

The organomercurial lyase MerB has the unique ability to cleave carbon-Hg bonds, and structural studies indicate that three residues in the active site (C96, D99 and C159 in *E. coli* MerB) play important roles in the carbon-Hg bond cleavage. However, the role of each residue in carbon-metal bond cleavage has not been well defined. To do so, we have structurally and biophysically characterized the interaction of MerB with a series of organotin and organolead compounds. Studies with two known inhibitors of MerB, dimethyltin (DMT) and triethyltin (TET), reveal that they inhibit by different mechanisms. In both cases the initial binding is to D99, but DMT subsequently binds to C96, which induces a conformation change in the active site. In contrast, diethyltin (DET) is a substrate for MerB and the SnIV product remains bound in the active site in a coordination similar to that of HgII following cleavage of organomercurial compounds. The results with analogous organolead compounds are similar in that trimethyllead (TML) is not cleaved and binds only to D99, whereas diethylead (DEL) is a substrate and the PbIV product remains bound in the active site. Binding and cleavage is an exothermic reaction, while binding to D99 has negligible net heat flow. These results show that initial binding of organometallic compounds to MerB occurs at D99 followed, in some cases, by cleavage and loss of the organic moieties and binding of the metal ion product to C96, D99 and C159. The N-terminus of MerA is able to extract the bound PbVI but not the bound SnIV. These results suggest that MerB could be utilized for bioremediation applications, but certain organolead and organotin may present an obstacle by inhibiting the enzyme