

Origin of Strong Affinity of Mercury for Soft Ligands and Mechanism of the Mercuric Ion Reductase MerA

University-Led Research

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ABSTRACT

Mercuric ion reductase, MerA, is the key enzyme in bacterial mercury-resistant (*mer*) system by reducing the mercuric ion Hg^{2+} to elemental Hg^0 . Each of the two subunits of MerA homodimer contains two cofactors, the dihydronicotinamide adenine dinucleotide phosphate (NADPH) and the flavin adenine dinucleotide (FAD). The essential cysteine residues of MerA catalysis include the inner pair C136/C141 (*Pseudomonas* Tn501 MerA numbering) and the C-terminal pair C558'/C559' of the other monomer. Here, quantum mechanical/molecular mechanical (QM/MM) simulations have been performed to study the different steps of MerA reduction, including a) equilibration between two redox states, NADPH/FAD and NADP^+ /FADH⁻, of the cofactors, b) Hg^{2+} -transfer from the C-terminal to the inner cysteine pairs, and c) the reduction of the C136-C141 disulfide and the C136-S-Hg-S-C141 complex by FADH⁻, the two-electron reduced FAD. These results collectively provide an atomistic understanding of the MerA mechanism, and may help to understand the metal-trafficking processes inside proteins and mechanisms of the enzymes containing flavin and/or NAD(P) cofactors.

Why Mercury (Hg) prefers soft ligands such as thiols has been generally rationalized by the hard and soft acids and bases (HSAB) theory, from which hard metals have stronger affinities for hard ligands relative to soft ligands, and vice versa. Here, however, the quantum chemical calculations of a series of inorganic anion complexes of Hg^{2+} show two opposite trends of the binding affinities. That is, the gas-phase binding affinity of two identical anionic ligands (forming HgL_2) increases with ligand hardness, in contrast, the aqueous-phase affinity increases with ligand softness. This switch in affinity upon hydration is shown to result mostly from interactions with only a small number (e.g. one or two) of water molecules. The results yield a clear, robust periodic trend within the chalcogenide and halide groups and are in agreement with the well-known experimentally observed preference of Hg^{2+} for soft ligands. By comparing the Hg^{2+} binding of one with two anions, the gas phase preferences are found to arise from the enhancement of reactivity of the cationic complex (HgL^+) with the hardness of L. This approach establishes a theoretical basis for understanding Hg speciation in the biosphere.