Determining Mechanisms of Hg Methylation by HgcA and intramolecular Hg transfer by MerA at the Atomic Scale

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Our team uses computational approaches to establish the physicochemical underpinnings of mercury (Hg) transformations in the environment in both aerobic and anaerobic contexts. The cobalamin-dependent protein HgcA was recently shown to be required for the production of methylmercury by anaerobic bacteria. In that work, a strictly conserved Cys residue in HgcA was predicted to be a ligand to Co(III), which has never been observed in any protein. Here, our main focus is on determining the detailed mechanism of Hg methylation carried out by HgcA. We have carried out density functional theory (DFT) calculations of model methylcobalamin complexes containing a lower-axial Cys or His ligand to cobalt, the latter of which is commonly found in other cobalamin-dependent proteins. In principle, methylcobalamin can transfer a methyl group as a carbocation, radical, or carbanion, but only the latter two species are plausible for transfer to an electrophilic substrate such as Hg(II). We find that Cys thiolate coordination to Co facilitates both methyl radical and methyl carbanion transfer to Hg(II) substrates, but carbanion transfer is predicted to be more favorable overall when condensed phase solvation effects are taken into account. Our calculations support the proposal that the strictly conserved Cys in HgcA enhances the methylation of Hg(II). In other work, we have investigated the capture and transfer of Hg2+ in the principal enzyme involved in bacterial mercury resistance, the mercuric reductase MerA. We performed quantum mechanical/molecular mechanical (QM/MM) calculations to characterize intramolecular Hg2+ transfer from the C-terminal pair of cysteines to the active site pair in the catalytic core of MerA. We find that the transport of this soft, divalent cation is made energetically feasible by pairing a competition between multiple cysteine thiolates for Hg2+ with a competition between Hg2+ and protons for the thiolates. Finally, we have computed the pKas of the cysteine pair in NmerA, the N-terminal metallochaperone domain of MerA, compared them with experimentally determined values, and here we provide insight into their unique Hg-binding properties.