

**Stony Brook University  
The Graduate School**

Doctoral Defense Announcement

**Abstract**

Structural Studies of Molybdopterin Synthase, an Essential Enzyme for Dithiolene  
Formation of the Molybdenum Cofactor

By

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The molybdenum cofactor is found in a variety of enzymes present in bacteria, plants and animals and is composed of closely related molecules which all contain molybdopterin, a tricyclic pyranopterins containing a cis-dithiolene group. Molybdopterin is important for the coordination of Molybdenum or Tungsten in virtually all biological life forms. Deficiencies in the molybdenum cofactor in humans cause severe neurological abnormalities that normally result in death during early childhood. The majority of the mutations causing this deficiency have been identified in proteins that are involved in the synthesis of the molybdopterin moiety of the cofactor. One of the enzymes affected by these previously characterized mutations is molybdopterin synthase which is responsible for the formation of the dithiolene group of molybdopterin. To further the understanding of the mechanistic action of the molybdopterin synthase, structural studies of the enzyme have been performed using X-ray crystallographic techniques.

MPT synthase is comprised of two subunits, MoaE and MoaD, and the activated enzyme carries a thiocarboxylate at the C-terminus of MoaD. The 2.0 Å structure of the MPT synthase in its apo-form and the 2.5 Å structure in complex with its substrate, precursor Z, reveals a distinct substrate-binding pocket which is 11 Å wide and allows the substrate to snugly fit into it. This newly defined pocket reveals the residues involved in substrate-binding and suggests possible roles for some of these residues during catalysis. Due to the structural similarity of the small MoaD subunit to the small subunit of thiazole synthase, an enzyme involved in thiamine biosynthesis, the sulfur transfer mechanism is proposed to be closely related, although MPT synthase is involved in a distinct sequence of two sulfur transfers events. The co-crystal structure of MPT synthase with precursor Z is the first ever reported for this class of sulfur transferases and provides a structural basis for understanding the effects of mutations which lead to molybdenum cofactor deficiency.

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**Program:** Molecular and Cellular Biology

**Dissertation Advisor:** Dr. Hermann Schindelin

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