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Biobased *n*-Butanol Prepared from Poly-3-hydroxybutyrate: Optimization of the Reduction of *n*-Butyl Crotonate to *n*-Butanol

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S *Supporting Information*

ABSTRACT: Using metabolic engineering approaches, the biopolymer poly-3-hydroxybutyrate (P3HB) can be overproduced in organisms such as bacteria and plants. Thermolysis of P3HB, either in isolated form or within biomass, yields crotonic acid, a potential bioderived platform chemical. Reduction of crotonic acid provides *n*-butanol, which has value as a fuel and as a commodity chemical. Herein, we report optimization work on the hydrogenation of the *n*-butyl ester of crotonic acid to *n*-butanol and the potential of this chemistry to be incorporated into the production of bio-*n*-butanol from P3HB containing biomass.

INTRODUCTION

n-Butanol is a widely used commodity and platform chemical,[1] which also possesses physical properties desirable for its use as a liquid fuel.[2,3] Since fossil-based starting materials (oil, coal, natural gas) within the Earth's crust are finite resources not renewable within a human time scale,[4] the production of versatile building blocks, which serve as the starting materials to prepare fuels and chemicals from renewable resources, is desirable. One such versatile target is *n*-butanol.[1] Indeed, the fermentation to produce a biobased *n*-butanol was first patented nearly a century ago.[5] Due to *n*-butanol's superior fuel properties compared to ethanol,[2,3] multiple organizations are pursuing pathways[6−12] to biobased *n*-butanol,[13] often via the fermentation of bacteria or yeast.

Herein, we report proof-of-concept work on the production of the commodity chemical *n*-butanol from *n*-butyl crotonate, a molecule that can be derived from crotonic acid produced via the direct pyrolysis of microbial or plant biomass containing the biopolymer poly-3-hydroxybutyrate (P3HB) (Scheme 1).[14−19] Crotonic acid itself is currently a specialty chemical with limited markets. Production of crotonic acid from P3HB producing plants provides the opportunity to create it as a cost-advantaged feedstock and platform chemical for conversion to a range of commodity and fine chemicals, such as *n*-butanol, fumaric acid, maleic anhydride, propylene, and acrylic acid/acrylates, which would otherwise be difficult to produce from plants.[14] The hydrogenation work reported herein, in combination with previously demonstrated P3HB production in switchgrass biomass[14,20] and thermolysis of switchgrass biomass containing P3HB to crotonic acid,[15,18] provides proof of concept for obtaining *n*-butanol from a renewable genetically engineered switchgrass feedstock.

To optimize the hydrogenation reaction, an alkyl crotonate was chosen as the substrate since the hydrogenation of an alkyl ester is known to be more feasible than that of the corresponding carboxylic acid.[21−23] In addition, free carboxylate groups can leach base-metal ions from heterogeneous catalysts.[22] *n*-Butyl crotonate is the preferred hydrogenation substrate, producing two equivalents of *n*-butanol, one of which can be recycled to prepare new *n*-butyl crotonate (Scheme 1). The high-yielding esterification of crotonic acid to *n*-butyl crotonate employing a heterogeneous catalyst is well-known,[24] as is the *n*-butylation of *n*-butyric acid.[25]

Since the hydrogenation of an alkene is known to be more feasible than the hydrogenation of a carboxylate,[26] we expected the initial/fast formation of *n*-butyl *n*-butyrate, as an unisolated intermediate, in the hydrogenation reaction of *n*-butyl crotonate. This intermediate is then, in a second slower/more difficult process, reduced to two equivalents of *n*-butanol. The experimental results reported herein confirm this prediction. The vapor-phase continuous hydrogenation of *n*-butyl *n*-butyrate over a commercial CuO + ZnO/Al_2O_3 catalyst has been previously studied.[27,28] In contrast, this study investigates the liquid phase continuous hydrogenation.

