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Preparative aerobic oxidations with basidiomycetous enzymes: CH-functionalization of adamantane

Tatyana S. Zhuk[a,b,*], Michael Goldmann[a], Julia Hofmann[a], Juliane C.S. Pohl[a], Holger Zorn[a]

[a] Institute of Food Chemistry and Food Biotechnology, Justus Liebig University, Heinrich-Buff-Ring, 58, 35392 Giessen, Germany
[b] Department of Organic Chemistry, Kiev Polytechnic Institute, pr. Pobedy, 37, 03056 Kiev, Ukraine

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ABSTRACT

The potential of basidiomycetous enzymes for selective alkane CH-functionalizations in aqueous media has been disclosed utilizing surface and submerged cultures. A screening displayed the high catalytic activity of *Dichomitus albidofuscus*, *Pholiota squarrosa,* and *Abortiporus biennis* in aerobic oxidations of adamantane as a model hydrocarbon. With isopropanol as a co-solvent, the oxidation was accelerated significantly without changes of the fungal growth. 1-Adamantanol was obtained in 40% preparative yield from the oxidation of adamantane by *D. albidofuscus*. The CH-positional selectivity ($3^\circ/2^\circ = 3.6$) and the deuterium kinetic isotopic effect ($k_H/k_D = 2.25$) values provide evidence for the participation of fungal metalloenzymes in the CH-activation step.

1. Introduction

The selective functionalization of saturated hydrocarbons (alkanes) still represents a major theoretical and practical challenge in organic synthesis [1–6]. Laboratory scale and industrial approaches are often based on hazardous chemicals (radicals, electrophiles or oxidants) and, despite enormous efforts, are still unsatisfactory. One of the challenges lays in overoxidation, as the primary oxidation products are typically more reactive than the starting alkanes. In Nature, however, C—H-bond functionalizations of saturated hydrocarbons often proceed highly selectively, namely the oxidation of methane to methanol by methane monooxygenase sMMO [7,8] or the insertion of a sulfur atom into unactivated C—H bonds by radical SAM enzymes in the final step of biotin biosynthesis [9]. The cytochrome P450 enzymes catalyze a multitude of oxidations in Nature and are intensively applied for new biocatalytic transformations [10] involving linear alkanes [11]. Many other biocatalytic approaches for the functionalizations of C—H bonds, such as the terminal hydroxylation of gaseous and liquid *n*-alkanes ($n = 2–9$) by AlkB [12] and other bacterial enzymes, [13] as well as the bioconversion of adamantane to 1-adamantanol [14] and further to 1,3-adamantanediol [15] using *Streptomyces* sp. SA8, have been reported. Additionally, many nickel, [16,17] ruthenium [18] and iron non-heme [19–21] complexes have been developed as "artificial metalloenzymes" mimicking oxidative biocatalysts. These catalytic systems, however, are much less effective than their natural counterparts [22].

Compared to many biocatalytic systems, those based on basidiomycetous fungi are distinguished by an unusually high stability of the enzymes, their nontoxicity and simplicity in use. Additionally, cultivation of the fungi as submerged cultures provides almost unlimited amounts of the catalysts. The enormous synthetic potential of basidiomycetes has been demonstrated recently by the oxidation of cyclohexane to cyclohexanol and cyclohexanone with fungal unspecific peroxygenases (UPO) [23] and the selective allylic oxidation of terpenes to the corresponding enones with lyophilisates of *Pleurotus sapidus* [24]. The H_2O_2-dependent UPOs from *Agrocybe aegerita* [25] and *Coprinellus radians* [4] are heme thiolate proteins that are fairly stable in a large number of organic solvents, such as acetone or dichloromethane, and catalyze the hydroxylation of alkanes. The enzymes showed 100% selectivity for the conversion of propane to 1-propanol, while mixtures of 2- and 3-alcohols were obtained from higher alkanes [4]. However, all of these biotransformations were studied for very low substrate amounts (<0.25 mmol), and the reaction products were analyzed by gas chromatography (GC–FID) and mass spectrometry (GC–MS) only, without isolation of the products. The suitability

* Corresponding author at: Department of Organic Chemistry, Kiev Polytechnic Institute, pr. Pobedy, 37, 03056 Kiev, Ukraine. Fax: +380 44 236 97 74.
E-mail address: t.zhuk@xtf.kpi.ua (T.S. Zhuk).

