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Inactivation path during the copper (II) catalyzed synthesis of Questiomycin A from oxidation of 2-aminophenol

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ABSTRACT

The catalytic oxidation of 2-aminophenol (OAP) to 2-amino-3H–phenoxazin-3-one (APX, Questiomycin A) was the object of numerous studies partly due to antimicrobial properties of Questiomycin A and mostly because it can be used as a model for the synthesis of the naturally occurring antineoplastic agent Actinomycin D. Several copper complexes were used as dioxygen and/or substrates activators in order to mimic the activity of phenoxazinone synthase, but the reported assays failed to provide reasonable mechanistic features in media compatible with natural conditions. The main purposes of our work were to use simple copper salts to perform oxidation of OAP in oxygenated aqueous solutions and to develop a reaction scheme able to explain the low yields in APX along with the operational inactivation of the catalyst. A 11-step kinetic model able to describe the inactivation of copper(II) catalyst during oxidation of OAP to APX in oxygenated solutions was developed, and the rate constants for both catalytic and non-catalytic branch were estimated either experimentally or using a computing program for detailed kinetic simulation. It was demonstrated that the inactivation path can be assigned to formation of the stable bis(*o*-iminosemiquinonato)copper(II) complex, a compound reported as a moderate antimicrobial agent.

1. Introduction

Catalytic activation of dioxygen by copper ions in selective oxidations of organic compounds was paid considerable attention over at least four past decades mostly due to the abundance of copper in biological systems [1–3]. Copper-containing enzymes are usually acting as oxygen carriers in oxidation reactions of a large variety of substrates (carbohydrates, amines, phenols etc.) [4,5]. The role of copper centers in these enzymes, along with their detailed structure, is not entirely elucidated at present and may differ from enzyme to enzyme [6,7]. Mimicking systems using copper complexes as dioxygen and/or substrates activators were widely studied for understanding the complex pathways and mechanistic features of biological oxidations [8–12]. In this context, the oxidative coupling of 2-aminophenol (OAP) to the stable product, 2-amino-3H-phenoxazin-3-one (APX) through catalytic activation of dioxygen/substrate was the subject of numerous studies [13–15] partly due to antimicrobial properties of APX (also known as Questiomycin A) but mostly because it can be used as a model for the synthesis of the naturally occurring antineoplastic agent Actinomycin D [16].

Many works were dedicated in the past years to synthesis, characterization of copper-, iron-manganese and cobalt (II) complexes which were used to mimic the activity of phenoxazinone synthase (PHS) [5,9,13], a two-copper centre oxidase isolated from *Streptomyces* [7] which catalyzes the oxidation of substituted 2-aminophenols to the phenoxazinone chromophore in the final step of the Actinomycin D biosynthesis. It is now widely accepted that the six-electron oxidative condensation of two molecules of OAP to form APX occurs via 2-aminophenoxyl free radicals [15,17,18]. The generation of aminophenoxyl radical is supposed to occur catalytically or in the absence of the catalyst (auto-oxidation), but the following dismutation, addition, cyclization and oxidation steps do not require catalyst assistance [19] (Scheme 1).

It is worth mentioning several works which proposed copper(I) and (II) salts (CuCl, $CuCl_2$, $CuSO_4$, $Cu(NO_3)_2$, $Cu(OCH_3)_2$) and oxides (CuO, Cu_2O) [17,20] or Fe, Mn and Co(II) based complexes [5,13,21] as mimic systems of PHS activity; most of them provided conversions of OAP to APX up to 90% [20,21]. However, the main disadvantages of these assays are that the studies were achieved in organic solvents (acetonitrile, dimethylformamide, methanol) [13,15,20] at temperatures ranging from 40 to 60 °C [13,17,20], which are not compatible to the natural conditions where PHS displays its optimum activity [7]. Monocopper–dioxygen adducts

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