Ligad Modulation of Mixed Valency and Redox Potentials of Cu_A Center and its Possible Roles in Proton-Coupled Electron Transfer

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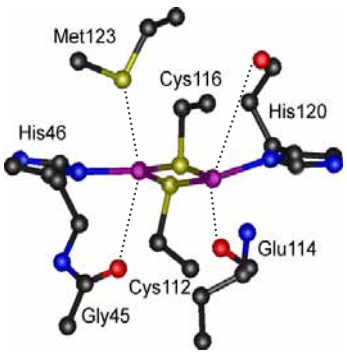
The Cu_A center is a mixed-valence dinuclear copper center, with each copper coordinated to a histidine and both coppers bridged by the thiolate sulfurs of two cysteine ligands (Figure 1). Until recently there were not many examples of fully delocalized mixed valence dinuclear copper compounds. Even rarer is the reversible conversion between different classes of compounds with delocalized and trapped valence states. We have demonstrated reversible transition between delocalized and trapped valence states of an engineered Cu_A center in azurin, triggered by pH (1). The C-terminal His is the site of protonation that resulted in a trapped valence. Since the corresponding C-terminal His in cytochrome *c* oxidases is along a major electron transfer (ET) pathway from Cu_A to heme *a*, and since the protonation resulted in an increased redox potential that will prevent ET flow from the Cu_A to heme *a*, the results strongly indicate that the Cu_A and the His may play an important role in proton-coupled ET. In addition, the same series of mutations at a conserved axial Met in both blue copper and Cu_A azurins indicate the Met has much less influence on reduction potentials in a Cu_A center (< 25 mV) than in a blue copper center (> 170 mV) (2-4). This finding may be important in understanding different roles of the two copper centers. The much wider range of redox potentials (> 1000 mV) is needed for blue copper proteins in order to transfer electrons to a variety of partners in many different biological systems. In contrast, the Cu_A center is part of cytochrome c oxidase that is at the end of the respiration chain with small potential differences (< 50 mV) between the redox partners. In this case, large variation of redox potentials is not desirable and could result in a loss of electron flow in the correct direction. The Cu_2S_2(Cys) diamond core structure of the Cu_A is one way to minimize changes in redox potential by axial ligand variations.



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