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Preface

Molybdenum in living systems

All forms of life make abundant use of metals available in their environments, and transition metals in particular are put to myriad uses, not least in the active sites of enzymes where the great variety of chemical transformations in which transition metal complexes can participate is harnessed to the metabolic needs of the organism. Although molybdenum lies on the very edge of the "biological" periodic table, it is indispensible to most life forms, and to almost all of the ones with which we are most familiar. The plants and animals upon whom our well-being relies, as well as we ourselves, depend on molybdenum-based chemistry to carry out some of the most important steps in the metabolism of carbon, nitrogen, and sulfur, and many of these transformations constitute critical steps in the global biogeochemical cycles of these elements. Interestingly, and unusually for a transition metal, the biology of molybdenum is based not on the cation Mo^{6+}, but instead on the anion MoO_4^{2-}. It is the high solubility (and therefore bioavailability) of molybdate that is the principal reason why molybdenum, which is present at only ~1 ppm in the earth's crust, has come to be so broadly distributed in biology. Although occasionally referred to on the basis its role as a metal activator of water as "redox-active zinc", molybdenum is perhaps more appropriately thought of as "redox-active phosphate" on the basis of how it works physiologically.

Major progress has been made in recent years in our understanding of the structure and function of metal-containing enzymes, as well as the biosynthesis of their prosthetic groups. Molybdenum is no exception. Over the past 25 years, and particularly in the past decade, there has been an explosion in our understanding of the structures of molybdenum-containing enzymes, how they work, and in particular in the biosynthesis of their molybdenum centers. The X-ray crystal structures for over 20 of the ~100 known molybdenum enzymes have been reported, and this figure does not include the structures of almost all the gene products involved in the biosynthetic pathway of the organic component of all molybdenum enzymes save nitrogenase, known variously in the literature as "molybdopterin" or "pyranopterin". As for nitrogenase itself, the assembly of its [8Fe–7S] and [Mo–7Fe–9S–X] P and M clusters has become a paradigm in studying how complex metal structures are assembled in the cell.

At the same time, however, our present understanding is scarce with regard to the intracellular trafficking of such structures and, ultimately, the manner in which they are correctly targeted and inserted into a given apoprotein. Further areas of focus for ongoing research include mechanisms of metal ion homeostasis, how cells sense diverse metal ions, how homeostatic mechanisms for molybdenum and other metal ions are integrated at the molecular and cellular level, and how the finely tuned interplay of these components ensures safe transport and function. Clearly, cellular malfunction and consequently disease are the result if any of the various key steps in metals allocation and insertion are perturbed and reduced cell division, growth proliferation and overall performance result from deficiencies of these metals. In this regard, it is worth drawing attention to a recent report by Adams and coworkers (Nature 466 (2010) 779–784) in which a proteomics approach is used to quantifiably understand the diversity of metal-containing proteins in a single organism, *Pyrococcus furiosus*. In this work, 158 of 343 metalloproteins identified on the basis of a combined tandem MS/ICP analysis of the organism's cytosol did not correspond to any known metalloprotein – of the 37 proteins identified as containing molybenum, only 19 (barely half) had amino acid sequences homologous to any known molybdenum enzyme. The authors conclude that we have only begun to understand the extent to which metals, and molybdenum specifically, are utilized in the cell. Clearly, there is work to be done.

In this special issue of *Coordination Chemistry Reviews*, the current state of our understanding of molybdenum in biology is presented from a broad range of perspectives, from physical and inorganic chemistry, through mechanistic enzymology to molecular and cell biology. This breadth of perspective reflects the unusually fertile, interdisciplinary interactions that are one of the principal reasons for the extraordinary recent progress in the field. Thus, contributions focusing on various aspects of our understanding of the synthesis, electronic structures and chemical reactivity of molybdenum complexes are to be found. Similarly, there are accounts of our efforts to understand the relationship of structure to reactivity in molybdenum-containing enzymes at the same fundamental level, both experimentally and computationally. Other contributions deal with the uptake of molybdenum, biosynthesis of the metal centers and the distribution of molybdenum-containing proteins in the biosphere, integrating in many cases aspects of the previous areas.

Our intent here has been to provide a valuable resource for workers in the field and, hopefully, to attract the attention of those investigators, both junior and senior, who might be interested in contributing to the field themselves in future. To this end, we are indebted to the contributing authors and the uniformly high quality of their accounts. We also express our gratitude to Dr. Barry Lever, Editor-in-Chief at *Coordination Chemistry Reviews*, who conceived this special issue and whose attention to every aspect of its development has made it a reality.

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