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Horse Liver Alcohol Dehydrogenase-Catalyzed Oxidative Lactamization of Amino Alcohols

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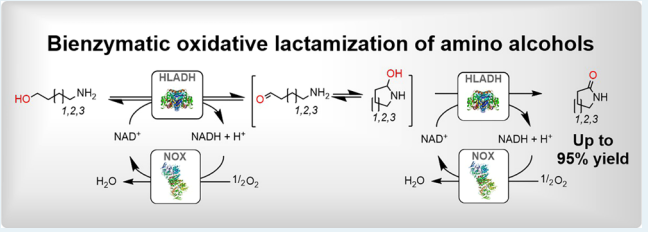
Supporting Information

ABSTRACT: A direct synthesis of lactams (5-, 6-, and 7-membered) starting from amino-alcohols in a bienzymatic cascade is reported. Horse liver alcohol dehydrogenase together with the NADH oxidase from *Streptococcus mutans* were applied for the oxidative lactamization of various amino alcohols. Crucial parameters for the efficiency of this cascade reaction were elucidated. This report represents a direct approach for biocatalytic oxidative lactamization reaction.



KEYWORDS: *lactams, enzymatic cascades, oxidoreductases, cofactor regeneration, horse liver alcohol dehydrogenase*

Lactams are monomers of polyamides/nylons, which are commonly used polymer materials in our daily life and industry.[1] Apart from that, lactams are also used as raw materials in the pharmaceutical industry and as laundry detergents for bleaching.[2] To date, the industrial synthesis of most of the lactams applies chemical synthesis methods established decades ago that need expensive metal catalysts, aggressive chemicals, high temperature, and depend on nonrenewable resources.[1,3] ε-Caprolactam (CPL), for example, is mostly produced from cyclohexanone, which itself originates from cyclohexane or phenol.[2a]

Synthesis of ω-amino acid (esters) as lactam precursors has attracted increasing interest in the biocatalysis community. More recently, Schmid and co-workers reported on direct terminal amino-functionalization of nonactivated C−H bonds catalyzed by a designer microorganism containing an alkane monooxygenase AlkBGT and ω-transaminase CV2025.[4] Kroutil and co-workers[5] developed a multienzymatic route to nylon-6 monomer 6-aminohexanoic acid by combining an esterase, a primary alcohol dehydrogenase, alanine dehydrogenase, and ω-transaminase starting from ε-caprolactone.

A recent study on the synthesis of lactams was reported by Turner and co-workers. Amino alcohols were first oxidized to amino aldehydes by a galactose oxidase (GOase) variant coupled with a molybdenum-dependent xanthine dehydrogenase (XDH)-catalyzed lactam formation.[6] It was elucidated that the reaction pH plays an important role in the cyclization of amino aldehyde intermediates, as the conversion increased with increasing pH values from 7.0 to 8.5.[6] Very recently, also the further chemical oxidation of monoamine oxidase (MAO-N)-derived imines into lactams was demonstrated.[7] Similarly, Chen and co-workers reported a whole-cell oxidation of some amines to lactams.[8]

So far, the most studied enzymatic lactamization method is lipase- or esterase-catalyzed reversible intramolecular aminolysis with amino esters or amino carboxylic acids.[1,9] The oxidative lactamization of amino alcohols represents an attractive alternative direct approach to obtain lactams. Especially transition metal-catalyzed approaches have been reported in recent years.[10] The transition metal-catalyzed oxidative lactonization, despite its versatility and conceptual beauty, however is plagued by a poor selectivity.

Recently, we have developed a biocatalytic route for the oxidative lactonization of diols to lactones.[11] Therefore, we asked ourselves whether this methodology may be applicable for the oxidative lactamization of amino alcohols (Scheme 1). In analogy to the transition metal (TM)-catalyzed oxidative/dehydrogenative lactamization of amino alcohols, we proposed an alcohol dehydrogenase (ADH)-catalyzed, NAD(P)$^+$-dependent oxidative pathway.

In a first set of experiments, we evaluated ADHs using 4-amino-1-butanol as the model substrate. In a spectrophotometric assay, the ADHs from horse liver (HLADH), *Thermus* sp. (TADH) and *Thermoanaerobacter ethanolicus* (*Te*SADH) showed significant activity in the oxidation of 4-amino-1-butanol (Figure 1).

