Metallothionein Zn(2+)- and Cu(2+)-clusters from first-principles calculations.

Detailed electronic structures of Zn(ii) and Cu(ii) clusters from metallothioneins (MT) have been obtained using density functional theory (DFT), in order to investigate how oxidative stress-caused Cu(ii) intermediates affect Zn-binding to MT and cooperatively lead to Cu(i)MT. The inferred accuracy is ~0.02-0.03 Å for metal-thiolate bond lengths for the models that are the most realistic MT models so far studied by DFT. We find terminal Zn-S and Cu-S bond lengths of 2.35-2.38 Å and 2.30-2.34 Å, whereas bridging M-S bonds are 0.05-0.11 Å longer. This electronic effect is also reflected in changes in electron density on bridging sulfurs. Various imposed backbone constraints quantify the sensitivity of cluster electronic structure towards protein conformational changes. The large negative charge densities of the clusters are central to MT function, and the smaller β-clusters are more prone to modification. Oxidative stress-associated Cu(ii) binding weakens the Zn-S bonds and is thus likely to impair the Zn(ii) transfer function of MTs, providing a mechanism for cooperative Cu(ii) binding leading to loss of Zn(ii) and dysfunctional Cu(i)MT clusters.