SUPPLEMENTARY MATERIAL

Exploring the Topography of Free Energy Surfaces and Kinetics of Cytochrome *c* Oxidases interacting with small ligands

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Figures (1-6) in the main article obtained from a canonical ensemble of 25000 configurations are reproduced here by using the data of just one trajectory (5000 configurations) to check the sensitivity of the free energy surfaces on the sampling procedure.

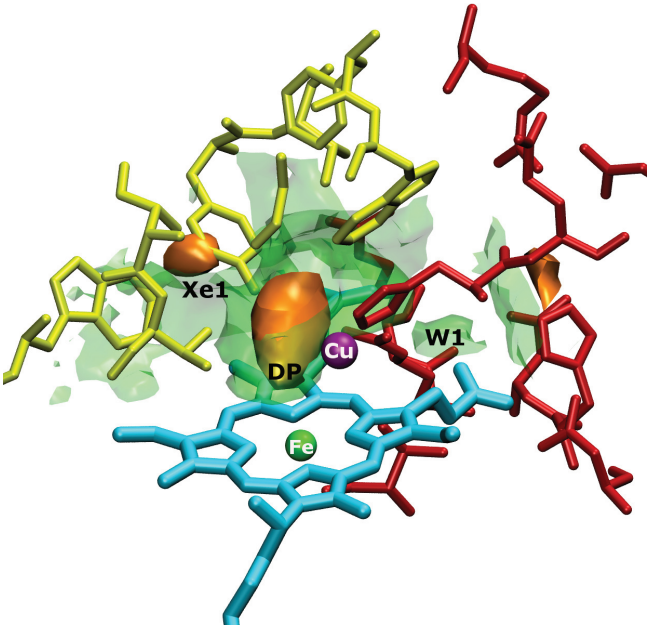

Fig. 1: Three-dimensional view of the ba_3-CcO active site interacting with O_2 ligand. The orange surfaces correspond to a free energy isovalue of −2.6 kcal/mol and the transparent green ones corresponds to 1.5 kcal/mol. The yellow residues depict the hydrophobic Xe1 cavity, while the red residues depict the hydrophilic W1 cavity. Iron atom is displayed in green, copper in purple and the heme-a_3 is represented in cyan.

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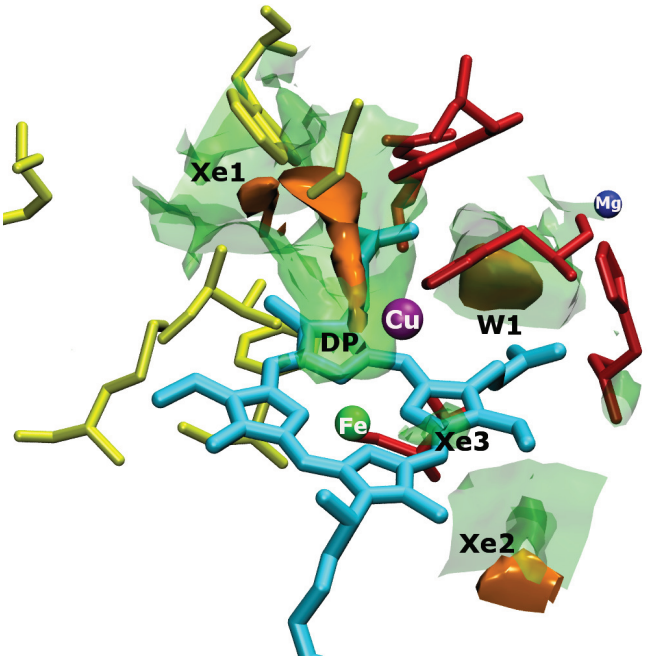

Fig. 2: Three-dimensional view of the active site of aa_3-CcO interacting with O_2 ligand. The orange surfaces correspond to a free energy isovalue of −0.85 kcal/mol and the transparent green ones corresponds to 1.6 kcal/mol. The yellow residues depict the hydrophobic Xe1 cavity and the red ones depict the hydrophilic W1 cavity. Xe2 and Xe3 cavities belonging to the channel accounted as the third one in the text and close to the hydroxyfarnesilethyl group are also shown. Iron atom is displayed in green, copper in purple, magnesium in blue and the heme-a_3 is represented in cyan.

