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Integration of Chemical and Biological Catalysis: Production of Furylglycolic Acid from Glucose via Cortalcerone

Thomas J. Schwartz,[†] Samuel M. Goodman,[†] Christian M. Osmundsen,[‡,§] Esben Taarning,[‡] Michael D. Mozuch,[∥] Jill Gaskell,[∥] Daniel Cullen,[∥] Philip J. Kersten,[∥] and James A. Dumesic*[,†]

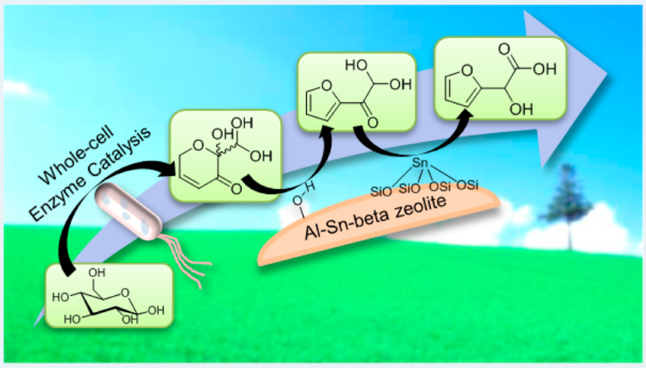
[†]Department of Chemical and Biological Engineering, University of Wisconsin-Madison, Madison, Wisconsin 53706, United States

[‡]Research & Development Division, Haldor Topsøe A/S, Lyngby, Denmark

[§]Department of Physics, Technical University of Denmark, Lyngby, Denmark

[∥]Forest Products Laboratory, Forest Service, U.S. Department of Agriculture, Madison, Wisconsin 53726, United States

Supporting Information



ABSTRACT: Furylglycolic acid (FA), a pseudoaromatic hydroxy-acid suitable for copolymerization with lactic acid, can be produced from glucose via enzymatically derived cortalcerone using a combination of Brønsted and Lewis acid catalysts. Cortalcerone is first converted to furylglyoxal hydrate (FH) over a Brønsted acid site (HCl or Al-containing beta-zeolite), and FH is subsequently converted to FA over a Lewis acid site (Sn-beta zeolite). Selectivity for conversion of FH to FA is as high as 80% at 12% conversion using tetrahydrofuran (THF) as a solvent at 358 K. Higher conversion of FH leads to FA-catalyzed degradation of FH and subsequent deactivation of the catalyst by the deposition of carbonaceous residues. The deactivated catalyst can be regenerated by calcination. Cortalcerone can be produced from 10% glucose solution using recombinant *Escherichia coli* strains expressing pyranose 2-oxidase and aldos-2-ulose dehydratase from the wood-decay fungus *Phanerochaete chrysosporium* BKM-F-1767. This enzymatically derived cortalcerone is converted in one pot to FA in a methanol/water solvent over an Al-containing Sn-beta zeolite possessing both Brønsted and Lewis acid sites, achieving 42% selectivity to FA at 53% cortalcerone conversion.

KEYWORDS: *Sn-beta zeolite, MPVO reaction, hydride transfer, poly(lactic acid), whole-cell enzyme catalysis, pyranose-2-oxidase*

INTRODUCTION

The development of biorenewable routes for the production of value-added chemical intermediates is of interest for reasons of both environmental and economic sustainability.[1] Notable among biorenewable chemicals is poly(lactic acid) (PLA), a biodegradable polymer that has been in commercial-scale production for several years.[2] Copolymers of lactic acid (LA) with another monomer are attractive targets for research, because the final properties of the polymer can be tuned by appropriate choice of comonomer. However, most copolymers reported have been purely aliphatic,[3−5] because aromatic or pseudoaromatic hydroxy-acids have not yet been produced from biomass. Vinyl-containing PLA-copolymers have also been recently reported using green feedstocks.[6] Polymandelide is a polylactide derivative based on mandelic acid, a hydroxy acid which possesses an aromatic side chain. It has been reported to possess properties similar to those of polystyrene,[7] although mandelic acid has not been produced from biomass. In this communication, we show that furylglycolic acid (FA), a biomass-derived, pseudoaromatic hydroxy-acid, can be produced by the integration of chemical and biological catalysis.