EXPERIMENTAL SECTION

All experiments were conducted in a custom-built continuous flow, fixed-bed hydrogenation apparatus containing a 30 cm^3 catalyst bed. The reactor itself had a volume of ~100 cm^3. The catalyst was centered in the reactor with the area above and below the catalyst filled with 5 mm glass beads. The standard H_2 gas space velocity used was 6000 h^{-1}, with the exception of experiment number 20 in which it was 8000 h^{-1}, and the liquid space velocity (calculated based on ambient temperature flows) of the starting material *n*-butyl crotonate was 0.5 or 1.0 h^{-1} (0.25 or 0.5 cm^3/min). Reactions were performed at 200, 250, or 300 °C and at H_2 pressures of 200, 400, or 600 psi. The flow of H_2 into the system was controlled with a mass flow meter (Brooks), and its pressure was adjusted using a back pressure

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Scheme 1. Synthesis of *n*-butanol from P3HB

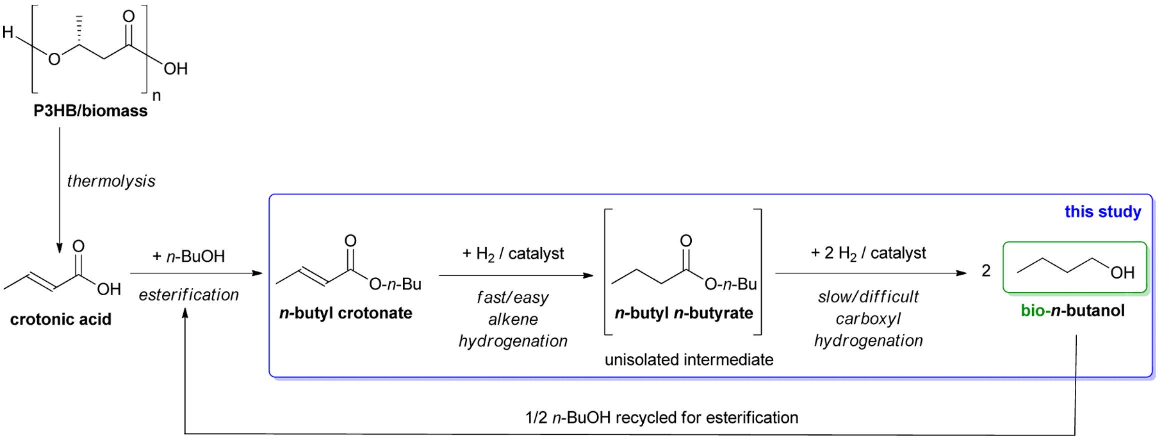

Table 1. Catalysts used for the hydrogenation of *n*-butyl crotonate to *n*-butanol

ID	catalyst	composition	particle size (mm)
A	JM-PRICAT CZ 40-18 T	51/32/5/12 $CuO/ZnO/CuCO_3/Al_2O_3$,C	6 × 5
B	JM-PRICAT CZ 30-18 T	39/45/16 $CuO/ZnO/Al_2O_3$,C	5 × 3
C	JM-KATALCO 83-3	50/30/20 $CuO/ZnO/Al_2O_3$,C	4 × 3
D	BASF-Cu 1986 T 1/8″	65/20/15 $Cr_2CuO_4/CuO/MnO_2$,SiO2,C	4 × 2
E	BASF-X 540 T 1/8″	60/10/30 $CuO/Al_2CuO_4/MnO_2,Al_2O_3$	4 × 2
F	BASF-Cu 0860 E 1/16″ 3F	60/40 CuO/SiO_2,CaO	4 × 1

regulator on the outlet of the system. The *n*-butyl crotonate liquid substrate was fed into the top of the packed reactor from a reservoir using an HPLC pump (Lab Alliance). Cooling of the product was achieved through a countercurrent heat exchange with the feed material line, providing preheating for the liquid feed. Collection of the products was achieved using a gas—liquid separator. The product composition was determined via quantitative GC-MS of 2−3 samples which were collected following the system reaching a steady state (60 min). The yield of formed *n*-butanol was calculated via (100[mol *n*-butanol]$_{out}$)/(2[mol *n*-butyl crotonate]$_{in}$). Commercial *n*-butyl crotonate (TCI America) was used as received. Evaluation samples of six industrial heterogeneous base-metal hydrogenation catalysts were provided by their commercial suppliers: PRICAT CZ 40-18 T, PRICAT CZ 30-18 T, and KATALCO 83-3 from Johnson-Matthey as well as Cu 1986 T 1/8″, X 540 T 1/8″, and Cu 0860 E 1/16″ 3F from BASF. Catalysts were cylindrical in shape. Approximate compositions of these catalysts derived from their MSDS forms are listed in Table 1. Detailed experimental parameters and all results of all performed experiments are provided in the Supporting Information.