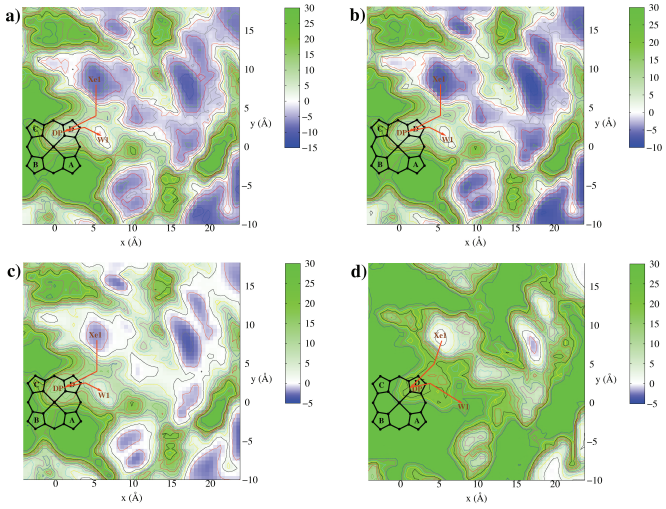

Fig. 3: Free energy contour plots for the ba_3-ligand systems. The contours represent free energy values (kcal/mol) averaged along the z coordinate. The origin of the coordinates system is on Fe atom and the heme lies on the *xy* plane. Panel a) CO, b) NO, c) O_2 and d) Xe. The red arrows indicate schematically the pathways to enter and to exit the active site.

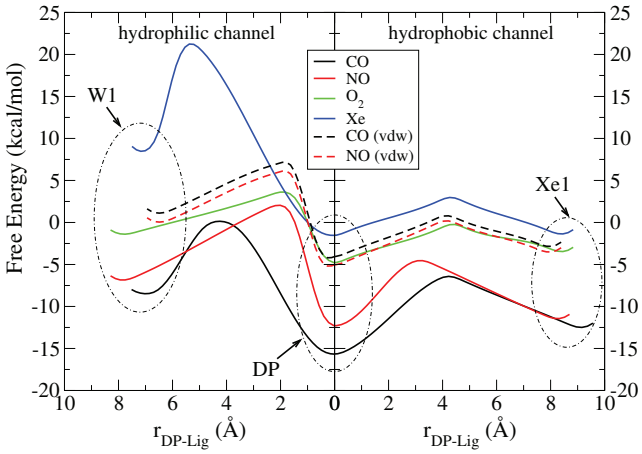

Fig. 4: Free energy profiles for the entrance of the ligand into the binuclear center through the hydrophobic channel and its exit through the hydrophilic channel in ba_3-ligand systems. The origin of the reaction coordinate (r_{DP-Lig}) is placed at the minimum of DP cavity.

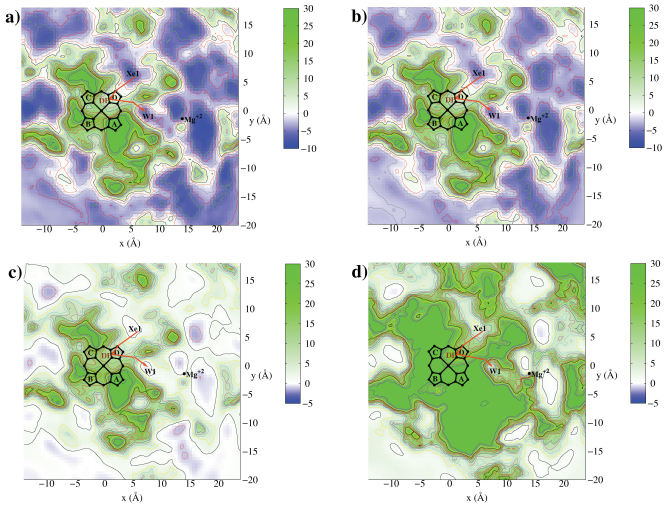

Fig. 5: Free energy contour plots for the aa_3-ligand systems. The contours represent free energy values (kcal/mol) averaged along the z coordinate. The origin of the coordinates system is on Fe atom and the heme lies on the *xy* plane. Panel a) CO, b) NO, c) O_2 and d) Xe. The red arrows indicate schematically the pathways to enter and to exit the active site.

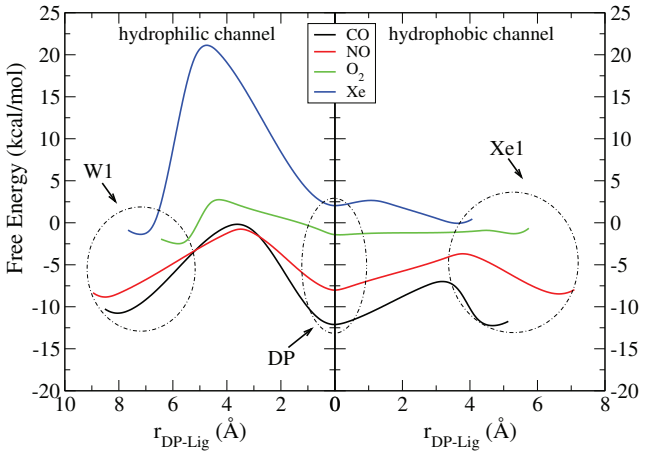

Fig. 6: Free energy profiles for the entrance of the ligand into the binuclear center through the hydrophobic channel and its exit through the hydrophilic channel in protein-ligand systems. The origin of the reaction coordinate (r_{DP-Lig}) is placed at the minimum of DP cavity.