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Review

Trinuclear copper complexes as biological mimics: Ligand designs and reactivities

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ABSTRACT

Tris-copper centers are present at the active site of multicopper oxidases (MCO) which couple the four-electron reduction of molecular oxygen to water with the oxidation of substrates. Modelling these sites with small molecular complexes has thus attracted the interest of many groups in the (bio)inorganic community over the past three decades and still appears a challenge. These enzymes and their model complexes presently enjoy a renewed interest as potential non-precious metal catalyst for the Oxygen Reduction Reaction. Moreover recent work has revealed that tris-copper centers can catalyze methane oxidation. Therefore the elaboration of tris-copper system constitutes an important and timely issue. The aim of the present review is to analyze the various attempts at preparing tris-copper complexes in terms of strategy of ligand design. Of course the challenge to be met is to force three independent binding sites to converge and react in concert. Three main approaches have been developed to anchor these binding sites based on the use of (i) a node either (a) a single atom node (tren-based systems and related), or (b) an *hexa*-atom node (mesityl-based systems and derivatives), (ii) macrocyclic systems, and (iii) combination of mono- and dinuclear sites. The structures of the different systems will be described and analyzed accordingly. Then the various reactivities exhibited by these systems will be presented so as to evaluate how the ligand design influences the reactivity and to discern promising future directions.

Contents

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1. Introduction

Metallobiosites have attracted huge interest among bioinorganic chemists for at least five decades starting from the desire to contribute an improved understanding of their structures, spectroscopic properties and mechanisms and moving to attempting to mimic their reactivities, hopefully in catalytic processes [1]. Multimetallic sites are the most challenging to mimic but also the most attractive since they are generally involved in small molecules (O_2, N_2, NO, CO, ...) activation, processes of current utmost interest for developing a sustainable chemistry. Among these sites, trimetallic ones have been less considered albeit they are found in important enzymes such as multicopper oxidases [2,3] or zinc hydrolases [4-6]. This probably stems from the intrinsic difficulty to elaborate multimetallic systems with an odd number of sites. Attempts at devising models of trimetallic biological sites have started almost a quarter century ago [7] and have encompassed various synthetic approaches, with a strong emphasis on copper systems owing to their continuous strong interest as catalysts for the oxygen reduction reaction (ORR) [8,9]. The purpose of this review is to analyze the various strategies used to devise trinuclear copper sites and the reactivities of the obtained systems. In all figures and schemes Cu^{I} and Cu^{II} ions will be colored in brown and in pink, respectively. The observed reactivities concern mostly dioxygen activation processes, but phosphate esters hydrolysis will be considered also. Indeed, whereas zinc, magnesium and manganese are involved in the related enzymes [6], model studies showed that tris-copper complexes are often as active as their zinc analogs if not more, which justifies to consider them in this survey. By contrast, this review will not include tris-copper complexes which have been studied for their magnetic properties and have been most often obtained through self-assembly of monomeric complexes. After a brief examination of the biological sites, tris-copper complexes will be presented according to the strategy developed for their elaboration. Finally their reactivities will be examined with respect to the ligand designs.

2. Biological trimetallic sites

2.1. Multicopper oxidases

Multicopper oxidases (MCO) are enzymes which couple the four-electron reduction of molecular oxygen to water with the oxidation of substrates. They can be divided in two sub-classes according to the nature of their substrates which can be either an organic cofactor (laccases, ascorbate oxidase, bilirubin oxidase) or a metal ion (Fe^{2+} in ceruloplasmin and Fet3p ferroxidases, Cu^{+} in CueO cuproxidase). Accordingly they are found in many organisms: bacteria, yeast, fungi and even insects [2,3]. Following the early X-ray structure determination of ascorbate oxidase [10,11], numerous structures are now available also for laccases, ceruloplasmin and bilirubin oxidases, among other enzymes [3,12,13]. All reveal that they have an active site with four copper centers arranged in the same manner (Fig. 1,A):

– A mononuclear center (denoted T1) in which a copper ion is coordinated by two histidines, a cysteine and more loosely by

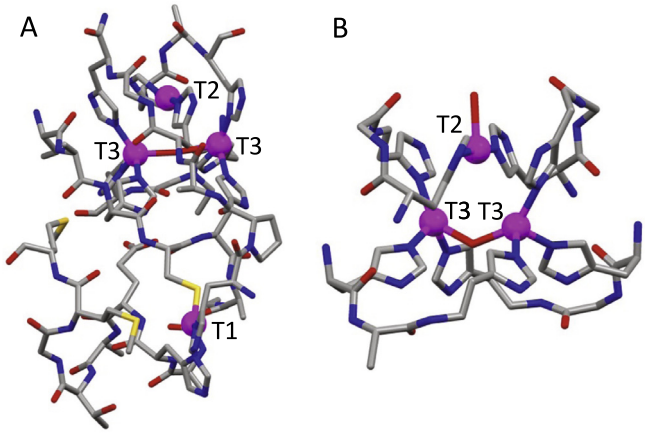

Fig. 1. X-ray structure of multicopper oxidases: A) Arrangement of the four copper centers in cuprous oxidase CueO from *Escherichia coli* (PDB 1kv7) [14]; B) Trinuclear active site of laccase from *Trametes versicolor* (PDB 1gyc) [15]. Adapted with permission from the given references.