Among the ADHs evaluated in this preliminary screening, the well-known HLADH excelled by its catalytic activity. For further studies, we focused on HLADH as the oxidation catalyst. We suspected the pH of the reaction mixture having a significant effect on the performance of the enzymatic oxidative

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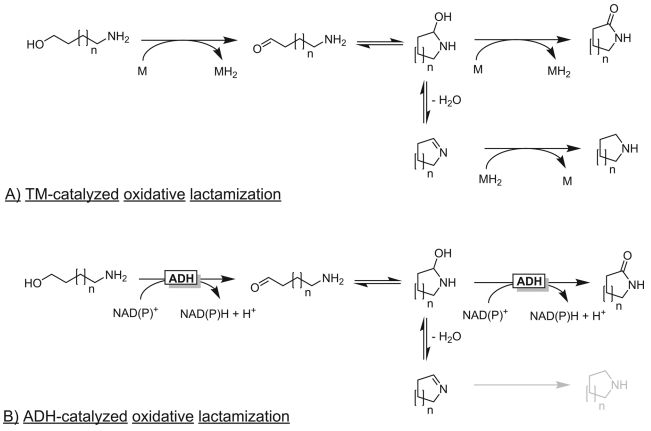
Scheme 1. Oxidative Lactamization of Amino Alcohols Using Transition Metal (TM) Catalysts (A) or Alcohol Dehydrogenases (ADH) (B) as Hydride Abstraction Catalysts[a]



[a]In both cases, the intermediate hemiaminal can undergo either a second dehydrogenation step or a dehydratization step. While in case of the TM-catalyzed reaction also reduction of the intermediate imine occurs, this is not observed in case of ADH-catalyzed reactions.

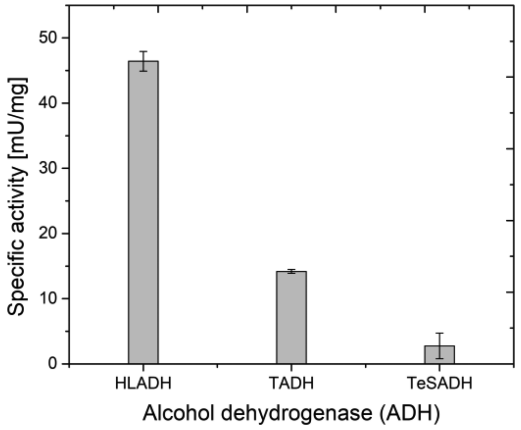


Figure 1. Screening of ADHs for the oxidation of 4-amino-1-butanol. Reaction conditions: c(4-amino-1-butanol) = 10 mM, $c(NAD(P)^+)$ = 1 mM, c(ADH) = 0.27 μM−8.75 μM (purified enzyme), 50 mM pH 9.0 CHES (N-Cyclohexyl-2-aminoethanesulfonic acid) buffer, 25 °C, and duplicate measurements. $NADP^+$ was added for the reaction with *Te*SADH.

lactamization reaction. First, because, like any other enzymatic reactions, the HLADH-catalyzed oxidation is pH-dependent. Second, the intramolecular ring-closure necessitates deprotonated amines to function as nucleophile. Therefore, we performed a range of HLADH-catalyzed oxidations of 4-amino-1-butanol between pH 7 and 11 and analyzed the reaction mixtures for their content in the desired γ-lactam (Figure 2).

Indeed, the yield of γ-lactam steadily increased with increasing pH at least until pH 11. Under the analyzed conditions, the activity of HLADH steadily increased with increasing pH up to pH 9 and then decreased at more alkaline conditions (Figure S5 of the Supporting Information, SI). Hence, the still increasing productivity at elevated pH values may most likely be attributed to the decreasing protonation state of the amine (Figure 2), which is reasonable considering that the intramolecular ring-formation necessitates the

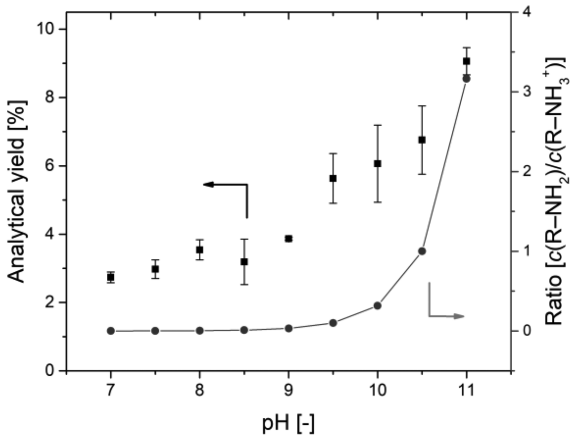


Figure 2. Effect of pH on the lactam formation (black squares) with stoichiometric amounts of NAD^+ and the ratio of $R-NH_2$ to $R-NH_3^+$ (dark gray circles) based on the pH. Reaction conditions: c(4-amino-1-butanol) = 10 mM, $c(NAD^+)$ = 20 mM, c(HLADH) = 0.1 mg/mL (0.01 U/mL, 2.5 μM, purified enzyme), buffer: KPi (50 mM, pH 7.0−8.0), CHES (50 mM, pH 8.5−10.0), sodium bicarbonate (50 mM, pH 10.5−11.0), 900 rpm, 25 °C, and 24 h. Duplicate reactions (1 mL in total) run in 1.5 mL glass-vials. The p*K*a value of $R-NH_2$/$R-NH_3^+$ was chosen as 10.5 as an average value.

