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Oxidative Decarboxylation of Short-Chain Fatty Acids to 1-Alkenes**

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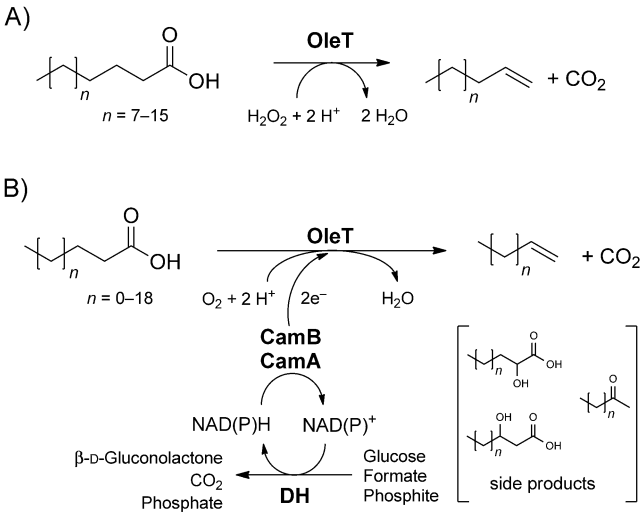
Abstract: *The enzymatic oxidative decarboxylation of linear short-chain fatty acids (C4:0–C9:0) employing the P450 monooxygenase OleT, O_2 as the oxidant, and NAD(P)H as the electron donor gave the corresponding terminal C_3 to C_8 alkenes with product titers of up to 0.93 g L^{-1} and TTNs of >2000. Key to this process was the construction of an efficient electron-transfer chain employing putidaredoxin CamAB in combination with NAD(P)H recycling at the expense of glucose, formate, or phosphite. This system allows for the biocatalytic production of industrially important 1-alkenes, such as propene and 1-octene, from renewable resources for the first time.*

Over the past decades, increasing efforts were undertaken to transform biomass into chemical compounds to provide a sustainable alternative to an oil-based chemical industry.[1,2] The industrial production of organic compounds currently proceeds via few intermediates, such as short-chain olefins and aromatic compounds.[3] In contrast, terminal alkenes play only a marginal role in biosynthesis.[3d] For the synthesis of 1-alkenes, saturated fatty acids (FAs; C*x*:0) are ideal starting materials as they contain carbon in low oxidation states and can be obtained in large quantities from natural resources. Various methods exist for the chemical synthesis of 1-alkenes (≥C9) from saturated FAs, but they usually require metal-based catalysts and high temperatures (>130 °C).[4] In 2011, Rude et al. reported the first enzymatic oxidative decarboxylation of saturated long-chain FAs (C16:0, C18:0, C20:0) into terminal olefins employing the P450 monooxygenase OleT and H_2O_2 as the oxidant (Scheme 1, path A; Table 1, entry 1).[5] Soon thereafter, the crystal structure of OleT was solved, and the substrate scope was expanded to C12:0 (Table 1, entries 2 and 3).[6] Liu et al. replaced H_2O_2 by an enzymatic electron-transfer system based on NADPH with which OleT can utilize O_2 as the oxidant;[6b] the problematic peroxide shunt is thus avoided.[7] Despite some differences in activities, α- and β-hydroxylations occurred as side reactions.[5,6,7c] A non-heme iron oxidase[8] was recently found to catalyze the decarboxylation of FA C10:0; however, total turnover numbers (TTNs) and productivities remained low (TTN ≤ 6.5, TOF ≤ 3.6 min^{-1} with C12:0 as the substrate) and the substrate range narrow (FAs C10:0–C14:0). Photobiocatalytic H_2O_2 formation led to similarly poor results with OleT (Table 1, entry 4).[7c] In this study, we developed a biocatalytic system to achieve the efficient decarboxylation of short-chain FAs, including butyric acid (Scheme 1, path B).



Scheme 1. Oxidative decarboxylation of saturated FAs to 1-alkenes with OleT. Path A: Decarboxylation of long-chain FAs (C12:0–C20:0) using H_2O_2 via the peroxide shunt. Path B: Enzymatic redox cascade process for the decarboxylation of FAs (C4:0–C22:0) using O_2 with NAD(P)H recycling. DH = dehydrogenase.

