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Dynamic modeling of the chemo-enzymatic epoxidation of α-pinene and prediction of continuous process performance

Janine Meyer-Waßewitz, Deniz Elyorgun, Carsten Conradi, Anja Drews*

HTW Berlin — University of Applied Sciences, Engineering II, School of Life Science Engineering, Wilhelminenhofstraße 75A, 12459 Berlin, Germany

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ABSTRACT

For the first time, a valid and reliable deterministic model for the description and prediction of the reaction dynamics of the chemo-enzymatic epoxidation in a continuous stirred tank reactor (CSTR) is presented. The model covers the different steps of the reaction cascade and all kinetic constants were found to be uniquely identifiable, which is a prerequisite for trustworthy model predictions. The chemo-enzymatic epoxidation is a multistep reaction, which consists of two consecutive reactions: the lipase-catalyzed peracid formation followed by a Prilezhaev epoxidation, wherein numerous factors govern the product formation. This makes the design of an optimal process particularly challenging and modeling mandatory. To obtain the model structure, the goodness of fit and (practical) parameter identifiability were taken into account. Different mass action kinetics, as well as mechanistic approaches, were investigated. Kinetic constants were fitted to experimental data using a multi-experiment fitting, and the practical identifiability of the estimated constants was shown. The developed CSTR process model, which describes the dynamics of the multistep chemo-enzymatic epoxidation of α-pinene, matched the experimental data very accurately. Moreover, it was successfully verified and validated over a broad range of operating conditions.

1. Introduction

The lipase-mediated epoxidation (Fig. 1) (Björkling et al., 1990) is a safe and environmentally friendly alternative to the traditional chemical epoxidation process. Epoxides are industrially important commodity chemicals and building blocks in organic synthesis (Gusevskaya et al., 1998), which can be produced by the addition of oxygen to alkenes (Sienel et al., 2000). However, the industrial applicability of the lipase-mediated epoxidation is limited by a loss of enzymatic activity due to the presence of oxidizing agents (e.g., H_2O_2). The enzyme *Pseudozyma antarctica* lipase B (formerly *Candida antarctica*, CalB) was found to very effectively mediate the epoxidation of alkenes (Björkling et al., 1992; Björkling et al., 1990; Rüsch gen. Klaas and Warwel, 1997; Warwel and Rüsch gen. Klaas, 1995). However, even the rather stable immobilized CalB becomes deactivated (Orellana-Coca et al., 2005; Törnvall et al., 2007; Yadav and Devi, 2002). A deeper understanding of such complex processes can be achieved by realistic and predictive mathematical models. The mathematical description of biological processes, e.g., biochemical reaction networks, involves ordinary differential equations (ODEs). The identifiability of the estimated model parameters (e.g., kinetic constants) is of outstanding importance w.r.t. model-based predictions (Flassig, 2014; Galvanin et al., 2013; Miao et al., 2011; Raue et al., 2009; Raue et al., 2011).

Abbreviations: CI, confidence interval; CERM, chemo-enzymatic reaction model; CERDM, chemo-enzymatic reaction model with enzyme deactivation; ERM, enzymatic reaction model; MM, Michaelis–Menten; p, phase; PL, profile likelihood; PW, potterswheel; SB, simbiology.

* *Corresponding author.*
E-mail address: J.Meyer@HTW-Berlin.de (J. Meyer-Waßewitz).

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Nomenclature

Symbols

c	Molar concentration (M)
β	Reaction order (–)
Ea	Activation energy (kJ mol^{-1})
F	Frequency factor (mol (L mol^{-1})$^{\beta}$h^{-1} g^{-1}, L h^{-1} g^{-1})
k	Kinetic constant
K	Michaelis–Menten constant (mol L^{-1})
N	Number of data (–)
R	Ideal gas constant (J mol^{-1} K^{-1})
$\dot{R}$	Reaction rate (M h^{-1})
ρ	Mass concentration (g L^{-1})
T	Temperature (°C, K)
t	Time (h)
τ	Residence time (h)
V	Volume (mL)
$\dot{V}$	Volumetric flow rate (mL min^{-1})
Θ	Parameter
y	Data point
χ	Goodness of fit