FA has an appropriate side chain to be used as a comonomer with LA. Polyesters with a pendent furan ring, as an FA-LA copolymer would be, have been reported to possess favorable characteristics.[8] Such a copolymer may resemble polymandelide, which in turn has properties similar to polystyrene.[7] Previous syntheses of FA have been laboratory-scale preparations.[9,10] While there are not obvious pathways to produce FA from typical sugar dehydration products, it is possible to produce this molecule using a combination of chemical and biological catalysis.

The integration of chemical and biological catalysis is an emerging field, which presents opportunities to produce molecules that are not accessible by either discipline alone. Much of the field has focused on the combination of homogeneous organometallic catalysts with enzymes.[11] Dynamic kinetic resolution has been one of the most prominent success stories,[12] including the use of one-pot and cascade schemes. Caiazzo and co-workers[13] have demonstrated one-pot

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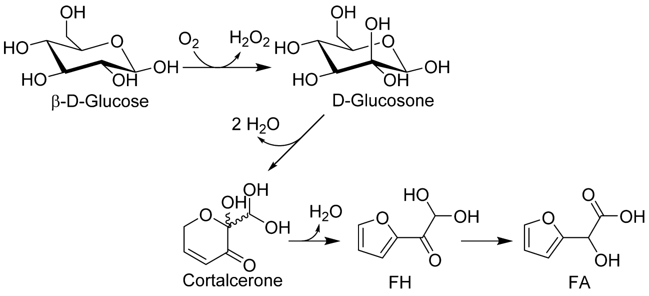
and cascade aminations, where the organometallic Pd catalyst and the enzyme operate synergistically. It is also possible to exploit synergies between enzymatic and heterogeneous catalysis. For example, hydrogen peroxide, which is a byproduct of many enzymatic oxidation reactions, can be used to perform catalytic epoxidations using zeolite catalysts.[14] New synthetic strategies can also be developed for molecules that can be produced by traditional means, and the combination of heterogeneous Sn catalysts with *Candida rugosa* lipase to yield enantiomerically pure D- or L-LA from sugars is a good example.[15] Kieboom and co-workers have combined in one pot enzymatic oxidation, homogeneously catalyzed dehydration, and hydrogenation over Pd/C to convert D-galactose to 4-deoxy-D-glucose derivatives.[16] More broadly, they suggest that combinations of chemical and biological catalysis can yield high value products.[17,18] Shanks[19,20] has suggested that biological catalysis can be used to generate platform molecules which are subsequently upgraded using chemical catalysis. Our group has recently employed such a strategy to produce high-value chemicals from the biologically derived platform molecule triacetic acid lactone.[21]

In this work, we have explored the production of FA using cortalcerone as an intermediate that can be produced enzymatically from glucose, as previously described[22] (see Scheme 1). Cortalcerone is first dehydrated to form furylglyoxal hydrate (FH), which is then upgraded to FA through an intramolecular Meerwein–Ponndorf–Verley–Oppenauer (MPVO) hydride shift. Dehydration of cortalcerone to FH has been reported to take place using Brønsted acids such as HCl.[23] However, the MPVO isomerization of FH to FA is heretofore unreported, although similar reactions have been demonstrated to take place over aluminum-containing zeolites[24] and bulk zirconia,[25] as well as Al-free Sn-containing beta zeolite (Sn-beta).[26,27] Herein we demonstrate the production of FA from FH using Sn-beta, and we demonstrate the production of FA from enzymatically derived cortalcerone using a bifunctional Al-containing Sn-beta zeolite (Al–Sn-beta).

Scheme 1. Pathway for Conversion of Glucose to Furylglycolic Acid (FA)[a]



[a]Conversion from glucose to glucosone to cortalcerone takes place enzymatically, while dehydration of cortalcerone to furylglyoxal hydrate (**FH**) requires a Brønsted acid and isomerization of **FH** to **FA** takes place over a Lewis acid.