Preliminary experiments with purified OleT and H_2O_2 as the oxidant resulted in significantly reduced catalytic activities on stearic (C18:0) and palmitic acid (C16:0) compared to reported values (Table 1, entries 5 and 6; see also the Supporting Information, Table S2),[5] whereas elevated H_2O_2 concentrations (>400 μM) led to visible protein precipitation. Thus far, $CYP_{BS\beta}$ and $CYP_{SP\alpha}$ are the only P450 monooxygenases among >20000 CYPs known to operate efficiently as peroxygenases.[7b,9] OleT displayed the highest productivity at a H_2O_2 concentration of 400 μM with a maximum TON of 72 (Table 1, entry 5). Fed-batch supplementation of H_2O_2[7a,10] reduced enzyme inactivation (TON = 99), but still resulted in low conversions (<3%; Table 1, entry 6). When electron-transfer components from spinach and putidaredoxin CamAB were used instead (Table 1, entries 7–9),[11] the decarboxylation of FA C18:0 with O_2 as the oxidant was improved (TTN = 2096; Table 2, entry 3). A lower CamAB concentration was found to be optimal for higher conversions (Figure S10). Although NAD(P)H can be oxidized by

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Table 1: Comparison of redox systems for the decarboxylation of FAs with OleT.[a]

Entry	OleT [μM]/ substrate [mM]	Oxidant/ electron source	1-Alkene [μM]	TOF [min^{-1}]	TON	Ref.
1	0.5/0.2 (C16:0)	H_2O_2 batch	max. 18	ca. 7	n.r.	[5]
2	4.6/0.012 (C20:0)[b]	H_2O_2 batch	n.r.	10020[b]	n.r.	[6a]
3	1/0.2 (C14:0)	H_2O_2 batch	194	1.1	194	[6b]
4	200/0.5 (C18:0)[c]	EDTA/FMN/*hν*	ca. 375	0.02	2.5	[7c]
5	0.32/1 (C18:0)	H_2O_2 batch[d]	23	n.d.	72	this study
6	0.32/1 (C18:0)	H_2O_2 fed-batch[e]	31	n.d.	99	this study
7	0.32/1 (C18:0)	O_2/NADPH[f]	124	n.d.	391	this study
Entry	Reaction time [min]	Oxidant/ electron source	1-Alkene [μM] C18:0/C16:0	TOF [h^{-1}] C18:0/C16:0	TON C18:0/C16:0	Coupling [%] C18:0/C16:0
8	150[g]	O_2/1 mM NADPH	118±23/33	47/13	118/33	11/3
9	60[g]	O_2/1 mM NADH	20±2/9	20/9	20/9	2/1
10	150	1 mM H_2O_2[h]	53±15/29	21/12	53/29	5/7
11	150	control[i]	0	0	0	0

[a] Entries 5–7 (duplicate experiments): 1 mM substrate (C18:0), 0.5% EtOH (v/v), purified OleT (1 μM), KPi buffer (pH 7.5, 0.1 M). Entries 8, 9, and 11 (triplicate experiments): 1 mM substrate (C18:0, C16:0), 2.5% EtOH (v/v), purified OleT (1 μM), CamAB (0.05 U mL^{-1}), catalase (1200 U mL^{-1}), KPi buffer (pH 7.5, 0.1 M). Entry 10 (triplicate experiment): 1 mM substrate (C18:0, C16:0), 2.5% EtOH (v/v), purified OleT (1 μM), KPi buffer (pH 7.5, 0.1 M) and H_2O_2. [b] Stop-flow kinetics measured over 30 s, no products characterized. [c] Cell-free lysates used. [d] H_2O_2 (1 mM), 16 h, 25 °C. [e] 27 × H_2O_2 (25 μM) every 15 min, 50 °C. [f] Spinach ferredoxin reductase/ferredoxin. [g] Time required to fully oxidize the cofactor. [h] Strong protein precipitation observed. [i] One of the following components was omitted: OleT, H_2O_2, CamAB, NAD(P)H, or substrate (C18:0).

Table 2: Oxidative decarboxylation of FA C18:0 by OleT with various electron sources.[a]

Entry	Electron source	Redox partner	OleT [μM]	1-alkene [mM]	TTN
1	D-glucose	GDH-CamAB	1.5	1.02	680
2	Na_2HPO_3	PDH-CamAB	1.5	2.61	1739
3	NH_4HCO_2	FDH-CamAB	1.5	3.14	2096
4	NH_4HCO_2	FDH-CamAB	3	1.42[b]	473
5	NH_4HCO_2	FDH-CamAB[b]	3[c]	1.57	522
6	D-glucose	GDH (no CamAB)	3	0	0

[a] Reaction conditions: 5 mM FA (C18:0), 2.5% EtOH, purified OleT, CamAB (0.05 U mL^{-1}), catalase (1200 U mL^{-1}), KPi buffer (pH 7.5, 0.1 M), NAD(P)H (200 μM), 1 mL scale, RT, 170 rpm, 24 h; GDH (12 U mL^{-1}) and D-glucose (100 mM) or FDH (2 U mL^{-1}) and NH_4HCO_2 (100 mM) or PDH (0.2 U mL^{-1}) and Na_2HPO_3 (100 mM). [b] Reaction time: 8 h. [c] The cell-free lysate (53 mg) contains the electron-transfer system Fdr/Fdx from *E. coli*.[6b]

CamAB in the absence of a suitable electron acceptor,[12] no formation of H_2O_2 could be detected after full oxidation of 1 mM NADH, indicating a direct electron transfer from CamAB to OleT and ruling out potential inactivation by H_2O_2. Accordingly, the absence of catalase had no significant impact on the productivity of the system (Table S3).

