a,17] However, $[Re_2(CO)_{10}]$ is inactive for the DODH reaction of **1** (entry 12, Table S1), probably because of the poor tolerance of $[Re_2(CO)_{10}]$ to the carboxylic acid group. In contrast, a high reaction rate was observed for the Re_2O_7-catalyzed DODH reaction of **1** in 3-pentanol (entries 13 and 14, Table S1). The reaction with the Re_2O_7 catalyst is even faster than that catalyzed by MTO in combination with TsOH. Re_2O_7 is hygroscopic and can react easily with moisture to form $HReO_4$,[20] which may promote the esterification and olefin extrusion steps in the DODH catalytic cycle. Addition of TsOH to the Re_2O_7 reaction system did not additionally improve the reaction efficiency (entries 15 and 16, Table S1).

As to the solvent for this reaction, 3-octanol is less active, even though it can be used at a higher temperature, probably because of the reduced polarity of 3-octanol (entry 1, Table S2). 2-propanol is almost inactive, as the reaction is carried out at a lower temperature given the lower boiling point (entry 4, Table S2). The investigation on the viability of using bioderived 1-butanol showed that the reaction efficiency is similar to that of 3-pentanol, and almost quantitative conversion of **1** into muconate was achieved in 12 hours with Re_2O_7 as the catalyst (entry 3, Table S2). In the 1-butanol system, only dibutyl muconate (**8**; Scheme 1) was observed, probably because of the reduced steric effect of the primary alcohol.

As the high yield of muconate from mucic acid was achieved, a subsequent transfer-hydrogenation reaction was demonstrated for the conversion of **2** or muconates into adipic acid (**3**) or its esters (Scheme 2). Firstly, muconic acid (**2**)



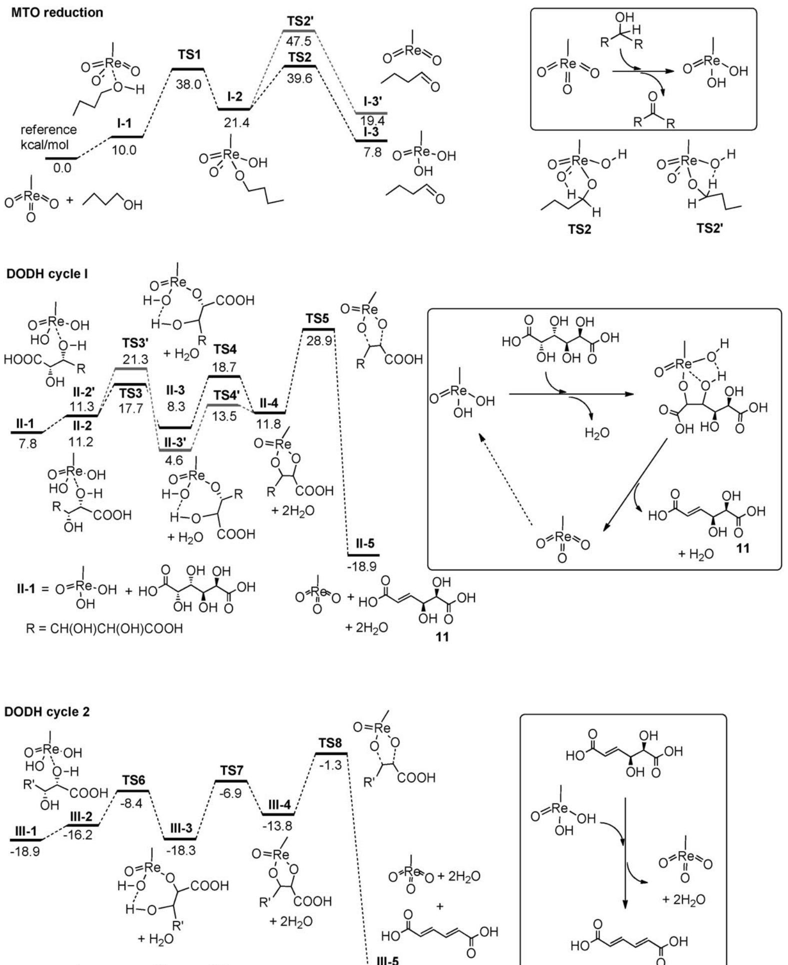
Scheme 2. Transfer-hydrogenation of *trans,trans*-muconic acid to adipic acid and its ester.



