ABSTRACT: Mercury's preference for soft ligands such as thiols has been conceptualized in the theory of hard and soft acids and bases (HSAB), i.e. hard (less polarizable) metals have higher affinities for hard ligands than for soft (more polarizable) ligands, and vice versa. We have made the surprising finding that absolute affinities of Hg²⁺ for two anionic ligands (L⁻) computed in the gas phase trend in the opposite direction to those affinities computed in water. That is, the gas-phase free energy of forming HgL²⁻ becomes more favorable with ligand hardness. In contrast, the aqueous-phase Hg²⁺ affinity increases with ligand softness. This switch in affinity upon hydration becomes apparent on addition of as few as two explicit water molecules and is obtained within both the chalcogenide and halide groups, in agreement with the long observed preference of Hg²⁺ for soft ligands in aqueous solution. Moreover, by comparing binding of one versus two anions to Hg²⁺, we found that the gas-phase trend for forming HgL²⁻ arises from the enhanced reactivity of HgL⁺++. Our approach establishes a quantitative theoretical basis for predicting Hg speciation in the biosphere.

Mercuric reductase, MerA, the key enzyme in the bacterial mercury resistance (mer) system, catalyzes the NADPH-dependent reduction of mercuric ion, Hg²⁺, to elemental Hg⁰. Each of the two monomers of the MerA homodimer contains a flavin adenine dinucleotide (FAD) cofactor that mediates electron transfer from NADPH to Hg²⁺ bound to the inner pair of cysteines in the active site (C136/C141 of Pseudomonas aeruginosa Tn501 MerA numbering). A second cysteine pair at the C-terminus of the other monomer (C558'/C559') is essential for acquiring and transferring Hg²⁺ to the inner pair. Here, quantum mechanical/molecular mechanical (QM/MM) simulations elucidate the steps of MerA reduction, (a) equilibration between two redox states of the cofactors, NADPH/FAD and NADP+/FADH⁻, (b) Hg²⁺-transfer from the outer C-terminal cysteine pair to the inner active site cysteine pair, and (c) the reduction of the C136-C141 disulfide and the C136-S-Hg-S-C141 complex by FADH⁻, the two-electron reduced FAD. This analysis establishes the first atomic-level, energetic description of the MerA mechanism and contributes generally to understanding intracellular metal trafficking and catalysis by the larger family of NAD(P)-dependent flavin-disulfide oxidoreductases.