Despite the higher oxidation rate of NADH (10 times that of NADPH, see Table S2), the coupling of electrons was 3–5.5 times lower (Table 1, entries 8 and 9). The lower productivity and coupling efficiency observed with FA C16:0 (Table 1, entries 8–10) suggest a preference of OleT for long-chain FAs.[5,7c,14]

For elevated substrate concentrations, a NAD(P)H regeneration system was employed: A glucose dehydrogenase (GDH) based system led to increased conversions (36% with 1 mM FA C18:0, Table S3, entry 1) and higher TTNs (up to 389 with 10 mM FA C18:0), with comparable product concentrations from both C18:0 and C16:0 of 1.16 mM (0.27 g L^{-1}) of 1-heptadecene and 1 mM (0.21 g L^{-1}) of 1-pentadecene after 24 hours (Table S3). However, inhibitory effects of gluconic acid (a by-product of NAD(P)H regeneration) at concentrations as low as 10 mM led to reduced productivity (Figure S12), which may be attributed to competitive binding of gluconic acid to the active-site residue R245 in OleT.[6a] Alternative systems based on phosphite dehydrogenase (PDH; NADPH-dependent)[15] and formate dehydrogenase (FDH; NADH-dependent)[16] proved to be more efficient: 1-Heptadecene concentrations of 2.6 mM (0.62 g L^{-1}) and 3.1 mM (0.75 g L^{-1}) were obtained from 5 mM FA C18:0 (52% and 62% conversion, respectively), yielding the highest TTN values reported for OleT thus far (1739 and 2096, respectively; Table 2, entries 2 and 3). Compared to a previously published whole-cell reaction system,[6b] the FDH-driven system gave a 9.5 times higher product titer (930 mg L^{-1} 1-alkene) and a 21 times larger volumetric productivity of 42.5 mg L^{-1} h^{-1} of the 1-alkene over a reaction time of eight hours (Table 2, entry 4, vs. 2 mg L^{-1} h^{-1}).[8] Reducing the NADH concentration (from 200 to 10 μM) had no impact on product formation (Table S4), and the product from C18:0 was isolated in 47% yield on the 50 mL scale. Freeze-dried cell-free lysate (CFL) was also tested as a stable "off-the-shelf" preparation and allowed the production of 0.37 g L^{-1} 1-heptadecene without the need for protein purification (1565 μM, 31% conversion; Table 2, entry 5).

Next, the FA chain length was varied from C4:0 to C22:0 (Table 3). The reactions were performed at 4 °C to prevent the loss of volatile short-chain olefins. This set-up resulted in surprisingly high activity levels, especially with FA C12:0 (Table 3, entry 6). In contrast to the OleT–RhFRed fusion system,[6b] the highest product concentrations were obtained with FA C18:0 at room temperature (0.93 g L^{-1}, Table 3,

Table 3: Substrate scope of the OleT/CamAB/FDH cascade process at room temperature and 4 °C.[a]

Entry	FA	1-Alkene [mM] RT/4 °C	1-Alkene [%] RT/4 °C	α-OH + β-OH + 2-alkanone [%][b] RT/4 °C
1	C22:0	n.d./n.d.	>99/93[c]	0/7
2	C20:0	n.d./n.d.	>99/>99[c]	0/0
3	C18:0	3.88/2.45	85/92	15/8
4	C16:0	1.11/2.06	69/80	31/20
5	C14:0	0.55/1.24	59/78	41/22
6	C12:0	0.27/3.26	>99/73	0/27
7	C11:0	0/0.19	0/>99	0/0
8	C10:0	0.04/0.07	>99/>99	0/0
9	C9:0	1.83/1.34	48/38	52/62
10	C8:0	2.45/2.25	>99/>99[d]	n.d./n.d.
11	C7:0	1.29/0.95	>99/>99[d]	n.d./n.d.
12	C6:0	1.17/0.77	>99/>99[d]	n.d./n.d.
13	C5:0	0.83/n.d.	>99[c]/n.d.	n.d./n.d.
14	C4:0	0.49/n.d.	>99[c]/n.d.	n.d./n.d.