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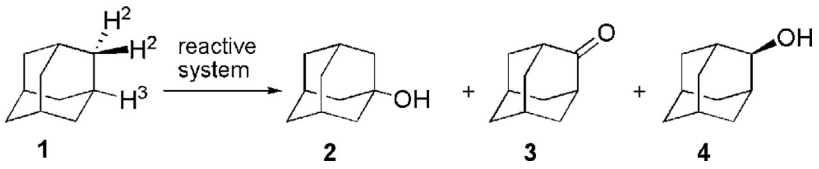
Table 1
The 3°/2°-selectivities for adamantane (**1**) oxidations by different oxygen-containing species.



1 **2** **3** **4**

#	Reactive system	3°/2° selectivity	Ref.
1	$H_2O_2/O_2/[n\text{-}Bu_4N]^+[VO_3]^-$/pyrazine-2-carboxylic acid	1.3	[44]
2	H_2O_2/O_2	1.4	[44]
3	*t*-BuOOH/Mn^{2+}	6	[45]
4	phthalimido-*N*-oxyl	33	[46]
5	$NO_3^{\bullet}$	62	[42]
6	Fe_2O-$(HB(pz)_3)_2(OAc)_2/Zn/O_2$	2.2	[47]
7	sMMO/O_2	3	[48]
8	$Fe_2O(OAc)_2Cl_2$-(2,2′-bipy)$_2$ or $Fe_2O(OAc(tmima)_2(ClO_4)_3/H_2O_2$	3.5	[49]
9	$Fe(PA)_2/H_2O_2$	4.0	[50]
10	Mn-porphyrin/$KHSO_5$	3–10	[51]
11	$[FeCl_2$-(TPA)$](ClO_4)$/*t*-BuOOH	9.5	[52]
12	$Fe_2O(2,2'$-bipy$)_4(H_2O)_2(ClO_4)_4$/*t*-BuOOH	10	[53]
13	P-450	11–48	[54]

of basidiomycetes for the oxidation of alkanes on a preparative scale is therefore still unknown. Possible drawbacks may comprise large reaction volumes, long reaction times as well as losses of the substrates and products by adsorption to the fungal mycelia. Furthermore, alkanes are poorly soluble in water, which is usually used as reaction medium for fungal oxidations [24,26].

In contrast to numerous mechanistic studies on the CH functionalization with methanotrophic bacteria and cytochrome oxygenases [27], only little is known about the oxidation of alkanes by basidiomycetes. Comparatively few of their enzymes have been isolated and intensely characterized [25,28–31] adding only little to the understanding of the mechanisms of their action [32,33]. For this purpose we have analyzed the positional 3°/2° substitution selectivity, which is strongly reagent-dependent, and the hydrogen/deuterium kinetic isotope effects (KIE) [34] resulting from the differences in the reaction rates of C—H and C—D bonds. Both experiments are useful in the analyses of CH-bond activation mechanisms providing information on the nature of the transition structures.

The tricyclic saturated hydrocarbon adamantane (**1**) containing two types of carbon atoms (CH and CH_2) was used as a model for many mechanistic studies on radical, electrophilic, and oxidative alkane activations [1,3,35–41]. Due to large amount of accumulated data concerning the 3°/2°-selectivities of the functionalization as well as KIE values, **1** is a perfect substrate for disclosing the mechanistic details of alkane oxidation by basidiomycetes, namely for the identification of the nature of the H-abstracting species. Depending on the oxidizing reagent the ratios of 3°-(1-adamantanol, (**2**))–2°- (2-adamantanol (**3**) and adamantanone (**4**)) vary significantly (Table 1). The existing examples involve different oxidative systems, e.g., H_2O_2/O_2, $H_2O_2/O_2/[n\text{-}Bu_4N]^+[VO_3]^-$/pyrazine-2-carboxylic acid, *t*-BuOOH/Mn^{2+} and many others, where, $HO^{\bullet}$, $MeOO^{\bullet}$, and *t*-$BuO^{\bullet}$, respectively, are involved in the H-abstraction step. (Table 1, entries 1–3) The selectivities increase significantly for bulky *t*-BuO [42], I_3C [40] and highly electrophilic phthalimido-*N*-oxyl, $NO_3^{\bullet}$ radicals. (Table 1, entries 4, 5) Concerning biotransformations of **1** the ratio of 3°/2° varies from 2.2 up to 11–48 depending on the use of bio- or biomimetic systems. (Table 1, entries 6–13) An average value of 2.6–4.2, slightly dependent on the solvent, is typical for Gif-type oxidations [43]. In addition, the KIE values for the reaction of **1** with traditional electrophiles and oxidants are very characteristic and also involve many examples [36,40].

