ChemPubSoc Europe

DOI: 10.1002/cssc.201500025

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Communications

Efficient, Chemical-Catalytic Approach to the Production of 3-Hydroxypropanoic Acid by Oxidation of Biomass-Derived Levulinic Acid With Hydrogen Peroxide

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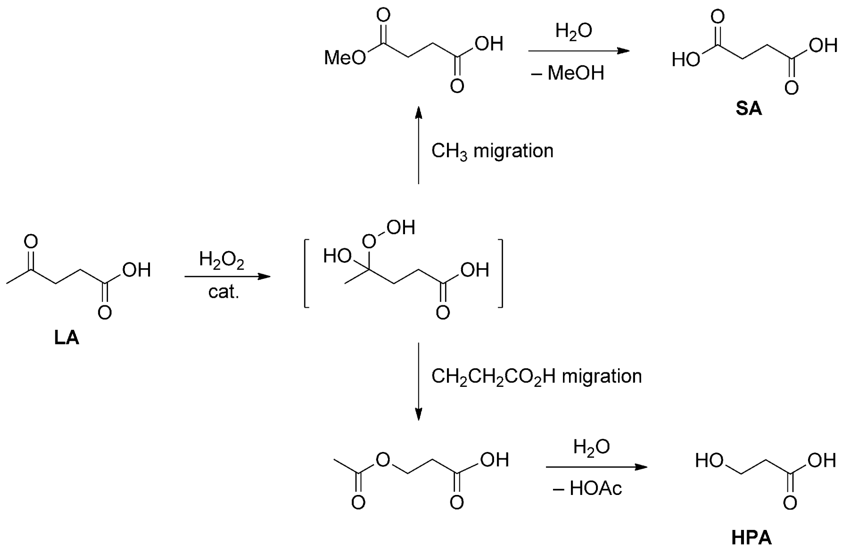
3-Hydroxypropanoic acid (HPA), a precursor to acrylic acid, can be produced in high yield by oxidation of the biomass-derived platform chemical levulinic acid. While treatment of levulinic acid with H_2O_2 under acidic conditions gives predominantly succinic acid, a remarkable reversal of selectivity is observed under basic conditions, leading either directly to HPA or, under modified conditions, initially to 3-(hydroperoxy)propanoic acid, which can be quantitatively hydrogenated to HPA.

3-Hydroxypropanoic acid (HPA) is considered a renewable target molecule of enormous latent potential, due to the fact that it provides a direct entry into the vast market for acrylic acid and its derivatives,[1] while at the same time unlocking the bio-compatible/degradable HPA homopolymer market, which also shows much promise.[2] The production of HPA from biomass sources is described in the literature almost exclusively by means of fermentation of glucose or glycerol. Although advances have been made, particularly in the development of recombinant yeast as producers,[3] a number of technical hurdles remain, particularly associated with performance and downstream processing.[4] HPA can also be produced via petrochemical approaches which have generally involved the hydration of acrylic acid or oxidation of allylic alcohol or propanediol,[5] but current initiatives place a greater premium on the production of chemical drop-ins from renewable resources, rather than making biochemicals from petroleum.

In principle, chemical-catalytic pathways offer much faster and more scalable routes to carbohydrate-derived renewables than fermentative approaches, and a straightforward opportunity for the production of HPA from biomass appeared to present itself in the selective oxidation of levulinic acid (LA). We have recently described the metal-free oxidation of LA with hydrogen peroxide to give succinic acid (SA) in good yield using an organic acid as the catalyst.[6] Even so, a number of chemical approaches to the conversion of carbohydrate derivatives (HMF, furfural, LA) to SA have been described,[7] but an analogous non-fermentative approach to HPA would define a new opportunity in biorefinery practice altogether.

Levulinic acid is a renewable feedstock of exceptional promise. It can be produced efficiently via the acidic processing of raw biomass,[8,9] and although this is practiced commercially only on a limited scale at present, economic projections have indicated that the production costs of LA could fall as low as US\$0.04–US\$0.10 per pound (1 lb = 0.453 kg).[10] LA can also be accessed in high yield by the hydrolysis of the biomass-derived platform molecule 5-(chloromethyl)furfural (CMF).[11] We reasoned that if the selectivity of the oxidation of LA to SA with hydrogen peroxide could be reversed to favor the alternative migration product (Scheme 1), a complementary route to HPA would also be forthcoming. Below, we are pleased to report the analogous conversion of LA into HPA using H_2O_2 under modified reaction conditions.



