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Bio-inspired amino acid oxidation by a non-heme iron catalyst

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ABSTRACT

This study reports the kinetics and mechanism of Fe(III)-catalyzed oxidative decarboxylation and deamination of a series of acyclic (α-aminoisobutyric acid, α-(methylamino)isobutyric acid, alanine, norvaline, and 2-aminobutyric acid) and cyclic (1-aminocyclopropane-1-carboxylic acid, 1-amino-1-cyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, and 1-aminocyclohexanecarboxylicacid) amino acids using hydrogen peroxide, *t*-butyl hydroperoxide, iodosylbenzene, *m*-chloroperbenzoic acid, and peroxomonosulphate as oxidant in 75% DMF–25% water solvent mixture. Model complex $[Fe^{IV}O(SALEN)]^{\bullet+}$ (SALENH$_2$: *N,N′*-bis(salicylidene) ethylenediamine) was generated by the reaction of Fe^{III}(SALEN)Cl and H_2O_2 in CH_3CN at 278 K as reported earlier. This method provided us high-valent oxoiron species, stable enough to ensure the direct observation of the reaction with amino acids.

1. Introduction

Model chemistry in relevance to metalloenzymes has progressed remarkably in recent years and contributed greatly to clarification of structure and mechanism of various enzymes. The other important contribution of the model systems to progress in enzymatic studies is to obtain information about structures and reactivities of substrate–metal intermediates and investigate how the model chemistry is related to the development of efficient catalysis by metal complexes. In nature ethylene is an important phytohormone, which regulates many physiological processes in plant growth and development such as fruit ripening [1,2]. Many efforts have been made to assay the ethylene forming enzyme (EFE) and to determine the genes encoding it. EFE is now called 1-aminocyclopropane-1-carboxylic acid oxidase (ACCO) [3–8]. ACCO is a dioxygen-activating ascorbate-dependent nonheme iron enzyme, which catalyzes the two electron oxidation of 1-aminocyclopropane-1-carboxylic acid (ACCH) to ethylene, CO_2, and HCN (Scheme 1). The structure of ACCO from *Petunia hybrida* has recently been reported [9,10].

It confirms, that the active site contains a single Fe(II) ion coordinated to three residues (two histidines and one aspartate), referred to as a “2-His-1-carboxylate facial triad” within the family of nonheme iron oxidases/oxygenases [11–14]. The mechanism of α-ketoglutarate-dependent enzymes has been studied extensively and it is accepted, that dioxygen activation at the iron center is linked to oxidative decarboxylation of the coligand, forming a high-valent oxoiron(IV) species as the reactive intermediate. Recently, a mononuclear oxoiron(IV) intermediate has been trapped in the reaction of 2-oxoglutarate-dependent dioxygenases (TauD and P4H) with dioxygen in the presence of substrate and cofactor [15,16]. In addition several synthetic oxoiron(IV) species were successfully prepared from biomimetic non-heme model complexes [17–26]. Pirrung et al. have determined ACC amine radical cation to be a key intermediate in the ACCO active site. A precedent for this kind of radical generation was established in earlier studies on the inactivation of cytochrome P450 (oxoiron) enzymes by cyclopropylamines [27]. They have proposed two types of reactions from the key intermediate: (1) direct ring opening of ACC amine radical cation followed by proton abstraction from the amino group (Path A in Scheme 2) and (2) proton abstraction from the amino group, followed by ring opening of ACC aminyl radical (Path B in Scheme 2) [28,29]. The stability and reactivity of ACC amine radical cation were also examined by using quantum chemical calculations. It was quantitatively demonstrated, that reaction (1) was more favorable than reaction (2). Therefore, ethylene synthesis should proceed predominantly through reaction (1) [30].

Known alternate substrates for the ACCO include 2-alkyl ACCH analogs and α-aminoisobutyric acid (AIBH) (Scheme 3). The former is processed to the corresponding 1-alkenes, whereas the latter is converted to acetone imine and CO_2 [28]. 1-amino-1-cyclobutanecarboxylic acid (ACBH), which has slightly lower ring strain than ACCH, was also used as a possible ACCH analog. At least three reaction pathways are available to the radical cations derived from this amino acid, namely decarboxylation (Path A in Scheme 3), hydroxyl rebound (Path B in Scheme 3) and ring opening path (Path C in Scheme 3). It was found, that the processing of ACBH by the EFE proceeds via ring expansion to produce dehydroproline. This result is consistent with a one-electron oxidation mechanism. The absence of hydroxylated intermediates refutes the

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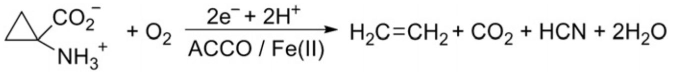


Scheme 1. Reaction catalyzed by ACC oxidase.

proposed *N*-hydroxylation mechanism previously suggested for ethylene biosynthesis [29].

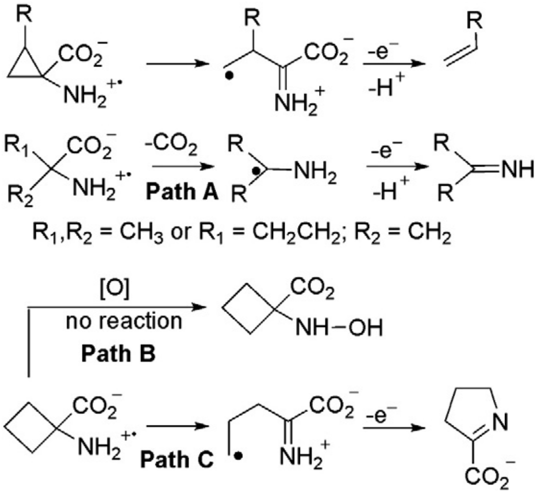
There are only few reported functional models of ACCO, and even less using iron [31]. Very recently we have demonstrated that the complex Fe^{III}(SALEN)Cl highly selectively and efficiently catalyzes the oxidation of ACCH and AIBH to ethylene and acetone, respectively and thus serves as one of the first functional models for ACCO [32].