Subscripts and superscripts

b	By-products
$CalB$	*Candida antarctica* lipase B
D	Deactivation
d	Experimental data
$d1$	Decomposition of PAA
$d2$	Decomposition of PO
E	Epoxidation
F	Forward, mass action kinetics
f	Forward, Michaelis–Menten kinetics
F, β	Forward, mass action kinetics with a nonlinear reaction order β
in	Influent
i	Index
j	Reaction index
k	k-th model value
l	l-th time point
M	Michaelis–Menten
P	α-Pinene
PAA	Peroxyacetic acid
PO	α-Pinene oxide
R	Reversible, mass action kinetics
r	Reversible, Michaelis–Menten kinetics
S	Side

Due to the numerous factors which govern the product formation of the chemo-enzymatic epoxidation, the design of an optimal process is particularly crucial. To obtain such a process, a dynamic model to predict the process performance of the dynamic reaction cascade for different operating conditions is required. So far, no model for the chemo-enzymatic epoxidation, neither for αpinene nor in the CSTR, has been described in the literature. Kinetics have been studied only for parts of the reaction, but other substrates have been used (Bhattacharya et al., 2012; Bhattacharya, 2012; Hilker et al., 2001; Kramer et al., 1994; Yadav and Borkar, 2006; Yadav and Devi, 2002) and practical identifiability has not been considered. A detailed comparison of the kinetic constants obtained in this work with those reported in the literature is presented in Section 3.1.2.

The goal of this study is to develop a practically identifiable model for the chemo-enzymatic epoxidation of α-pinene that can reproduce experimental data and can to some extent be used to predict the process behavior outside of the experimentally investigated regions of the parameter space.

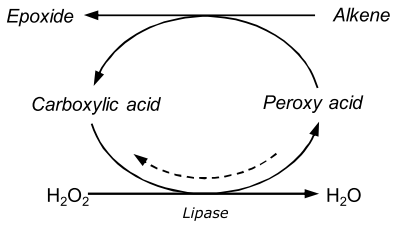

Fig. 1 – Chemo-enzymatic epoxidation: lipase-mediated peroxy acid production, followed by the spontaneous chemical epoxidation.
Adapted from Björkling et al. (1992) and Björkling et al. (1990).

1.1. Previous work

To counterbalance the process limitations, the enzymatic reaction was investigated in fed-batch and continuous stirred tank reactor (CSTR) experiments where the CSTR was found to be superior regarding enzymatic productivity (Meyer et al., 2017b). The reaction was performed in an organic single-phase (osp) solution, which was pre-saturated with the substrate H_2O_2 to avoid (i) direct contact of the enzyme with the highly concentrated aqueous H_2O_2 and (ii) liquid/liquid interfaces, which harm the enzyme (Baldascini and Janssen, 2005; Hailing, 1994; Ross et al., 2000). The continuous osp process was found to enable a high productivity with a reduced demand of enzymes (Meyer et al., 2017a). Finally, the ospCSTR with the optimized operating conditions enabled selectivity, high catalytic productivity (118 $g_{PO}g^{-1}{}_{CalB}$), and high space-time yields (880 $g_{PO}L^{-1}\,d^{-1}$) to the chemo-enzymatic epoxidation of α-pinene (Meyer-Waöewitz et al., 2017). These results and the corresponding experimental data form the basis for the development of the dynamic model (presented in this work), whereof, the model selection criteria were the χ^2/N value (small value denotes a high model fit) and the practical identifiability of the kinetic constants.

2. Materials and methods

2.1. Enzymes and chemicals

Immobilized lipase B from *Pseudozyma antarctica* (formally *Candida antarctica*, CalB immo) was purchased from c-LEcta, Germany. Hydrogen peroxide (50 wt%) and α-pinene ((1S)-(–), 98 %) were purchased from Sigma-Aldrich, Germany. Ethyl acetate (≥ 99.8 %) was obtained from Th. Geyer, Germany.

2.2. Analysis

To determine the concentration of peroxyacetic acid and hydrogen peroxide simultaneously, precolumn derivatization was applied (Pinkernell et al., 1997). The substances were analyzed by HPLC (module 1, Waters, USA) equipped with a LiChrosorb 100-5 RP 18, 25 cm × 4.6 mm column (Knauer, Germany), for further details see Meyer et al. (2017a).

By using gas chromatography, the concentrations of α-pinene and of α-pinene oxide were determined (3800 Varian GC system equipped with a FactorFour™ column VF-5 ms, 30 m, Varian, USA). The injection temperature was 200 °C, see Meyer-Waßewitz et al. (2017).

2.3. Continuous CSTR set-up

The experimental set-up (Fig. 2) consists of a stirred tank (max. volume 0.1 L), two pumps, a propeller stirrer driven by an over-