nucleophilic, nonprotonated amine functionality. Additionally, the protonation state may also affect the kinetic characteristics of the enzyme with the amino alcohol. This assumption is supported by the rather low affinity of HLADH toward 4-amino-1-butanol at lower pH values. The kinetic assay done at pH 7 revealed a K_M value for the amino alcohol as 34.9 (±10.4) mM (the simulation fitting is suboptimal), whereas that of at pH 11 was 3.8 (±0.30) mM (Table 1, Figure S7). It is worth to mention here that the effect of pH on enzyme affinity toward target substrate(s) was documented in the literature.[12]

So far, stoichiometric amounts of NAD^+ were used (i.e., 2 equiv of NAD^+ with respect to 4-amino-1-butanol). This obviously is not desirable from an economic point-of-view,[13] which is why we evaluated the water-forming NADH oxidase from *Streptococcus mutans* (*Sm*NOX)[14] for the in situ NAD^+ regeneration (Scheme 2).

Re-evaluation of the pH range of this bienzymatic reaction cascade exhibited an optimum between pH 8 and 10 (Figure S16), which can be attributed to the rather narrow pH range of *Sm*NOX (Figure S10) compared to that of HLADH (Figure S5). Hence, this pH range (8−10) was a compromise between oxidation and reduction. The *Sm*NOX showed the highest activity at pH 7 (100% relative activity) whereby >70% relative activity was observed between pH 6 and 8. When it comes to the stability, *Sm*NOX showed >60% residual activity between pH 6 and 10 (Figure S11), which was higher than the stability of HLADH in this pH range (Figure S6).

More interestingly, however, was that, under otherwise identical reaction conditions, the in situ NAD^+ regeneration system using catalytic amounts of NAD^+ (5 mol %) excelled over the reaction using stoichiometric NAD^+—even in buffer with an optimized ionic strength value (Figure S14)—by more than doubled yield in γ-lactam (Figure S15) (17% vs 6.7%). Currently we are lacking a fully plausible explanation for this observation. Possibly, the fast reoxidation of NADH eliminated inhibitory effects of NADH on the HLADH-catalyzed oxidation.

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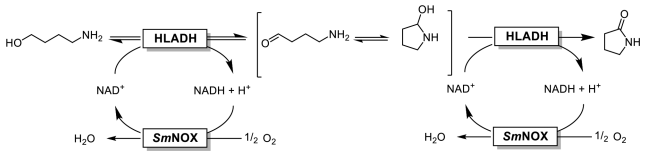
Table 1. Kinetic Parameters of HLADH Toward Amino Alcohols

substrate	V_{max} (U/mg)	$K_{M,\ sub}$ (mM)	$K_{i,\ sub}$ (mM)	$K_{i,\ sub}/\ K_{M,\ sub}$
4-amino-1-butanol[a]	0.82 ± 0.07	34.9 ± 10.4	–	–
4-amino-1-butanol[b]	0.68 ± 0.02	17.8 ± 2.2	–	–
4-amino-1-butanol[c]	0.73 ± 0.01	3.77 ± 0.30	–	–
5-amino-1-pentanol[b]	3.35 ± 1.57	29.6 ± 16.9	9.33 ± 5.30	0.32
6-amino-1-hexanol[b]	7.64 ± 1.18	6.71 ± 1.48	11.0 ± 2.63	1.64

[a]pH 7. [b]pH 9. [c]pH 11.

Scheme 2. In Situ Regeneration of NAD^+ with *Sm*NOX in the HLADH-Catalyzed Oxidative Lactamization of 4-Amino-1-butanol to γ-Butyrolactam



In the following experiments using a Design of Experiment (DoE) approach, eight parameters (i.e., T, O_2, pH, *c*(4-amino-1-butanol), *c*(HLADH), *c*(*Sm*NOX), *c*(NAD^+), and reaction time) for the lactamization reaction were screened and the key ones (pH, *c*(HLADH), and *c*(NAD^+)) were identified (Table S6). These key reaction parameters were then fixed to 8 (from Figure S16), 1 mg/mL (0.1 U/mL, 25 μM) and 1 mM, respectively, in the further experiments. The pH value of 8 verified the activity and stability data of ADH and NOX at this pH.