Scheme 3. The conversion of **1** into adipic acid esters by a DODH/transfer-hydrogenation process in one pot.

could be quantitatively converted into **3** or the monoester **9** in 3-pentanol at 200 °C in 12 to 24 hours. Similar results were achieved when different catalysts (Ru/C, Pd/C, or Pt/C) were used. Encouraged by this result, crude muconates, which were obtained from the DODH reaction, were directly used as the feedstock for the transfer-hydrogenation reaction. Remarkably, the muconates obtained from **1** by a DODH reaction were fully converted into the adipic acid esters **9** and **10** (see Table S3). The reaction was highly selective and no other by-product was observed. Since both the DODH and transfer-hydrogenation reaction could be conducted in 3-pentanol, the one-step conversion of **1** into **3** or its esters was tested (Scheme 3). In a closed reaction system with MTO, TsOH, and Pt/C catalysts, **1** was converted into adipic acid esters in 75 % yield within 48 hour at 200 °C (entry 7, Table S4). The moderate efficiency is due to the low reaction rate for the DODH step in the closed system, as mentioned above. Thus, when the reaction was carried out in a one-pot, two-step manner, that is, run at 120 °C under air flow for 12 h and subsequently in a sealed system at elevated temperature (160–200 °C) for another 12 h, the reaction efficiency was dramatically increased and a 99 % yield of the adipic acid esters (96 % isolated yield) was achieved directly from **1**. The adipic acid esters could be further hydrolyzed to give free adipic acid (**3**) in 94 % yield upon isolation. In a 5 g scale experiment, a high yield (98 %, isolated) of adipic acid esters was also achieved (see the Supporting Information). As mucic acid can be obtained from renewable galactose on large scale by the already established procedure,[15] the method developed herein provides a highly efficient synthetic protocol for the production of renewable adipic acid (**3**).

Although the mechanism of the DODH reaction for vicinal diols has been well discussed,[13,21] there are still some unclear points, especially for the current mucic acid feedstock. In the MTO catalyst case, Toste et al.[13a] suggested the reaction sequence started from the reduction of Re^{VII} to Re^{V} in the complex methyldioxorhenium (MDO), with a subsequent MDO-catalyzed DODH reaction. However, Wang et al.[21] proposed a different active species, methyloxodihydroxyrhenium (MODH), using density functional theory (DFT) calculations. To resolve the controversy, we performed detailed DFT calculations for the mucic acid DODH process to understand the reaction mechanism. For the first step of the MTO reduction reaction, our results showed that reduction of MTO to MODH by a two-step hydrogen transfer process is thermodynamically and kinetically favorable relative to MDO (Scheme 4). The energy barrier is 39.6 kcal mol^{-1} for MODH as compared to 47.5 kcal mol^{-1} for MDO, while the relative energy is 7.8 kcal mol^{-1} for MODH as compared to 19.4 kcal mol^{-1} for MDO. In the second step, MODH was firstly applied in the DODH reaction of **1**. In the DODH cycle 1, α/β OH groups of **1** are activated and



Scheme 4. Energy diagram and proposed mechanism of MTO-catalyzed DODH reaction for the conversion of mucic acid into muconic acid in alcohol.