Scheme 1. Baeyer–Villiger oxidation of LA with H_2O_2.

At the outset, we had identified H_2O_2 as a reagent of great potential for the oxidation of LA due to its well known Baeyer–Villiger-type mechanism of action,[12] that could in fact lead

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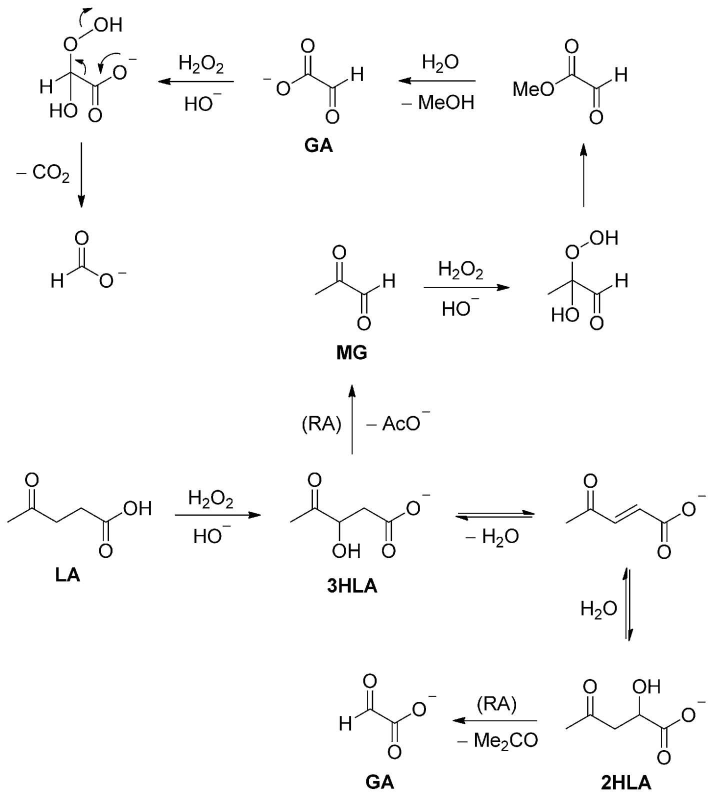
Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201500025.

either to SA or HPA, depending on which group undergoes migration. Running the reaction under acidic conditions favors methyl group migration by a wide margin to give SA in good yield.[6] Remarkably, we found that the selectivity of the migration could be controlled by switching the pH of the medium from acidic to basic. Thus, LA was dissolved in 30% aq. H_2O_2 and potassium hydroxide was added. The reaction was heated to 115 °C and further portions of base and H_2O_2 were added over the course of about 10 min. Unlike the same reaction in acid, rapid evolution of oxygen was observed at each addition. The mixture was allowed to stir undisturbed for a period of time before a final portion of H_2O_2 and KOH was added. The entire process was complete within about 90 min. Quantitative analysis by NMR using an internal standard showed that HPA was being produced in 47% yield. The mass balance consisted of acetic acid (89%), formic acid (29%), and methanol (9%). A volatiles trap further detected traces of acetone (ca. 1%). Running the same reaction at a lower temperature (60 °C) reduces the yield of HPA (22%) but increases the yield of acetone (10%).

The range of observed products indicated processes other than those shown in Scheme 1 are operative in this chemistry. Specifically, the fact that more acetic acid is produced than HPA demonstrates that more than one route to this product is available. The most likely scenario is oxidation of the enolate of LA to give 3-hydroxylevulinic acid (3HLA) (Scheme 2).[13] Retro-aldol cleavage of 3HLA yields acetate and methylglyoxal (MG). Baeyer–Villiger oxidation of MG is favored at the keto group, since the aldehyde exists mainly in the form of a hydrate. Methyl migration leads to the glyoxylic acid ester, which hydrolyzes to glyoxylate (GA), which itself breaks down on further oxidation to formate and CO_2. However, in no case does this explain the observation of acetone in the reaction mixture. Here, we propose an alternative pathway involving dehydration of 3HLA and rehydration to 2-hydroxylevulinic acid (2HLA). Retro-aldol of 2HLA yields acetone and again GA. To test these mechanistic postulates, we submitted an independent sample of MG to the reaction conditions and in fact, only formate and methanol were observed in the NMR spectrum. A sample of GA produced only formate under the same conditions. The observation of methanol may also derive from Baeyer–Villiger oxidation of acetone and subsequent hydrolysis of the methyl acetate.

