Catalytic mechanism of Hg-C bond cleavage by the organomercurial lyase MerB

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The bacterial organomercurial lyase, MerB, catalyzes the cleavage of Hg-C bonds in organomercurial species such as methylmercury ($[CH_3Hg(II)]^+$). Two cysteines (Cys196 and Cys159) and an aspartic acid (Asp99) are known to be required for catalysis, but the detailed reaction mechanism has not yet been determined conclusively. We have performed hybrid density functional theory calculations on an active-site model of MerB derived from an X-ray crystal structure of the Hg(II)-bound product complex. Stationary point structures and energies were computed for two mechanisms that have been proposed in the literature. The calculations favor a two-step mechanism in which Asp99 first abstracts a proton from one of the two cysteines and subsequently protonates the organic leaving group. We show that coordination of organomercurials by two cysteine thiolates is sufficient to activate Hg-C bonds. Natural Population Analysis reveals that MerB lowers the activation energy of the Hg-C bond cleavage reaction by redistributing electronic charge into the leaving group and away from the catalytic proton.