Concerning practical aspects the biotransformation of **1** is an appropriate model reaction due its availability from Nature [55] or synthetically [56] and wide use of adamantane derivatives as pharmaceuticals [57–60], polymeric [61], and electronic [62–64] materials. We, thus, selected **1** as a model compound for oxidation by surface and submerged cultures of basidiomycetes.

2. Experimental

2.1. Organisms

The basidiomycetes used in this work were supplied by the Centraalbureau voor Schimmelcultures (CBS, Baarn, Netherlands), the Deutsche Sammlung für Mikroorganismen und Zellkulturen (DSMZ, Braunschweig, Germany), the Friedrich-Schiller-University Jena (FSU), and the culture collection of the Justus Liebig University Giessen (LCB).

The stock cultures of the fungi were maintained on a solid medium containing 15 g/L malt extract (Fluka, Neu-Ulm, Germany) and 15 g/L Agar–Agar (Roth, Karlsruhe, Germany).

2.2. Submerged cultures

The culture medium was prepared by dissolving malt extract (30 g) and soy peptone (3 g) in 1 L of deionised water. The pH was adjusted to 5.6 with 1.0 M NaOH prior to autoclaving. For preparation of the precultures, a 1 cm^2 agar plug from the leading mycelial edge was transferred into 100 mL malt extract medium and then homogenized with a T 25 digital Ultra-Turrax homogenizer (IKA, Staufen, Germany; 30 s, 10.000 r min^{-1}). The precultures were grown on an incubation shaker (Orbitron, Infors HAT, Bottmingen, Switzerland; 150 r min^{-1}, deflection 25 mm) under exclusion of light at 24 °C for 7 days. Afterwards, the precultures were homogenized, and 10% (v/v) of the homogenate were inoculated for

Table 2
Oxidation of adamantane (**1**) to 1-adamantanol (**2**) and 2-adamantanone (**3**) by *A. biennis*, *D. albidofuscus*, and *P. squarrosa* in the presence of alcohols (according to GC–MS analyses).

#	Alcohol	*Abortiporus biennis*	*Dichomitus albidofuscus*	*Pholiota squarrosa*
1	i-PrOH	**1**, 80% **2**, 20%	**1**, 20% **2**, 79% traces of **3**	**1**, 100%
2	i-BuOH	**1**, 100%	**1**, 100%	**1**, 100%
3	t-BuOH	**1**, ca. 100% traces of **2**	**1**, ca. 100% traces of **2**	**1**, 100%
4	n-BuOH	**1**, 100%	**1**, 100%	**1**, 100%
5	s-BuOH	**1**, 100%	**1**, 100%	**1**, 100%

submerged cultivation into a 1000 mL Erlenmeyer flask containing 400 mL medium.

2.3. Biotransformation of adamantane (1)

(a)1 (125 mg, 0.92 mmol per plate) was placed as a solution in diethyl ether into the agar of petri dishes. The plates were inoculated with a 1 cm^2 agar plug of the respective fungus and incubated at 24 °C for 14 days under aerobic conditions. The cultures were mixed with 12 mL of saturated $NaClO_4$ solution, and the mycelium was removed by filtration. The aqueous solution was extracted with diethyl ether (3 × 30 mL) and EtOAc (1 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to a defined volume of 8 mL at a pressure of 240 mbar. 1 μL was measured by GC–MS.