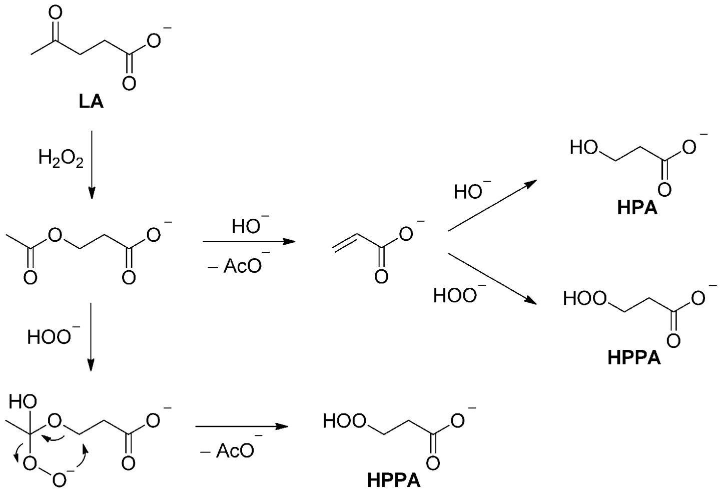


Scheme 2. Mechanism for the formation of acetone, formate, methanol, and excess acetate in the oxidation of LA to HPA. RA = retro-aldol.

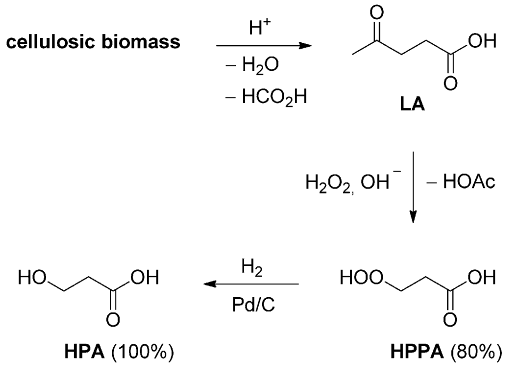
An interesting by-product was observed in the reaction conducted at 60 °C, which was not detected in the higher-temperature process. It appeared similar to HPA but showed a greater downfield shift of the methylene group adjacent to oxygen in its ^{1}H NMR spectrum. We speculated that this was the corresponding hydroperoxide, that is, 3-(hydroperoxy)propanoic acid (HPPA), and were able to confirm this proposal both by iodometric titration and by derivatization with MeI and Ag_2O to give methyl 3-(methylperoxy)propanoate. The yield of HPPA at 60 °C was low, but further reducing the reaction temperature appeared to favor this product. Ultimately, it was found that carrying out the reaction between 0 °C and room temperature over the course of about 6 h resulted in the production of HPPA in 82% yield by ^{1}H NMR integration, which was confirmed by isolation of the product in 80% yield. The expected, equivalent yield of acetic acid (80%) was also observed, alongside HPA (5%) and formic acid (4%). To avoid distillation of water in the isolation of HPPA, the product was extracted with ether. Conversion of HPPA to HPA by O–O bond hydrogenolysis over Pd/C was facile and quantitative, and hence this approach to HPA is considered to be the method of choice.

The question arises as to how HPPA occurs in the oxidation of LA with H_2O_2. We propose two reasonable pathways for the generation of HPPA, one or both of which may be operative. First, and most straightforward, it is possible that, instead of hydrolysis of the acetate, elimination to an acrylate intermediate may occur as shown in Scheme 3. The higher nucleophilicity of hydroperoxide anion may explain the selectivity for HPPA over HPA in this lower temperature reaction. Alternatively, attack on the acetate carbonyl by hydroperoxide anion would give a tetrahedral intermediate which could rearrange as shown to give HPPA and acetate.

In conclusion, we introduce here a new concept for the derivation of 3-hydroxypropanoic acid from biomass, as summarized in Scheme 4. The process is fully chemical-catalytic, comparatively fast, operates under mild conditions, and gives HPA in high yield (>80% overall from LA). The mass balance of the reaction consists mainly of acetic acid, which is itself a useful commodity chemical. Since LA can be de-



Scheme 3. Mechanisms for the formation of HPPA by oxidation of LA with H_2O_2.



