Modeling Study of Oxygen Activation in Cytochrome *c* Oxidase: Roles of Residues at the Active Site

Yoshinori Naruta, Jin-Gang Liu, Xing-Mei Ouyang, Takefumi Chishiro,
Takumi Higa, and Fumito Tani
Institute for Materials Chemistry and Engineeing Kyushu University

The active site of cytochrome c oxidase, at which dioxygen reduction takes place, is composed of heme a_3 and Cu_B dinuclear center. Heme a_3 is axially ligated by a histidinyl imidazole, while Cu_B has tridentate chelation with three histidine ligands, one (His^{240}) of which is linked to a tyrosine residue (Tyr^{244}) via a covalent bond (in the bovine enzyme sequence). The function of this unprecedented Tyr-His cross-link has provoked considerable interests, and has been proposed to function either as an electron and proton donor to the dioxygen bound to heme a_3 or to provide a means to fix Cu_B in an optimal configuration and distance from heme a_3 during the catalytic O_2 reduction. The roles of Cu_B are another issues, which have not been well-defined too.

In order to clarify these issues, we have stepwise constructed the closely mimicking active-site models containing a N^4Cu complex, a His-Tyr equivalent, and an axial N ligand to the heme.[1] In these models, all groups were linked by tethers in one molecule. The reduced form $[Fe^{II}\ Cu^{I}]$ gives the corresponding peroxo complex at low temperature. At this stage any effect of the Tyr equivalent on the peroxo complex are not observed. However, upon its warming, the model with a free Tyr equivalent shows the conversion of the peroxo $[Fe^{III}\text{-}O_2\text{-}Cu^{II}]$ the corresponding supeoxo complex $[Fe^{III}\text{-}O_2\bullet\ /\ Cu^{I}]$. The bound O_2 is quite stable and does not revert to the corresponding deoxy form. These results suggest the roles of Tyr group and the Cu complex in the early stage of the oxygenation.

We will also discuss on the difference of the coordination mode of O_2 by the Cu_B mimics with N^3/N^4 ligands.

1. (a) J.-G. Liu, Y. Naruta, *et al. Chem. Commun*. **2004**, 120; (b) *Angew. Chem. Int. Ed.* **2005**, *44*, 1836.