(b) 1 (50 mg, 0.37 mmol) was added to 110 mL submerged cultures of ABI, DAL, or PSQU after 168 h of growth in malt extract medium in 250 mL Erlenmeyer flasks. For each fungus 30 flasks were prepared. During 15 days, 2 flasks were analyzed every day. The cultures were mixed with EtOAc/*n*-hexane (1/1, 30 mL) and centrifuged (4.500 g /10 min /4 °C). The supernatant was separated and extracted with EtOAc/*n*-hexane (3/1, 3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to a defined volume of 10 mL at a pressure of 240 mbar. Quantitative analyses were performed by GC–FID using 1,3-dimethyladamantane as internal standard (IST). 300 μL from a stock solution of 0,36 mg mL^{-1} 1,3-dimethyladamantane in EtOAc were mixed with 1 mL of the sample, from which 1 μL was analyzed by GC–FID.

2.4. Biotransformation of adamantane (1) with co-solvents

Hydrcarbon **1** (50 mg, 0.37 mmol) was dissolved in the respective alcohol (Table 2) (5 mL) and added to cultures of ABI, DAL, or PSQU grown for 168 h in malt extract medium. After incubation for further 8 days, the culture media (115 mL) were extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine (1 × 10 mL) and water (2 × 10 mL). The organic extract was dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting reaction mixtures were analyzed by GC/MS (HP5890 Series II GC, column HP Ultral, 50 m × 0.2 mm with HP5971A detector), where the ratios of the oxidation products **2**–**3** were determined by the integration and statistically corrected to give the 3°/2° functionalization sectivities.

2.5. Preparative oxidation of adamantane (1) by D. albidofuscus

150 mg (1.1 mmol) of **1** were dissolved in 5 mL of *iso*-propanol and added to a 168 h old culture of *D. albidofuscus* (125 DAL) (40 mL of pre-culture) grown in malt extract medium (400 mL). After 8 days of incubation, the culture medium (440 mL) was extracted with pentane (3 × 30 mL), CH_2Cl_2 (5 × 30 mL), washed with brine (1 × 30 mL) and water (2 × 30 mL). The combined organic extract was dried over anhydrous $MgSO_4$ and evaporated to dryness. Purification of the crude product by column chromatography on silica gel (eluent pentane, then pentane/diethyl ether, 1/1) gave 71 mg of adamantane (**1**) and 65.4 mg of 1-adamantanol (**2**) as a colorless solid with ^1H and ^{13}C NMR spectra identical to the authentic reference standard.

2.6. Determination of kinetic isotope effects

All kinetic experiments were performed competitively for adamantane (1) (68 mg, 0.5 mmol) vs 1,3,5,7-tetradeuterioadamantane (70 mg, 0.5 mmol) using the same conditions as for preparative oxidation of 1 by *D. albidofuscus*. The relative concentrations of deuterated and nondeuterated products were determined by GC/MS analysis (HP5890 Series II GC, column HP Ultral (50 m × 0.2 mm, cross-linked methyl silicon) with HP5971A mass selective detector by mass selective integration.

3. Results and discussion

3.1. Screening of basidiomycetous oxidative activity towards saturated C—H-bonds

In a broad screening of various basidiomycetes, 30 different species from the orders Agaricales, Gloeophyllales, Polyporales, Corticiales, Hymenochaetales, Russulales, and Auriculariales (see SI for details) were tested for the oxidation of **1**. Either malt extract (MEA) or a minimal medium with or without glucose were employed for fungal growth.

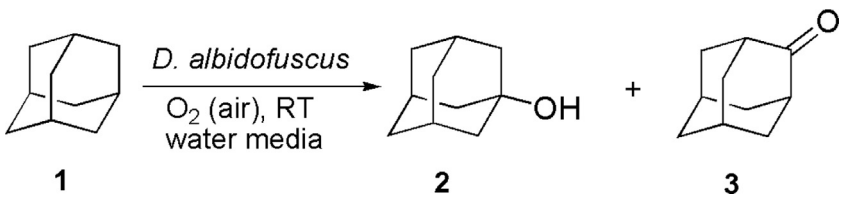
This first screening round indicated high oxidative activities of *Abortiporus biennis*, *Pholiota squarrosa,* and *Dichomitus albidofuscus* where 1-adamantanol (**2**) was identified as the main product together with trace amounts of 2-adamantanone (**3**). This set of products is characteristic for the oxidation of adamantane (**1**) with oxygen-centered radicals that are involved in the CH activation step (Scheme 1).

