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The *bis*(μ-thiolato) di-copper centre in cytochrome oxidase: A novel conformational switch for electron transfer

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Cytochrome oxidase is a ubiquitous membrane-bound enzyme involved in the terminal stage of the respiratory electron transfer chain in cellular respiration. The enzyme consists of three metal active centres namely, the binuclear copper (CuA) site, six-coordinated heme *a*(Fe: *a*) site and the binuclear iron–copper catalytic site (Fe: *a*3-CuB). We are interested in the understanding of the structural and mechanistic aspects of the biochemical functions of cytochrome oxidase and have been involved in detailed spectroscopic and kinetic studies of the enzyme and its analogues.

The binuclear copper (CuA) site forms the first electron entry point in the enzyme. It is located in sub-unit II of the enzyme exposed to the matrix side of the membrane. This CuA site consists of a novel *bis*(μ-thiolato) bridging by two cysteine (C220 & C216) residues. The other ligands to the copper centres are His181, His224, Glu218 and Met227. The native enzyme has been shown to consist of mixed valence coppers at this site with an average charge of 1·5 units on each copper. The mechanism of electron transfer to and from the CuA site in cytochrome oxidase is a subject of immense interest.

The soluble fraction of the sub-unit II cloned and over-expressed in *E. coli* has been studied as a model of the electron entry site (CuA) of cytochrome oxidase. The CuA site in the sub-unit II was found to exist in a *p*H induced conformational equilibrium with a high *p*H conformer being preferred at elevated temperatures. Such conformational fluctuations can provide a gating mechanism for the electron transfer process. We discuss some of our recent results on this conformational equilibrium in the dicopper site in the light of understanding of the functional properties of the intact enzyme.