Next, we explored the substrate scope of the oxidative lactamization system. Two further aliphatic amino alcohols (5-amino-1-pentanol and 6-amino-1-hexanol) and two aromatic amino alcohols ((2-(2-aminoethyl)phenyl)-methanol and (2-(aminomethyl)phenyl) methanol) were evaluated. Under the optimized conditions with higher concentrations of both enzymes, the analytical yield of γ-lactam could reach 95% in 24 h. While 5-amino-1-pentanol and 6-amino-hexanol, the two homologues of 4-amino-1-butanol, were readily converted with much lower yields of 38% and 14% (albeit at lower rates, Figure 3). The two aromatic amino alcohols were converted very sluggishly (data not shown) and hence not included in the further analyses. The turnover number (TON) value of HLADH (mol_{lactam}/mol_{HLADH}) for the synthesis of γ-butyrolactam was 380, whereas the TON values for the synthesis of δ-valerolactam and ε-caprolactam were found as 152 and 56, respectively.

A further kinetic analysis of the three aliphatic substrates revealed that the "best substrate", i.e., 4-amino-1-butanol, which gave the highest yield in Figure 3 was not most readily converted by HLADH. As shown in Table 1, both V_{max} and K_M values for this substrate were less favorable as compared to the other two substrates. However, this substrate, in contrast to the others, did not exhibit any excess substrate inhibition (Figure S7, Table 1).

Furthermore, formation of the five-membered ring of γ-lactam is sterically more favored as compared to six- and especially seven-membered rings.[9a] Hence, the effect of substrate inhibition may also be increased by less favorable ring-closure kinetics with increasing chain-length.

Next, we performed the synthesis of γ-butyrolactam in 0.1 L scale using cell free extracts of HLADH and *Sm*NOX. The isolated crude product (40 mg) was analyzed by NMR (^1H and ^{13}C; Figures S25 and S26), which proved a simple yet efficient synthesis of lactam starting from the amino alcohol using two enzymes.

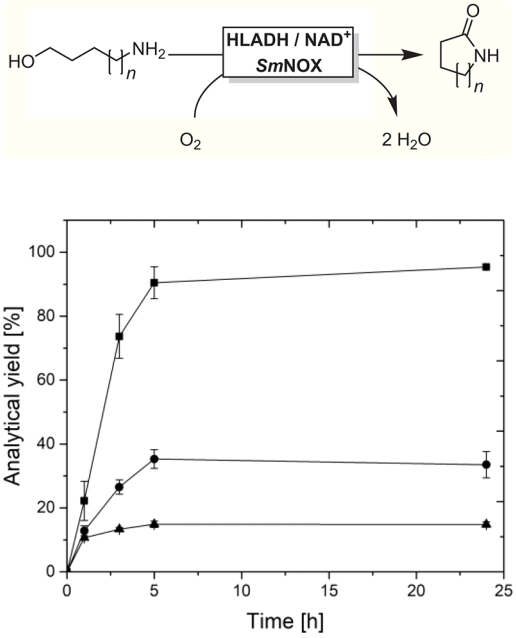


Figure 3. HLADH-catalyzed oxidative lactamization of amino alcohols. Reaction conditions: *c*(amino-alcohol) = 10 mM, *c*(NAD^+) = 1 mM, *c*(HLADH) = 1.0 mg/mL (0.1 U/mL, 25 μM, purified enzyme), *c*(*Sm*NOX) = 1.0 mg/mL (5 U/mL, 20 μM, purified enzyme), buffer: pH 8.0 KPi (50 mM), 25 °C, 900 rpm. Square = γ-butyrolactam, circle = δ-valerolactam, and triangle = ε-caprolactam. Duplicate reactions (1 mL in total) run in 1.5 mL glass-vials.

Here, we present (to the best of our knowledge) the first study on the direct synthesis of lactams from amino alcohols coupling an alcohol dehydrogenase and a NADH oxidase in a bienzymatic cascade. The γ-lactam (5-membered) was synthesized with 95% analytical yield, whereby the yield decreased with increasing ring-size (38% for 6-membered and 14% for 7-membered lactam), as also known from the literature for ring-closure reactions. The future work will focus on using nonconventional media to increase the volumetric productivities of (achiral and chiral) lactam synthesis to industrially relevant conditions. The well-known low process stability of NOXs might seem to hamper the technical scale application whereas newly identified or newly designed NOXs could enable the use of these interesting enzymes in larger scale.[15] However, there might also exist other potential ADHs for direct synthesis of lactams, which will be explored in our future experiments.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02355.

General, heterologous expression and purification of enzymes, analysis of ADH and *Sm*NOX activity, characterization of HLADH and *Sm*NOX, HLADH-catalyzed lactamization of amino alcohol with stoichiometric and in situ NAD^+, design of experiment for evaluation of key parameters of the reaction, hydrolysis of lactam products, gas chromatography methods, NMR spectra of synthesized γ-butyrolactam, and additional references (PDF)

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Notes

The authors declare no competing financial interest.

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