EXPERIMENTAL DETAILS

E. coli BL21(DE3) expressing pyranose 2-oxidase of *Phanerochaete chrysosporium* in pET21a(+) (Novagen) as described previously[28,29] was used to oxidize glucose to glucosone. In contrast to earlier studies, recombinant whole cells were used for catalysis. Aldos-2-ulose dehydratase (AUDH) cDNA from *P. chrysosporium* RP78, a homokaryotic strain derived from BKM-F-1767 (ATCC 24725) was cloned, and the sequence deposited in GenBank under accession number KF699142. This 900 amino acid sequence differs at 4 positions from the AUDH of *P. chrysosporium* ATCC 32629 reported by Claesson et al.[30] The BKM-F-1767 *AUDH* cDNA was commercially synthesized with codon bias for optimized expression in *E. coli* with plasmid pJexpress414 (DNA2.0, Menlo Park, CA, U.S.A.). Transformed *E. coli* BL21(DE3) cells expressing BKM-F-1767 AUDH were used to produce cortalcerone from glucosone. Anhydrous furylglyoxal, FH, and FA were synthesized according to procedures described elsewhere.[10,31] Al-free Sn-beta and Al–Sn-beta,[32−34] and bulk zirconia[35] were prepared as described in the literature. Other zeolite catalysts were purchased from Zeolyst International (Conshohocken, PA). Reactions were carried out in thick-walled glass batch reactors, and products were analyzed using high performance liquid chromatography. Thermodynamic calculations presented in the Supporting Information were carried out using Gaussian09[36] software. Full experimental details can be found in the Supporting Information.

RESULTS AND DISCUSSION

Initial studies examined two Al-containing zeolites (USY and beta), zirconia, and Al-free Sn-beta for catalytic activity in converting FH to FA. As shown in Table 1, the Al-containing zeolites were not selective for the reaction (yielding other products that were not identified), while zirconia achieves only modest selectivity. Sn-beta showed the best performance for conversion of FH to FA, achieving 64% selectivity at 18% conversion (Entry 4, Table 1). Altering the Si/Sn ratio does not

Table 1. Conversion of FH to FA[a] over Al-Containing Zeolites (USY and Al-beta), Zirconia, and Sn-beta Zeolite

entry	catalyst	Si/Al or Si/Sn	solvent	conv. (%)	sel. to FA (%)	rate[b]
1	USY	8	THF	15	9	0.7
2	Al-beta	25	THF	11	11	0.9
3	ZrO_2		THF	30	20	3.1
4	Sn-beta	400	THF	18	64	5.8
5	Sn-beta	150	THF	36	47	9.0
6	Sn-beta	400	THF	39[c]	48[c]	1.5[c]
7	Sn-beta	400	THF	12[d]	80[d]	6.0[d]
8	Sn-beta	400	water	9[e]	10[e]	0.7[e]
9	Sn-beta	400	water	22	18	2.5
10	Sn-beta	400	5%[f] water/THF	21	17	1.8
11	Sn-beta	400	2%[f] water/THF	17	41	3.4
12	Sn-beta	400	THF	16[g]	54[g]	4.6[g]
13	Sn-beta	400	1:1 water/MeOH	7	53	1.7
14	Sn-beta	400	9:1 water/MeOH	16	40	3.1

[a]All reactions carried out with mass ratio of catalyst:FH = 0.5 for 4 h at 358 K except where indicated. [b]Rate of FA formation (μmol g^{-1} min^{-1}). [c]24 h reaction. [d]3 h reaction. [e]338 K reaction. [f]Vol %. [g]Catalyst reused after TGA analysis.

appear to affect selectivity (measured at 36–39% conversion). Rather, a decrease in the Si/Sn ratio (i.e., an increase in the acid site density) resulted in an increase in the reaction rate per mass of catalyst, measured at 36–39% conversion (comparing Entries 5 and 6, Table 1). As discussed below, the low selectivity and depressed activity at high conversion (Entry 6, Table 1) are a result of side reactions and deactivation of the catalyst by deposition of carbonaceous residues.