■ RESULTS AND DISCUSSION

Catalyst Screen. To increase the economic viability of the hydrogenation process, we choose to focus this study on base-metal heterogeneous hydrogenation catalysts and avoided the use of catalysts containing a precious metal. Using six industrial catalysts (Table 1), efforts were focused on maximizing the yield of *n*-butanol while minimizing the amount of product decomposition. An incomplete reaction resulting in the intermediate *n*-butyl *n*-butyrate being present in the product stream is preferable compared to overreaction of *n*-butanol into other products, even if a higher yield of *n*-butanol is achieved in the latter case. This is because *n*-butyl *n*-butyrate can be recycled, whereas side product formation constitutes an irreversible loss of material. Under most of the conditions used in this study (200−400 psi of H_2 above the liquid phase and at a temperature of, or below, 250 °C) both the substrate *n*-butyl crotonate and the intermediate *n*-butyl *n*-butyrate as well as most of the *n*-butanol product are expected to be in the liquid phase.[29]

First, the reduction of *n*-butyl crotonate to 2 mol of *n*-butanol promoted by each one of the six hydrogenation catalysts was evaluated under the identical conditions of 400 psi H_2 pressure, 250 °C, and a substrate liquid space velocity of 1 h^{-1} through the hydrogenation apparatus (Table 2, Experiments 1−7). The highest yields of *n*-butanol were obtained using the PRICAT CZ 40 catalyst [A] (75−86%, experiments 1 and 2), whereas the Cu 0860 catalyst provided the lowest amount of *n*-butanol (58%, experiment 7) in the product stream.

Each of the catalysts was also screened (Table 2, Experiments 8−15) at a 50 K lower temperature (200 °C), while keeping all other parameters constant, to determine the effect of temperature onto the hydrogenation reaction. In general, the lower temperature resulted in an increased amount of *n*-butanol being present in the product stream and a decreased formation of other materials. This suggests that pathways converting *n*-butanol to the observed side products, vide infra, are more populated at higher temperatures. Under these 200 °C conditions, BASF catalyst Cu 1986 [D] showed the most

Table 2. Comparison of catalysts at two different temperatures[a]

		250 °C (mol %)			200 °C (mol %)	
catalyst	no.	yield *n*-butanol	estimated yield others	no.	yield *n*-butanol	estimated yield others
A	1, 2	86, 75	6, 18	8, 9	75, 69	10, 26
B	3	72	24	10	71	26
C	4	71	26	11	83	12
D	5	67	31	12, 13	90, 86	5, 13
E	6	73	25	14	84	15
F	7	58	39	15	67	18

[a] H_2 pressure = 400 psi, liquid (*n*-butyl crotonate) space velocity = 1 h^{-1}.

potential, providing up to a 90% yield of *n*-butanol (experiments 12 and 13).

Effect of an Increased Temperature. The effects of increasing the reaction temperature past 250 °C were also determined using the PRICAT CZ 40 catalyst [A]. Notably, at 300 °C (Table 3, Experiment 16) a significantly lower amount of *n*-butanol was found to be present in the product stream compared to the experiments performed at lower temperatures. It was accompanied by a large amount of hydrocarbons, the most abundant of which was 3-methyl-heptane; however, C7 hydrocarbons and oxygenates were also observed. The formation of 3-methyl-heptane is noteworthy, since it has been suggested as a suitable replacement of conventional diesel fuel due to its favorable oxidation kinetics.[30]

Table 3. Effect of an increased temperature[a]

		(mol %)		
T (°C)	no.	yield *n*-butanol	estimated yield others	yield 3-methyl heptane
200	8, 9	75, 69	10, 26	nd, nd
250	1, 2	86, 75	6, 18	nd, trace
300	16	28	54	16

[a] PRICAT CZ 40 catalyst [A], H_2 pressure = 400 psi, liquid (*n*-butyl crotonate) space velocity = 1 h^{-1}, nd = not detected.

Effect of an Increased H_2 Pressure. Catalysts PRICAT CZ 40 [A] and Cu 1986 [D] were chosen to study the effect of H_2 pressure on the desired reduction of *n*-butyl crotonate to *n*-butanol (Table 4). Further reactions of *n*-butanol to side products were also found to be effected by pressure (Scheme 2). The effect of H_2 pressure was variable and often dependent on temperature. At 200 °C, an increase of the H_2 pressure from 200 to 400 psi resulted in an increased amount of *n*-butanol present in the product stream of both catalysts (experiments 17 versus 8 and 9 for PRICAT CZ 40 [A] and experiments 19 versus 12 and 13 for Cu 1986 [D]). Likely, a higher H_2 pressure suppresses follow-up reaction pathways of *n*-butanol, such as shifting its dehydrogenation equilibrium to the left side, vide infra (Scheme 2). This trend was not as apparent for the reactions performed at 250 °C. The effect of increasing the gas space velocity was also tested in one experiment by increasing the H_2 flow (experiment 20 versus 12 and 13). A small reduction in *n*-butanol yield was noted in this case.