eliminated (Scheme 4). The process progressed through three transition states (TS3, TS4, and TS5 in Scheme 4). Interestingly, for the transition-state TS3, the hydrogen transferred from an α-hydroxy group (OH_α) is kinetically favorable, but thermodynamically unfavorable as compared to TS3′ where the hydrogen of the β-hydroxy group (OH_β) is transferred. However, the hydrogen transfer steps are not the rate-limiting steps in the whole cycle. The highest energy barrier (21.1 kcal mol^{-1}) in this process is associated with the third transition-state TS5, which is accompanied with breaking C–O bonds to form the intermediate **11**and to reform MTO. The second DODH cycle from **11** to muconic acid (**2**) is similar to the first cycle, but with a much lower energy barrier (17.6 kcal mol^{-1}). This result indicates that the second DODH cycle is much faster than the first cycle, which is consistent with the fact that **11** was not observed experimentally. To provide a comprehensive comparison, the elimination of β- and γ-hydroxy groups in the first DODH cycle were also calculated, and the results showed much higher energy barriers in the first cycle (29.5 kcal mol^{-1}), as well as the second cycle (25.4 kcal mol^{-1}; see Figures S2 and S3). Hence, the elimination of β- and γ-hydroxy groups in the first DODH cycle is unlikely to happen. In addition, Toste's active species, MDO, has also been calculated in the mucic acid DODH process. In this case, the energy barrier of the first transition-state TS3D is 21.7 kcal mol^{-1}, which is much higher than 9.9 kcal mol^{-1} of the MODH process TS3 (see Figure S4). Interestingly, the energy barrier of the first transition state in the second cycle (TS6D) is also 21.4 kcal mol^{-1}, which is much higher than the 10.5 kcal mol^{-1} of the MODH process (TS6) as well (see Figure S5). In both the DODH cycles 1 and 2, MDO and MODH exhibit the same transition states, that is, TS4 and TS5, and TS7 and TS8. The energy barrier of the entire processes (including MTO reduction step) for the MDO pathway (47.5 kcal mol^{-1}) is much higher than that for the MODH one (39.6 kcal mol^{-1}). Therefore, MODH is the identified intermediate in the MTO-catalyzed DODH reaction for **1**. The reaction starts with the α,β-positions first instead of the β,γ-positions, thus resulting from the activation of the α-hydroxy group by the carboxylic acid group at the chain end.

In conclusion, we have demonstrated the highly efficient synthetic protocol for the conversion of mucic acid (**1**) into muconic acid (**2**) and then adipic acid (**3**) through the oxorhenium-complex-catalyzed DODH and Pt/C-catalyzed transfer-hydrogenation sequence. Quantitative yields were achieved for conversion of **1** into **2** and adipic acid esters either in separate sequences or in a one-pot process. The mechanism of the MTO-catalyzed DODH reaction for **1** has also been studied by DFT computations, which disclosed a possible MODH intermediate. The DODH reaction occurs preferentially at the α, β-positions rather than β, γ-positions. The results presented herein not only demonstrated a highly efficient, simple, and green protocol for the production of renewable adipic acid from sugar acid. More importantly, for the first time, the mechanism of the MTO-catalyzed DODH reaction for this useful aldaric acid transformation was studied in detail. This work sheds light on the huge potential of producing industrial chemicals from various sugar acids.

Experimental Section

Larger scale synthesis of adipic acid esters from mucic acid: A mixture of mucic acid (25.0 mmol, 5.25 g), MTO (1.25 mmol, 300 mg), TsOH (1.25 mmol, 215 mg), and 3-pentanol (250.0 mL) was charged into a pressure flask. The reaction mixture was stirred at 120 °C for 12 h. A water separator was used to remove the produced water. After that, 1.56 g of 5.0 % Pt/C was added into the flask. The flask was sealed and the reaction mixture was stirred at 160 °C for another 12 h. The reaction mixture was then cooled down to room temperature. The catalysts were separated by filtration through Celite-545, the solvent was removed by evaporation, and the obtained adipic acid esters were purified by flash column chromatography ($CHCl_3$/MeOH 10:1) to give colorless liquid (6.84 g, 98 % yield, dipentyl ester/ monopentyl ester 93:7).

Hydrolysis of adipic acid dipentyl ester: The separated adipic acid dipentyl ester (286.0 mg, 1 mmol) was refluxed for 12 h in an EtOH/ H_2O solution of sodium hydroxide (0.133 mol L^{-1}, 15.0 mL; EtOH/ H_2O 1:2). After that, the reaction mixture was evaporated to dryness, and the obtained solid was dissolved in 10.0 mL deionized water. The pH value of the aqueous solution was adjusted to about 3.0 with 1 M HCl. The solution was again evaporated to dryness, and the obtained solid was stirred in 10.0 mL methanol for 3 min. The mixture was then filtered through Celite-545, and the filtrate was evaporated to afford adipic acid as a white solid. The product was vacuum dried at 60 °C overnight, and adipic acid was obtained at 94 % yield (136.8 mg).

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