Given that the enzymatic production of cortalcerone takes place in aqueous medium and Sn-beta has been demonstrated[37] to be a water-tolerant Lewis acid, we examined the conversion of FH to FA in water. As shown in Table 1 (Entries 8 and 9), high selectivity for conversion of FH to FA is not possible in purely aqueous medium, regardless of reaction temperature. Indeed, even the presence of small amounts of water decreases the selectivity for conversion of FH to FA (comparing Entries 10 and 11 with Entry 4, Table 1). As discussed below, this behavior is the result of FA-catalyzed degradation of FH, which takes place in water regardless of the presence of the Sn-beta catalyst. Neutralizing the acid functionality of FA by performing the reaction in mixtures of methanol and water resulted in substantial improvements in selectivity compared to reactions carried out in pure water (comparing Entries 13 and 14 with Entry 9 in Table 1).

The highest selectivities for production of FA were observed for reactions in tetrahydrofuran (THF) solvent, where selectivity as high as 80% can be obtained at 12% FH conversion, although selectivity decreases with increasing conversion (see Table 1, Figure 1). Given the improvement in selectivity observed for reactions carried out in THF, the use of a biphasic reactor could be a promising reaction system; however, the partition coefficient of FH in aqueous/organic systems is not favorable using nonpolar solvents (see Supporting Information, Table S1). Additionally, the use of long-chain alcohols for the organic phase is precluded by the formation of either hemiacetals, which would be too large to fit into the pores of Sn-beta, or diacetals which are sterically hindered and unreactive for MPVO reactions.

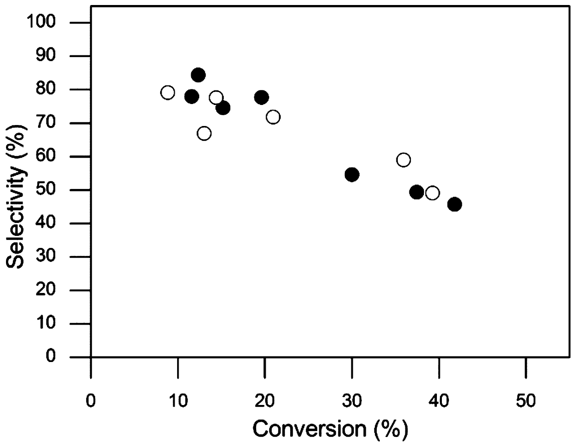


Figure 1. Influence of FH conversion on selectivity to FA for reactions carried out with Sn-beta (Si/Sn = 400) at 348 K (○) and 358 K (●).

Measurement of the apparent reaction kinetics for the reaction in THF, using the initial rate of FA formation, (see Supporting Information, Figures S2 and S3) gave a reaction order of 0.22 ± 0.07 with respect to the FH concentration. The apparent activation energy was determined to be 71.6 ± 3.5 kJ mol^{-1}. The fractional order is likely the result of the catalyst operating at high surface coverage by organic species.

As shown in Figure 1, the selectivity to FA is dependent on FH conversion, with higher conversion resulting in lower selectivity, suggesting that FH and/or FA undergo degradation at high FA concentrations. This idea is supported by the addition of fresh catalyst after 24 h of reaction at 358 K, followed by an additional 24 h of reaction. The selectivity to FA decreases from 48% to 33%, and conversion of FH increases from 40% to 59% during the second 24 h of reaction, indicating that the addition of fresh catalyst does not produce an increase in FA concentration due to degradation reactions at high FA concentrations.

Reuse of the Sn-beta catalyst recovered after reaction for 24 h led to only 9% FA selectivity at 18% FH conversion after reaction for 4 h at 358 K. Thermogravimetric analysis (TGA) of the same catalyst revealed 2.5% mass loss over the range of 400 to 700 K, with a maximum rate of loss at 534 K (see Supporting Information, Figure S4). Reuse of the catalyst after TGA analysis yields 54% selectivity at 16% conversion, with a rate comparable to that of the fresh catalyst (Entry 12, Table 1), indicating that activity can be recovered by calcination. The observed mass loss indicates formation of carbonaceous deposits on the catalyst, which would be consistent with deposition of residues from the degradation of FH and/or FA at high FA concentrations.