Effect of Substrate Liquid Space Velocity (Flow Rate). The liquid space velocity used in these experiments was either 1.0 or 0.5 h^{-1} (0.50 or 0.25 cm^3/min actual flow) as measured by the flow of liquid at ambient conditions. However, qualitative observation of the liquid product collected in the gas liquid separator after ~30 min of liquid pumping through the 100 cm^3 of total reactor space at a 0.5 cm^3/min flow rate indicated that the actual liquid space velocity was approximately 6 times higher due to thermal expansion. The influence of the substrate *n*-butyl crotonate liquid space velocity (flow rate through the reactor bed) was investigated under two sets of conditions, both using Cu 1986 as the catalyst (Table 5). Only a small effect on the yield of *n*-butanol was observed. A reduced liquid space velocity (substrate flow rate), i.e., increased residence time in the reactor bed, resulted in less intermediate *n*-butyl butyrate remaining but did not lead to an increase in the amount of *n*-butanol present in the product stream. This finding is consistent with the hypothesis that a lower flow rate allows an increased formation of *n*-butanol, which, however, now also has more time to further react, forming the observed byproducts. In all tests the H_2 flow was significantly higher than the liquid flow, meaning in an industrial process provisions for recycling of excess H_2 must be made. The lack of gaseous coproducts in this reaction results in a mostly pure H_2 exhaust stream which can be reutilized with little additional processing.

Table 4. Effect of an increased H_2 pressure[a]

				(mol %)	
catalyst	no.	$p(H_2)$ (psi)	T (°C)	yield *n*-butanol	estimated yield others
A	17	200	200	54	23
A	8, 9	400	200	75, 69	10, 26
A	18	200	250	77	3
A	1,2	400	250	86, 75	6, 18
D	19	200	200	63	19
D	12, 13	400	200	90, 86	5, 13
D	20	400[b]	200	80	19
D	21	600	200	71	28
D	22	200	250	85	7
D	5	400	250	67	31

[a] Liquid (*n*-butyl crotonate) space velocity = 1 h^{-1}. [b] Gas (H_2) space velocity = 8000 h^{-1}, all other experiments used 6000 h^{-1}.

Further Reactions of *n*-Butanol. In several experiments, in addition to the expected reduction intermediate *n*-butyl *n*-butyrate and the desired reduction product *n*-butanol, several other compounds were detected in the product stream. Their formation can be rationalized via known reactions of *n*-butanol (Scheme 2). The Guerbet reaction of *n*-butanol produces 2-ethyl-hexanal. While we did not observe this particular compound as verified using an authentic sample in a GC-MS comparison, an isomeric compound of it with an identical molecular weight, i.e., a saturated C8 ketone or aldehyde with a molecular formula of $C_8H_{16}O$, was a major byproduct detected via GC-MS in the product stream of several reactions. The Guerbet reaction of *n*-butanol, and *n*-butanal formed from it via a facile dehydrogenation, has been previously observed under reaction conditions similar to ours.[31−33] Additionally, at temperatures above 150 °C acidic heterogeneous catalyst supports such as Al_2O_3 and SiO_2 are known to catalyze the dehydration of *n*-butanol to 1-butene, which can then further react to form products such as *cis*-2-butene, *trans*-2-butene, di-*n*-butyl ether, and *n*-butyl-*sec*-butyl ether.[34−38] All intermediate reactions in the proposed pathway for the formation of 3-methyl-heptane are known to occur under similar conditions to the ones employed in these experiments.[39−42]