This study reports the first kinetic data obtained by direct observation of the stoichiometric and catalytic reactions of Fe^{III}(SALEN)Cl with a series of acyclic (α-aminoisobutyric acid (AIBH), α-(methylamino) isobutyric acid (N-Me-AIBH), alanine (ALAH), norvaline (NORH), and 2-aminobutyric acid (ABH)) and cyclic (1-aminocyclopropane-1-carboxylic acid (ACCH), 1-amino-1-cyclobutanecarboxylic acid (ACBH), 1-aminocyclopentanecarboxylic acid (ACPH), and 1-aminocyclohexanecarboxylicacid (ACHH)) amino acids using hydrogen peroxide (H_2O_2), *t*-butyl hydroperoxide (TBHP), iodosylbenzene (PhIO), *m*-chloroperbenzoic acid (MCPBA), and peroxomonosulphate (PMS) as oxidants. A synthetic model complex, [Fe^{IV}O(SALEN)]$^{\bullet+}$ was generated by the reaction of Fe^{III}(SALEN)Cl and H_2O_2 in CH_3CN at 278 K, as reported earlier [33,34]. This preparation provided us high-valent oxoiron species stable enough to ensure the direct observation of the reaction with amino acids. In contrast to the formation of high-valent oxo species with H_2O_2, [Fe^{III}(SALEN)(OIPh)] and iron(III)-phenoxyl radical are formed with PhIO and MCPBA, respectively [35–37].

2. Experimental

2.1. Materials

All manipulations were performed under pure dinitrogen or argon atmosphere unless otherwise stated, using standard Schlenk-type inert-gas techniques. Solvents used for the reactions were purified by literature methods and stored under argon. Fe^{III}(SALEN)Cl was prepared according to the literature [38]. All other chemicals were commercial products and were used as received without further purification.



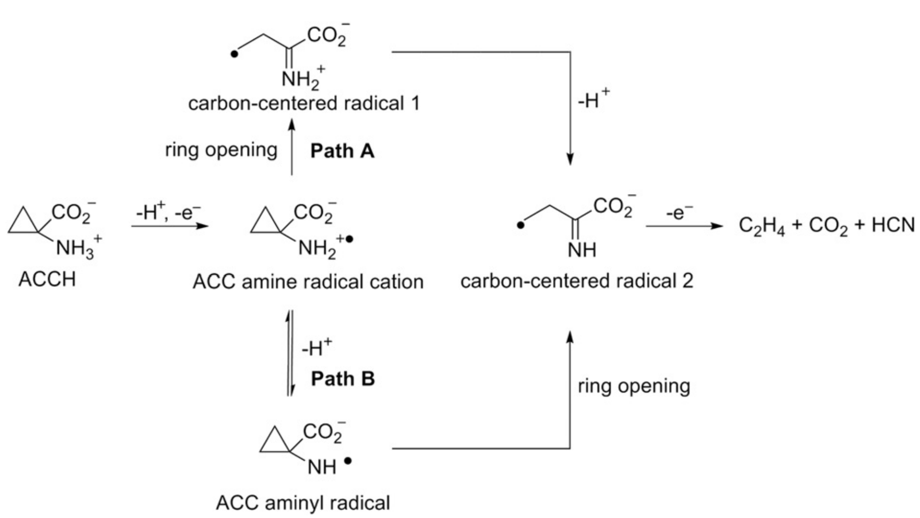
Scheme 3. Proposed mechanism for the oxidation of cyclic and acyclic substrates by ACC oxidase.

2.2. Analytical and physical measurements

Infrared spectra were recorded on an Avatar 330 FT-IR Thermo Nicolet instrument. UV–vis spectra were recorded on an Agilent 8453 diode-array spectrophotometer using quartz cells. GC analyses were performed on a Hewlett Packard 5890 gas chromatograph equipped with a flame ionization detector and a 30 m Supelcowax column. Microanalyses were done by the Microanalytical Service of the University of Pannonia.

2.3. Determination of products

Reactivity assays were performed as follows: a respective amino acid (ABH, ACCH, ACBH, ACHH, ACPH, AIBH, N-Me-AIBH, ALAH, NORH) was dissolved in 10 mL of DMF/H_2O (DMF: *N*,*N*-dimethylformamide) mixture (3/1) in a sealable tube of 20 mL. With MeCN (10 μL) as inner standard, NH_4OH and the catalyst were then added to the mixture. Hydrogen peroxide was added through the septum with a syringe and the evolved acetone, acetaldehyde, methyl-ethylketone cyclobutanone, cyclopentanone, cyclohexanone or ethylene was measured by removing 0.25 mL of the headspace with a gastight syringe and the sample was injected into a gas chromatograph. The concentration of the corresponding product in the headspace is linearly proportional to the concentration of the product in the reaction mixture (Fig. S1–S9). In case



Scheme 2. Possible mechanisms for oxidation of ACCH by ACC oxidase.