As shown in Table 2, FH is stable in water and FA is not, regardless of the presence of the Sn-beta catalyst. Moreover, it appears that FA can catalyze the degradation of FH because significant degradation of FH occurs when FA is also present in solution. Given that FA is a Brønsted acid, this observed instability suggests that FH and FA are susceptible to Brønsted-acid catalyzed degradation in water. Indeed, FH is stable in the presence of FA in a 1:1 mixture of methanol and water, although there is still a small amount of FA degradation due to the presence of water. The acid-catalyzed degradation of FH potentially involves ring hydrolysis and subsequent condensation, as has been proposed for the acid-catalyzed degradation of 5-hydroxymethylfurfural[38] (see Supporting Information, Figure S7). The resulting high molecular-weight condensation products would be deposited on the catalyst, consistent with the observed catalyst deactivation.

Table 2. Stability of FH and FA under Reaction Conditions[a]

	FH only	FA only	FA and FH	
solvent	conv (%)	conv (%)	FH conv (%)	FA conv (%)
water	2	21[b]	38	30
THF	4	n.d.[c]	21	4
THF + TFA	10	n.d.		
1:1 water/MeOH	n.d.	6	n.d.	9

[a] 358 K for 4 h. [b] Reaction of FA in water in the presence of Sn-beta resulted in 23% conversion. [c] Not detected.

While hydrolysis and condensation describe the behavior of FH and FA in water, they do not account for the decrease in selectivity observed at high conversions in THF solvent. Importantly, while FH and FA are both stable independently in THF (see Table 2), degradation of FH occurs in the presence of FA, whereas FA is stable in THF with or without the presence of FH. This behavior suggests that FH degradation is catalyzed by FA when FA is present at high concentrations, and it shows that degradation of FA requires the presence of water.

Table 3. Conversion of Cortalcerone to FA with Bifunctional Al–Sn-beta[a]

entry	catalyst	Si/Al	Si/Sn	solvent	conv. (%)	sel. to FH (%)	sel. to FA (%)[b]
1	Al-beta	50	--	water	15	20	n.d.[c]
2	Sn-beta	--	400	water	28	n.d.	n.d.
3	Al-beta	50	--	1:1 water/MeOH	7	27	n.d.
4	Sn-beta	--	400	1:1 water/MeOH	33	n.d.	n.d.
5	Al-beta + Sn-beta	50	400	1:1 water/MeOH	40	8	36
6	Al–Sn-beta	50	400	1:1 water/MeOH	14	21	11
7	Al–Sn-beta	50	200	1:1 water/MeOH	15	21	32
8	Al–Sn-beta	200	200	1:1 water/MeOH	53	5	42
9	Al–Sn-beta	200	200	1:1 water/MeOH	76[d]	3[d]	34[d]
10	Al–Sn-beta	200	200	1:9 water/MeOH	20	1	47
11	Al–Sn-beta	200	200	9:1 water/MeOH	56	5	17

[a]All reactions carried out with mass ratio of catalyst:cortalcerone = 0.25 for 0.5 h at 358 K except where indicated. [b]FA is analyzed via HPLC as a combination of ester and free acid. [c]Not detected. [d]Catalyst:cortalcerone = 0.5.

Furthermore, addition of a stoichiometric amount of trifluoroacetic acid (TFA) to FH in THF results in an amount of degradation comparable to that observed in the presence of FA, confirming that FH is unstable in the presence of Brønsted acids. Similar addition of TFA to FA in THF has no effect, indicating that the degradation reactions involve the hydrated glyoxal group of FH. For example, two FH molecules can dimerize through nucleophilic addition, as has been described for the dimerization of methylglyoxal[39,40] (see Supporting Information, Figure S8 for more detail). This behavior would also take place in water, which could further explain the above-noted conversion of FH in the presence of FA in water. Thus, FH is unstable in the presence of Brønsted acids in both THF and water, whereas FA is susceptible to acid-catalyzed degradation in water only.

The degradation of FH observed at high FA concentrations suggests that it would be desirable to convert cortalcerone to FA over a bifunctional catalyst containing Brønsted and Lewis acid sites, thereby minimizing the FH concentration. This approach also has the benefit of simpler processing, as both reactions can be performed in one pot without the need for intermediate separations. Brønsted acid sites are required to convert cortalcerone to FH, because the Lewis acid sites on Sn-beta do not catalyze this dehydration reaction (see Table 3). In this respect, an Al-containing beta zeolite (Al-beta), a heterogeneous Brønsted acid, is active for dehydration of cortalcerone to FH, achieving 20% selectivity to FH at 15% cortalcerone conversion (see Table 3).

