Mechanism of Hg-C protonolysis in the organomercurial lyase MerB

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The bacterial organomercurial lyase, MerB, catalyzes the demethylation of organomercurials via Hg-C protonolysis. Two Cys residues in the active site are required for catalysis, but the source of the catalytic proton and the detailed reaction mechanism have not been determined. Here, two proposed reaction mechanisms for MerB protonolysis are investigated using density functional theory calculations. A model of the active site was constructed from an X-ray structure of MerB. Calculations with the methylmercury substrate rule out direct protonation of the leaving group by Cys96. Instead, the calculations support a two-step mechanism in which Asp99 abstracts a proton from Cys96 and then protonates the nascent carbanion leaving group to cleave the Hg-C bond and release the hydrocarbon product. Computed activation barriers for three organomercurial substrates reproduce experimental reaction rates. Analysis of atomic charges using Natural Population Analysis reveals how MerB lowers the barrier in the Hg-C protonolysis reaction.