Mercury Methylation by HgcA: Theory Supports Carbanion Transfer to Hg(II)

Contact: Jerry Parks (parksjm@ornl.gov, 865-574-9259)
DOE/Office of Science/Biological & Environmental Research

Objective
• Use quantum chemistry to understand the mechanism of mercury methylation by HgcA.

New Science
• Density functional theory calculations on models of methylcobalamin with cysteine coordinated to cobalt, as predicted for HgcA in Parks et al. 2013.
• Calculations suggest cysteine coordination facilitates transfer of both a methyl radical (CH$_3$\textsuperscript{.}) and methyl carbanion (CH$_3$\textsuperscript{-}).
• Carbanion transfer to Hg(II) is more favorable overall when solvent effects are included.

Significance
• Our data suggest that bacterial mercury methylation proceeds by a methyl transfer mechanism that has not been observed previously for any cobalamin-dependent protein.

Many proteins use corrinoid cofactors to facilitate methyl transfer reactions. Recently, a corrinoid protein, HgcA, has been shown to be required for the production of the neurotoxin methylmercury by anaerobic bacteria. A strictly conserved cysteine residue (Cys) in HgcA was predicted to be a lower-axial ligand to Co(III), which has never been observed in a corrinoid protein. Here, we use density functional theory to study homolytic and heterolytic Co–C bond dissociation and methyl transfer to Hg(II)substrates with model methylcobalamin complexes containing a lower-axial Cys or histidine (His) ligand to cobalt, the latter of which is commonly found in other corrinoid proteins. We find that Cys thiolate coordination to Co facilitates both methyl radical and methyl carbanion transfer to Hg(II) substrates, but carbanion transfer is more favorable overall in the condensed phase. Thus, our findings are consistent with HgcA representing a new class of corrinoid protein capable of transferring methyl groups to electrophilic substrates.