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ARSENIC INTERACTIONS WITH SMALL THIOL MOLECULES: MODEL REACTIONS FOR ARSENITE AND MONOMETHYLARSENITE BIOCHEMISTRY

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The toxicity of arsenic is believed to originate from the affinity of As^{3+} and As^{5+} species for cysteine (Cys) thiols (S^-) in key target proteins, including enzymes that have catalytically essential Cys residues. In spite of these known biological As-thiol interactions, the solution chemistry of As and simple thiol ligands is not well understood. Consequently, we have undertaken a study to quantify the binding reactions of biologically-relevant As species with a set of simple monothiol and dithiol ligands. The arsenic species being investigated are arsenite ($As(OH)_3$) and monomethylarsenite ($As(CH_3)(OH)_3$), and the thiols in this study include the monothiol glutathione (GSH) and the dithiols dithiothreitol (DTT), dimercaptosuccinic acid (DMSA), and dihydrolipoic acid (DHLA). To quantify arsenic binding to simple thiols in solution and thereby provide data (i.e. binding constants) and insight for future studies of As-protein interactions, we are using a combination of colorimetric (UV-visible absorption) and calorimetric (heat flow) measurements. The former indicates the formation of As-thiol complexes by the appearance of charge transfer absorption bands in the near-UV, and the data have been analyzed with SPECFIT fitting software. The latter detects the net heat that is released (or absorbed) upon complex formation, thereby allowing us to quantify the thermodynamics (enthalpy and entropy) of As-thiol interactions. In this study we are able to compare As interactions with mono- and dithiols, quantify differences between arsenite and monomethylarsenite binding to thiols, and determine the bonding differences in a series of vicinal dithiols that form 5-, 6- and 7-membered rings with As^{3+}.