Because the biological production of cortalcerone takes place in water, it would be attractive to convert cortalcerone to FA in an aqueous/organic solvent system. Thus, initial reactions combining the use of both Brønsted and Lewis acid catalysts were carried out using a mixture of 50% w/w methanol in water as the solvent and lyophilized, enzymatically derived cortalcerone as the reactant. Methanol was chosen to favor the formation of FA as its methyl ester, thereby preventing the acid group from catalyzing undesirable degradation reactions of FH and FA, and water was included in the solvent mixture to moderate the formation of acetals with FH. This solvent system was studied first using a physical mixture of Al-beta and Sn-beta, achieving 36% selectivity to FA at 40% cortalcerone conversion, with only 8% selectivity to FH. This result demonstrates that FA can be produced from enzymatically derived cortalcerone when both Brønsted and Lewis acid sites are present. We subsequently studied this solvent system using bifunctional catalysts containing both Sn and Al.

Entries 6–8 in Table 3 show that the highest yield of FA (42% selectivity at 53% conversion) can be achieved using Al–Sn-beta with a high Si/Al ratio and a low Si/Sn ratio, corresponding to a low Brønsted acid site density and high Lewis acid site density (as confirmed by FTIR spectra of adsorbed pyridine, Supporting Information, Table S2). For the two catalysts with low Si/Al ratio (Entries 6 and 7, Table 3), the high Brønsted acid site density results in increased FH degradation and deposition of carbonaceous residues on the catalyst, leading to low overall activity. Similar behavior is observed when cortalcerone is reacted over pure Al-beta, where conversion is low because of deposition of carbonaceous resides, as revealed by TGA (Supporting Information, Figure S6). Correspondingly, the overall catalyst activity improves when the Si/Al ratio is increased and the number of Brønsted acid sites is decreased (Entry 8, Table 3). Decreasing the Si/Sn ratio increases the number of water-tolerant Lewis acid sites, and increases the selectivity to FA. Additionally, as observed above, the selectivity to FA appears to depend on conversion, with decreasing selectivity at high conversion (Entry 9, Table 3). TGA measurements of this spent catalyst again confirmed the presence of carbonaceous deposits (see Supporting Information, Figure S5).

Increasing the methanol content of the solvent (Entry 10, Table 3) results in a decrease in catalytic activity, which is possibly a side effect of reaction of the hydroxyl groups of cortalcerone with methanol. In spite of the lower activity, the selectivity to FA remains high because of the high methanol content. Indeed, the selectivity is only marginally higher than that observed in 1:1 water/methanol, indicating that high methanol concentrations are not necessary to obtain the best observed selectivity. Conversely, decreasing the methanol content results in lower selectivity because of increased degradation of FH and FA (Entry 11, Table 3), indicating that methanol is important for prevention of FA-catalyzed degradation.

■ CONCLUSIONS

We have demonstrated the conversion of FH to FA using tin-containing beta zeolites. Conversion of FH in THF over Al-free Sn-beta can achieve 80% selectivity to FA at 12% conversion, although selectivity decreases with increasing conversion because of Brønsted acid catalyzed degradation reactions of FH. While the catalyst undergoes deactivation from deposition of carbonaceous residues, the catalyst can be fully regenerated by calcination. Further, bifunctional catalysts containing both

Brønsted and Lewis acid sites (i.e., beta-zeolite containing both Al and Sn) are effective for conversion of enzymatically derived cortalcerone to FA in one pot in a methanol−water solvent system, achieving 42% selectivity at 53% conversion.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental methods, details of cortalcerone synthesis, partition coefficient measurements, apparent reaction kinetics measurements, thermogravimetric analysis of spent catalysts, details of potential FH and FA degradation pathways, and catalyst characterization by FTIR spectroscopy of adsorbed pyridine. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dumesic@engr.wisc.edu.

Notes

The authors declare no competing financial interest.

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