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Review

Molybdenum enzymes in higher organisms

Russ Hille[a,*], Takeshi Nishino[a,b], Florian Bittner[c]

[a] Department of Biochemistry, University of California, Riverside, CA 92521, United States
[b] Department of Biochemistry and Molecular Biology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, Japan
[c] Department of Plant Biology, Technical University of Braunschweig, 38023 Braunschweig, Germany

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ABSTRACT

Recent progress in our understanding of the structural and catalytic properties of molybdenum-containing enzymes in eukaryotes is reviewed, along with aspects of the biosynthesis of the cofactor and its insertion into apoprotein.

* Corresponding author. Tel.: +1 951 827 6354.
E-mail addresses: russ.hille@ucr.edu (R. Hille), nishino@nms.ac.jp, takeshin@ucr.edu (T. Nishino), f.bittner@tu-bs.de (F. Bittner).

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1. Introduction and scope

Molybdenum enzymes have long been recognized to be important in eukaryotes, dating to 1954 and the near-simultaneous demonstration of molybdenum in xanthine oxidase [1], aldehyde oxidase [2], and nitrate reductase [3]; molybdenum was subsequently identified as a component of sulfite oxidase in 1971 [4]. In the intervening time, and especially in the past decade, our understanding of the structures and function of these enzymes has developed to the point where it is possible to speak with confidence as to the precise manner in which the chemical transformations catalyzed by these enzyme occur and, in the context of high-resolution X-ray crystal structures, the specific means by which reaction rate is accelerated by these biological catalysts. At the same time, our understanding of the biosynthetic pathway by which the organic cofactor that accompanies molybdenum in eukaryotic systems is formed and the process by which molybdenum is incorporated and the resultant moiety inserted into apoprotein have all become increasingly well understood. Finally, new genomics and proteomics approaches continue to identify new molybdenum-containing proteins [5].

Historically, molybdenum enzymes from eukaryotes have been divided into two groups [6]: the xanthine oxidase family that includes the eponymous enzyme as well as the aldehyde oxidases; and the sulfite oxidase family, including both vertebrate and plant sulfite oxidases as well as the plant nitrate reductases. As indicated in Fig. 1, members of the xanthine oxidase family possess an $LMo^{VI}OS(OH)$ coordination sphere, where L is a pyranopterin cofactor that coordinates the metal via an enedithiolate side chain. (While the cofactor is frequently elaborated as a dinucleotide in prokaryotic enzymes, most frequently of guanine or cytosine, in all eukaryotic enzymes examined to date it is found as the mononucleotide shown in Fig. 1.) By contrast, the sulfite oxidases and nitrate reductase have an $LMo^{IV}O_2$(S-Cys) coordination sphere, with the cysteine ligand contributed by the polypeptide. Although both types of center possess a square-pyramidal coordination geometry with an apical Mo=O and three sulfurs and an oxygen in the equatorial plane, it has been pointed out that the orientation of the molybdenum coordination sphere with respect to the pyranopterin cofactor is opposite in the two families of protein [7]. With the pyranopterin group oriented to the left of the metal as shown in Fig. 2, the apical Mo=O points *up* for all members of the xanthine oxidase family, and *down* for all members of the sulfite oxidase family. In addition to these enzymes, several of which have been investigated for many years, a new protein catalyzing the oxidative hydroxylation of compounds such as amidoximes has recently been described in both humans and plants [8,9] which, as discussed further below, appears to have a distinct molybdenum coordination sphere and may represent a new family of eukaryotic molybdenum enzymes.

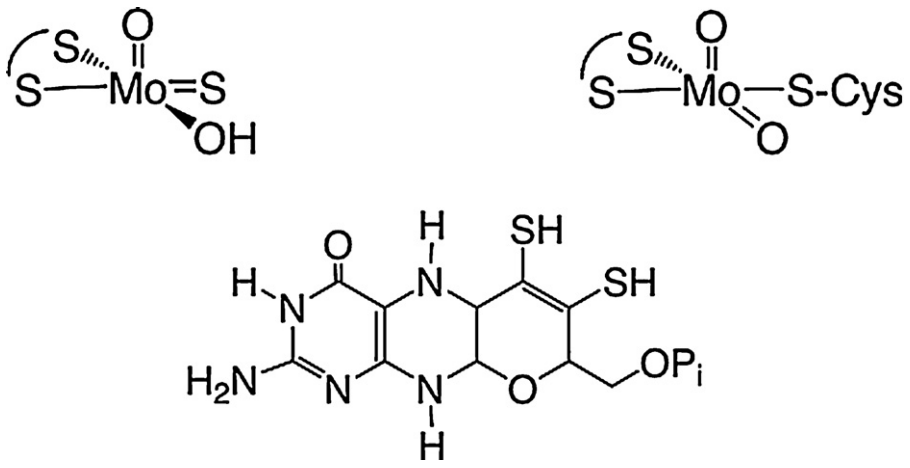

Fig. 1. Structures of the molybdenum centers of the xanthine oxidase and sulfite oxidase families of molybdenum enzymes. *Upper left*, the active site of bovine xanthine oxidase, *upper right*, the structure of chicken sulfite oxidase. Shown at *bottom* is the pterin cofactor (variously referred to in the literature as pyranopterin or molybdopterin) that coordinates the metal via its enedithiolate side chain.

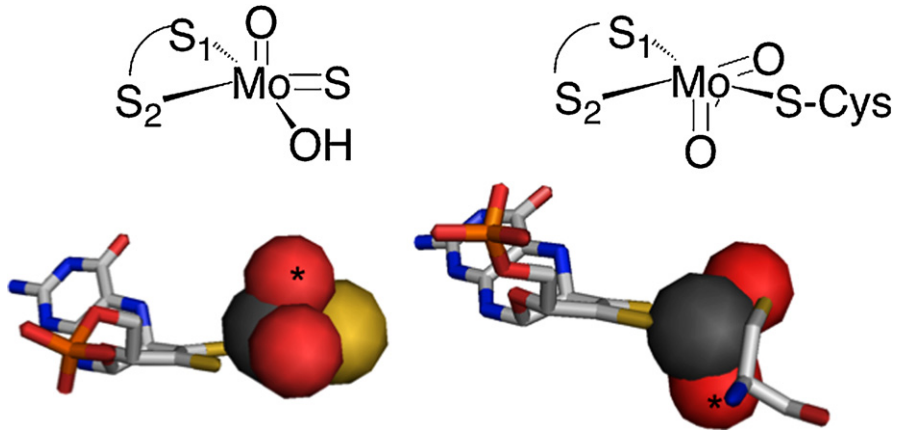

Fig. 2. The orientations of the molybdenum centers of xanthine oxidase and sulfite oxidase relative to the coordinated pyranopterin ligand. With the pyranopterin oriented as shown, the apical Mo=O (asterisk) of the molybdenum coordination sphere points up in all members of the xanthine oxidase family, and down in all members of the sulfite oxidase family.