3.2. Time course for adamantane (*1*) biotransformation

In the next step, the selected fungi were grown submerged in malt extract medium containing 50 mg of **1**. According to the GC–MS data, the adamantane derivatives **2** and **3** were formed. During the culture period of 14 days the formation of fungal biomass and the pH of the media were monitored. In parallel, the production of adamantane derivatives was analyzed quantitatively using 1,3-dimethyladamantane as an internal standard in GC–FID analysis (Fig. 1). After 3 days, about 1.4 g of dry biomass was obtained with *A. biennis* per 110 mL of culture medium (Fig. 1a). This amount remained constant for 3 days and then slightly decreased together with an increase of the pH from 5 to 7.5, indicating a beginning lysis of the fungal mycelium. Only traces of **2** were detected in the reaction mixture after 24 h, and the maximum formation of **2** (0.64%) was achieved after 4 days (Fig. 1b). In contrast, *D. albidofuscus* grew well until the 8th culture day and formed up to 0.54% of **2** (Figs. 1c,d). *P. squarrosa* formed only traces of **2** together with further oxidation products of **1** (data not shown).

3.3. Biotransformation of adamantane (*1*) with co-solvents

In these preliminary experiments, *A. biennis* and *D. albidofuscus* displayed similar efficiencies and selectivities in the oxidation of **1**. *A. biennis* grew faster and produced higher amounts of biomass which may complicate the preparative isolation of the reaction products. In all experiments, the conversion rates of **1** were lower than 1%, most probably due to its poor solubility in water. Higher



Scheme 1. Aerobic oxidation of adamantane (**1**) by surface cultures of *D. albidofuscus* (DAL).

conversion rates were achieved by addition of various C_3—C_4 alcohols that increased the actual concentration of **1** in the reaction media. The addition of up to 5% of these organic solvents to the culture media did not retard the growth of the fungi, but dramatically increased the efficiency of the oxidation (Table 2). According to the GC–MS data, the presence of *i*-PrOH increased the conversion rates of **1** to 20% with *A. biennis* and up to 80% with *D. albidofuscus*. Only traces of products were detected with *t*-BuOH and no reaction occurred with other C_4-alcohols. No oxidation products of **1** were identified with *P. squarrosa* in the presence of alcohols, as the alcohols strongly impeded the growth of this fungus. These results clearly indicated the ability of the selected basidiomycetes to activate the aliphatic CH-bonds.

3.4. Preparative biotransformation of adamantane (1)

To evaluate the potential of this bioconversion for preparative applications, the oxidation of **1** by *D. albidofuscus* in the presence of *i*-PrOH as a co-solvent was scaled-up. Using 1.1 mmol of **1** in 400 mL medium and 1% *i*-PrOH, a nearly quantitative conversion of **1** was achieved. The extraction of the reaction mixture (including culture supernatant and mycelium) with diethyl ether resulted in