[a] Reaction conditions are described in the Experimental Section. [b] GC area. [c] A large amount of substrate was recovered (see the Supporting Information). [d] Detected by headspace GC-MS analysis. n.d.: not determined.

entry 3). Remarkably, short-chain FAs (< C9) could be decarboxylated, covering the whole range from FAs C11:0 to C4:0 (0.04 to 2.45 mM 1-alkene formed) for the first time. Head-space analysis by GC-MS from reactions with short-chain FAs (C8:0-C4:0) confirmed the formation of the respective terminal olefins (see the Supporting Information for details). Yields were strongly dependent on the reaction temperature and the substrate chain length, with the highest reactivity for FA C18:0 at room temperature (max. 3.88 mM from 10 mM C18:0) and C12:0 as the best substrate at 4 °C (3.26 mM 1-undecene).

Overall, the conversions of FAs C10:0–C16:0 were higher at 4 °C. With this system, propene can be obtained from butyric acid in a single step, contradicting the previously postulated specificity of OleT for long-chain FAs.[5,6,7c,14] Long-chain FAs (C22:0–C14:0) are assumed to mainly interact with the substrate channel,[6a] whereas smaller substrates are accommodated in the binding pocket, as shown for the related enzyme $CYP_{BSβ}$.[17] FAs with intermediate chain lengths (C10:0–C11:0) do not bind effectively and therefore are poor substrates (Table 3, entries 7 and 8). Overall, decarboxylation was the predominant reaction (86–99% selectivity with FAs C18:0–C22:0), whereas formation of the α/β-hydroxylated products was strongly dependent on chain length and reaction temperature (62% α/β-hydroxylation with FA C9:0 at 4 °C). Furthermore, traces of the 2-alkanones were detected with FAs C16:0 and C18:0, presumably arising from enzymatic "over-oxidation" of the β-hydroxy acids (as shown for CYP52A17),[18] followed by spontaneous decarboxylation of the corresponding β-ketoacids.

The successful decarboxylation of short-chain FAs can be explained by the more favorable reaction conditions: 1) High substrate loadings (up to 10 mM vs. 200–500 μM)[5,6,7c] overcome low substrate affinities, as shown for P450 BM3,[19] and 2) electrons are provided in excess by a class I electron-transfer system. The good compatibility of CamAB and OleT is likely due to the similar coordination of the proximal cysteine thiolate in OleT and $P450_{Cam}$ in the ferrous state (Fe^{2+}),[6a] which enables the binding of O_2 to the heme iron.[20] Most bacterial P450 enzymes rely on class I electron-transfer systems,[13b] which explains the improved catalytic performance of OleT in combination with CamAB compared to previously described systems (OleT–RhFRed or Fdr/Fdx).[6b]

The significantly improved performance of OleT with O_2 as the oxidant in combination with NAD(P)H as the electron donor, as opposed to H_2O_2 alone, raises doubts on its initial classification as a peroxygenase.[5] For peroxygenases to function as such in their natural environment, either compartmentalization within the bacterial host (e.g., in peroxisomes) or extracellular secretion, which is typical for fungal heme-peroxygenases, is required.[10a,21] As the use of O_2 as the oxidant and NAD(P)H as the electron donor in the "biosynthetic" redox cascade resulted in drastically improved TTNs, OleT seems to act as a monooxygenase.

In conclusion, with the present system, the oxidative decarboxylation of fatty acids by OleT proceeded with product titers of up to 0.93 $g\,L^{-1}$ and TTNs of greater than 2000 at low catalyst loadings (0.06%). Propene and 1-butene were thus obtained from short-chain FAs in a direct biocatalytic process for the first time.

Experimental Section

General procedure for the decarboxylation of fatty acids (C22:0–C4:0): The reaction mixture contained purified OleT (3 μM for C22:0–C14:0, 6 μM for C12:0–C4:0), CamAB (0.05 $U\,mL^{-1}$), catalase (1200 $U\,mL^{-1}$), FA (10 mM), EtOH (5%), KPi buffer (pH 7.5, 0.1M), NADH or NAD^+ (200 μM), FDH (2 $U\,mL^{-1}$), and NH_4HCO_2 (100 mM). All reactions with FAs C22:0 to C6:0 were performed at atmospheric pressure, room temperature (or 4 °C) on a 1 mL scale at 170 rpm for 24 h. FAs C5:0 and C4:0 were converted at room temperature on a 10 mL scale under continuous stirring.

Keywords: 1-alkenes · biocatalysis · fatty acids · OleT · oxidative decarboxylation

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