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**X-Ray Absorption Studies of Human Matrix Metalloproteinase-2 (MMP-2) Bound to a Highly Selective Mechanism-Based Inhibitor: Comparison to the Latent and Active Forms of the Enzyme**

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**ABSTRACT:** Malignant tumors express high levels of zinc-dependent endopeptidases called matrix metalloproteinases (MMPs), which are thought to facilitate tumor metastasis and angiogenesis by hydrolyzing components of the extracellular matrix (ECM). Of these enzymes, gelatinase A (MMP-2) and B (MMP-9), have especially been implicated in malignant processes and thus they have been a target for drugs designed to block their activity. Therefore, understanding their molecular structure is key for a rational approach to inhibitor design. Here, we have conducted X-ray absorption spectroscopy (XAS) of the full-length human MMP-2 in its latent, active, and inhibited states and report the structural changes at the zinc ion site upon enzyme activation and inhibition. We have also examined the molecular structure of MMP-2 in complex with SB-3CT, a recently reported novel mechanism-based synthetic inhibitor that was designed to be highly selective in gelatinases. It is shown that SB-3CT directly binds the catalytic zinc ion of MMP-2. Interestingly, the novel mode of binding of the inhibitor to the catalytic zinc reconstructs the conformational environment around the active site metal ion back to that of the pro-enzyme.