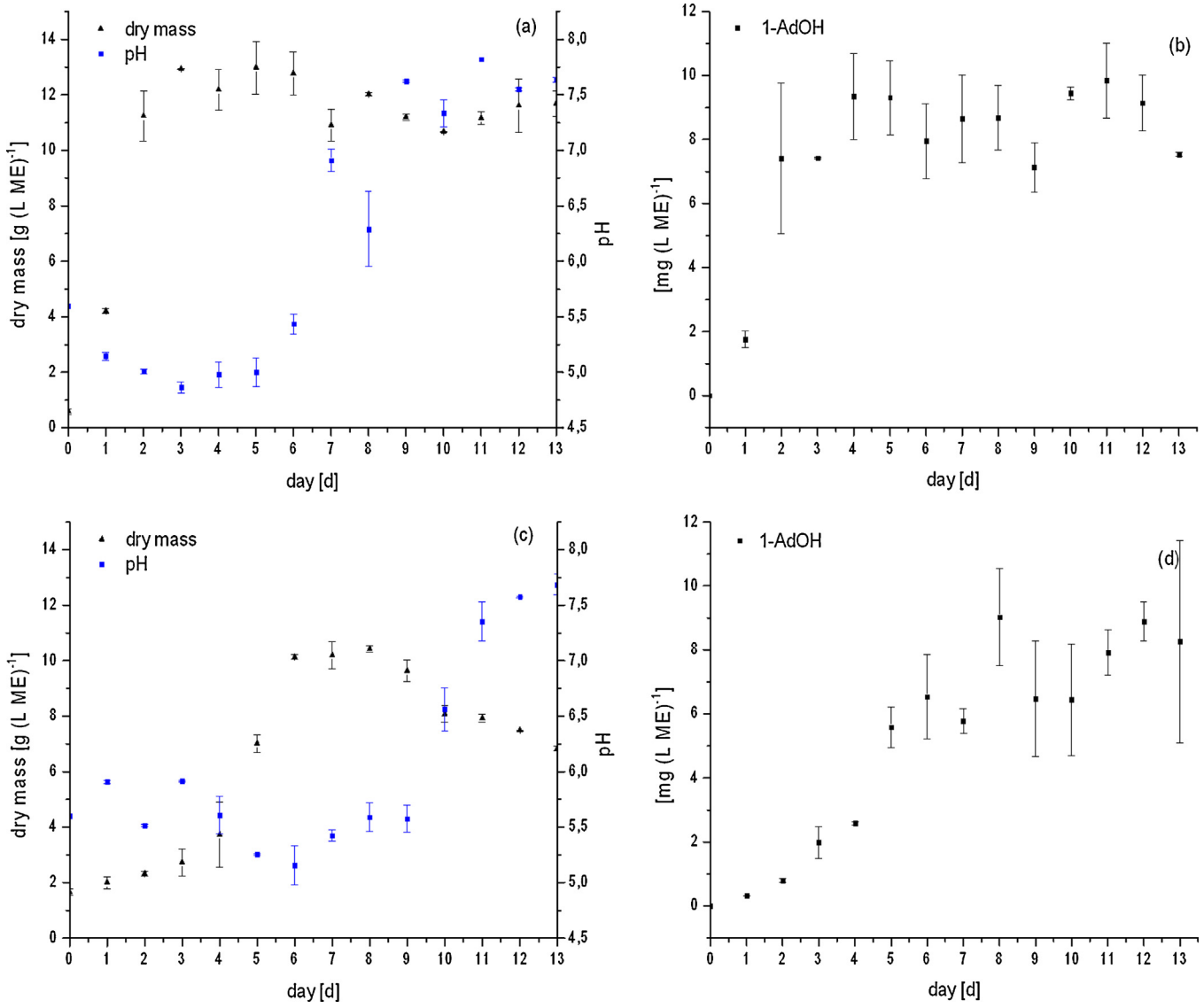


Fig. 1. (a) pH and production of dry mass in submerged cultures of *A. biennis*; (b) formation of oxidation products of **2** in submerged cultures of *A. biennis*; (c) pH and production of dry mass in submerged cultures of *D. albidofuscus*; (d) formation of oxidation products of **2** in submerged cultures of *D. albidofuscus*.

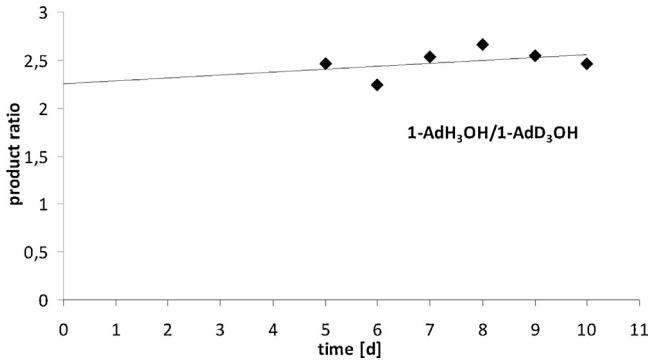


Fig. 2. Ratio of non-deuterated and deuterated **2** formed by oxidation of **1** by *D. Albidofuscus.*