Scheme 2. Proposed pathways for the formation of observed byproducts

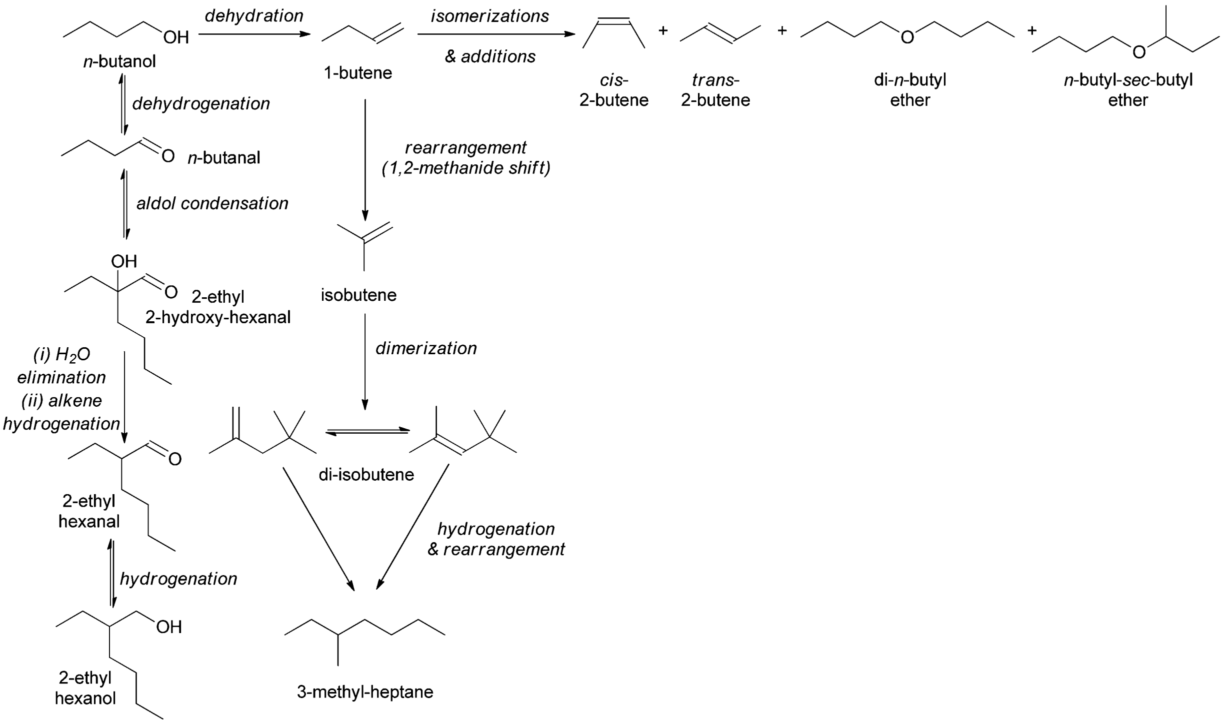

Table 5. Effect of substrate liquid space velocity (flow rate)[a]

				(mol %)	
BuCr liquid space velocity[b] (h^{-1})	no.	T (°C)	BuBu (wt %)	yield n-butanol	estimated yield others
0.5	23	200	0.6	89	10
1.0	12, 13	200	4.9, 0.9	90, 86	5, 13
0.5	24	250	0.6	65	34
1.0	5	250	1.7	67	31

[a] Cu 1986 catalyst [D], H_2 pressure = 400 psi. [b] In our reactor, 0.5 h^{-1} = 0.25 cm^3/min and 1.0 h^{-1} = 0.5 cm^3/min.

■ CONCLUSIONS

In this study we demonstrate that *n*-butanol can be synthesized from *n*-butyl crotonate. This reaction is a key component and a step forward in the overall proof-of-concept efforts to convert poly-3-hydroxybutyrate (P3HB) containing biomass, such as P3HB containing switchgrass, to bio-*n*-butanol (Scheme 1). We have previously demonstrated proof-of-concept work to convert P3HB containing switchgrass biomass to crotonic acid employing mild pyrolysis conditions[15,18] and have made significant advances towards the production of this biopolymer in switchgrass with P3HB levels of up to 7.7% dwt achieved in leaf tissue.[14] The optimized conditions for the reduction of neat *n*-butyl crotonate to *n*-butanol are a hydrogen pressure of 400 psi, a reaction temperature of 200 °C, a substrate liquid space velocity of 1 h^{-1}, and a CuO-containing catalyst, such as the commercially available BASF-Cu 1986. These reaction conditions provide a yield of *n*-butanol in the high 80s percentage.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, apparatus description, and sample product gas chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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The authors declare the following competing financial interest(s): D.S. and K.D.S. are employees of Metabolix, Inc.

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