Scheme 4. Overall process from biomass to HPA.

rived from raw cellulosic biomass in high yield, this practical, two-step method appears highly attractive for the industrial production of renewable acrylate derivatives, other C_3 chemicals (e.g., 1,3-propanediol, malonic acid), and the HPA homopolymer, while completely avoiding fermentation pathways.

Experimental Section

Oxidation of levulinic acid to 3-(hydroperoxy)propanoic acid with hydrogen peroxide: Levulinic acid (4.00 g, 34.5 mmol) was dissolved in 30% aq H_2O_2 (24 mL) at 0°C. To the resulting solution was added dropwise with stirring 5.2 M aq KOH (28.8 mL, 150 mmol). The ice bath was replaced by a water bath and the mixture was allowed to stir for 1.5 h. The water bath was then removed and the mixture was allowed to stir an additional 2.5 h. Finally, another portion of 30% aq H_2O_2 (8.0 mL) was added. The solution was allowed to stir until NMR indicated full conversion of the levulinic acid, ca. 2 h after the final addition of H_2O_2. The mixture was cooled in an ice bath and acidified to pH 3–4 with conc HCl. A measured amount of 1,4-dioxane was added as internal standard and the reaction mixture was analyzed by ^{1}H NMR. The product yields determined by this method were 3-(hydroperoxy)propanoic acid (82%), acetic acid (80%), 3-hydroxypropanoic acid (5%) and formic acid (4%). The 3-(hydroperoxy)propanoic acid product could be isolated by continuous extraction (5 h) of the acidified reaction mixture using ether as the extraction solvent. [**Caution**: oxidizable solvents should not be used here]. After the evaporation of the volatiles, 3-(hydroperoxy)propanoic acid was obtained as a colorless oil (2.91 g, 80%) along with a small quantity of 3-hydroxypropanoic acid. ^{1}H NMR (300 MHz, D_2O): $\delta = 4.18$ (t, $J = 5.9$ Hz, 2H), 2.67 ppm (t, $J = 5.9$ Hz, 2H); ^{13}C NMR (75 MHz, D_2O): $\delta = 175.9$, 71.9, 32.8 ppm.

Hydrogenation of 3-(hydroperoxy)propanoic acid to 3-hydroxypropanoic acid: The above-produced 3-(hydroperoxy)propanoic acid (2.90 g, 27.4 mmol) was dissolved in 30 mL of methanol. Palladium on activated carbon (10 wt% Pd, 30 mg) was added and the reaction flask was carefully evacuated and then backfilled with hydrogen three times. The system was pressurized to 3.8 atm hydrogen and shaken for 40 min. The mixture was filtered through a short plug of Celite, which was further rinsed with methanol (30 mL). The solvent was evaporated to give pure 3-hydroxypropanoic acid (HPA) as a colorless oil (2.48 g, 100%). ^{1}H NMR (600 MHz, D_2O): $\delta = 3.83$ (t, $J = 6.0$ Hz, 2H), 2.59 ppm (t, $J = 6.0$ Hz, 2H); ^{13}C NMR (150 MHz, D_2O): $\delta = 176.5$, 57.2, 36.8 ppm.

The Supporting Information contains further details on materials, experimental procedures, and NMR spectra.

Keywords: 3-hydroxypropanoic acid · biomass · catalysis · levulinic acid · renewable resources

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Received: January 6, 2015

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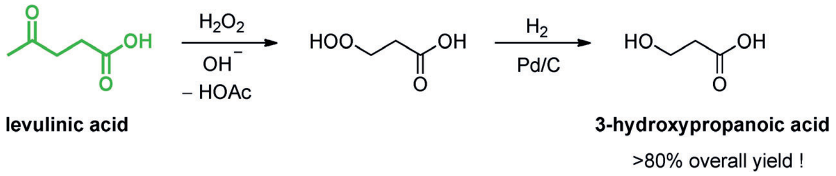

Just say no to fermentation: The first selective, chemical-catalytic approach to renewable 3-hydroxypropanoic acid (HPA) has been accomplished by gentle oxidation of biomass-derived levulinic acid with hydrogen peroxide and hydrogenolysis of the resulting hydroperoxide intermediate. HPA is a green building block of major potential for the production of renewable acrylate derivatives.