a combined yield of 44% of crude **2** with small amounts of **1** and **3**. We supposed that substrates and products were tightly adsorbed to the mycelia due to the high hydrophobicity of the adamantane cage. Extraction with pentane added 10% of **1**–**2** mixture to the balance. Therefore, CH_2Cl_2 was chosen as a solvent, and additional 20% of **1** was extracted. Lyophilization and disruption of the mycelia by grinding under liquid nitrogen with subsequent extraction did not further improve the reaction balance. After combining all organic extracts and purification by column chromatography on silica gel, 39% of pure **2** were obtained. The physico-chemical properties of **2** were identical to those of an authentic reference standard [65]. To the best of our knowledge, this is the first example of a preparative aerobic functionalization of an alkane by basidiomycetes which opens up new perspectives for the mild aerobic oxidation of alkanes in aqueous media. Futhermore, based on the observed 3°/2° ratio of ca. 3.6, the participation of free OH-radicals may be excluded for the aerobic oxidation of **1** by *D. albidofuscus* suggesting that fungal metalloenzymes are most likely accountable for the oxygen transfer.

3.4. Kinetic isotope effects of adamantane (1) biotransformation

Additional proof for the participation of metal-oxo complexes in the CH activation step arises from the k_H/k_D KIE values. The competitive method, where two substrates are present in the same vessel, was chosen for the determination of KIEs [34]. This approach avoids unintended variations of the experimental conditions and allows to estimate the ratio of reactants with high precision. A KIE value of approximately 1 indicates that the cleavage of the C—H-bond is not the rate limiting step and is characteristic for processes where HO-radicals participate in C—H-activation [66] as found for Fenton-type reactions ($\leq$1.18) [43]. The KIE values increase for high-valent metal-oxo-catalyzed hydroxylations of **1**, namely, for RuO_4-mediated oxidations (4.8–7.8 depending on the solvent) [67,68]. For the metalloporphyrine-catalyzed oxidation of **1**, the KIEs are often higher for iron (2.8–8.7) [69] than for manganese based cores (3.1–4.9) and are also sensitive to the oxidant [69].

Accordingly, the KIE was calculated for **1** by oxidizing a mixture of its protio- (AdH_4) and 1,3,5,7-tetradeuterio- (AdD_4) [38] forms from the ratio of non-deuterated and deuterated forms of **2** with further extrapolation to the beginning of the experiment (Fig. 2). The measurements were carried out at moderate conversion rates (<40%) and required slightly longer times due to the reduced reactivity of AdD_4. Calibration of the MS detector was performed for standard mixtures of AdH_4/AdD_4 and AdH_3OH/AdD_3OH in different ratios and concentrations. The experimental value of ca. 2.25 ± 0.05 determined in this study is in good agreement with values observed for metal-catalyzed aerobic oxidations of **1** [69] and clearly may exclude the participation of the free HO-radicals. Both, the 3°/2° selectivity and the KIE value for the oxidation of **1** strongly indicate the participation of fungal metalloenzymes in the oxygen transfer. Metalloenzymes like catalases [70] and multi-copper laccases [71–74] play a key role in the proteome of basidiomycetes. Catalases [70,75] contain an iron ion in their active sites and transform H_2O_2 into oxygen and water [76]. They are involved in the natural degradation of lignocelluloses and also catalyze the oxidation of various organic compounds including phenols, methoxyphenols, aminophenols, and diamines [77]. Fungal UPOs, which have been shown to oxidize aromatic as well as aliphatic compounds contain iron and magnesium ions [32,78]. The extracellular enzymes of *A. biennis*, *D. albidofuscus*, and *P. squarrosa* responsible for the oxidation of adamantane remain to be identified on a molecular level in ongoing research. However, based on the data presented here, the contribution of peroxidase type metalloenzymes in the aerobic oxidation of adamantane is to be expected.

4. Conclusions

An efficient aerobic oxidation of adamantane by submerged cultures of basidiomycetes in aqueous media was confirmed by analytical and preparative experiments. The 3°/2° selectivity of the introduction of the hydroxyl group as well as the KIE values agreeable suggested the participation of fungal metalloenzymes as key players in the activation of the C—H bond. The suggested hydrocarbon oxidations do not require hazardous chemicals, occur under room temperature and pressure and is almost waste-free. Further extension of this approach to wider range of mono-, poly- and non-cyclic aliphatic compounds that challenge the CH-activations methods are currently underway in our labs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcatb.2015.08.002.

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