CHANGES OF IRON STATE AND LOCAL IRON ENVIRONMENT OF MALARIAL PIGMENT'S SUBSTITUTE IN PRESENCE OF CHLOROQUINE

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Malaria remains the world's most prevalent vector-borne disease, which causes serious health problem particularly in African and Asiatic countries [1]. The most severe form of malaria is caused by Plasmodium falciparum (Pf) parasite. The intraerythrocytic stage of Pf involves hemoglobin proteolysis and detoxification of heme molecules into an inert crystalline material, called malarial pigment, or hemozoin. The crystal structure of hemozoin has been solved by X-ray powder diffraction in the last years and its synthetic analogue, β-hematin was synthesized [2]. The ferriprotoporphyrin IX is believed to be a target for commonly used antimalarial drugs but their interactions are still not understood on molecular level.

In presented work we are especially interested in drug-induced perturbations of the structures of soluble β-hematin-like compound, iron(III) (meso-porphyrin-IX anhydride) called meso-hematin. Similarly to its insoluble parent compound, β-hematin, this compound is also built of dimers. The XAS measurements on frozen sample of meso-hematin in solution were performed at ESRF (station ID26). Pure acetic acid and acetic acid with water of volume ratio respectively 30:1 and 15:1 were used as solvents. The high resolution XANES and EXAFS spectra on iron K-edge enabled us to reveal the evolution of iron oxidation state and local environment of Fe atoms in investigated solutions upon chloroquine drug addition. The main difference revealed by EXAFS concerns the coordination number of the ligand oxygen, which is lower in the presence of chloroquine for both the water containing solutions. On the other hand the Fe-O distance is significantly shorter in solution with smaller H_2O/acetic acid ratio and at the presence of drug. Analysis of the XANES revealed small changes in local iron geometry and its spin state, being close to $S = 3/2$, instead of $S = 5/2$ observed in natural product of malaria parasite – microcrystalline hemozoin.

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References

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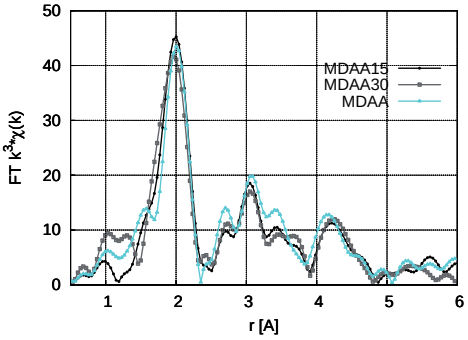

Figure 1. Comparison of Fourier transformed EXAFS oscillationsof solved meso-hematin without (MDAA) and with (MDAA15, MDAA30) water addition.

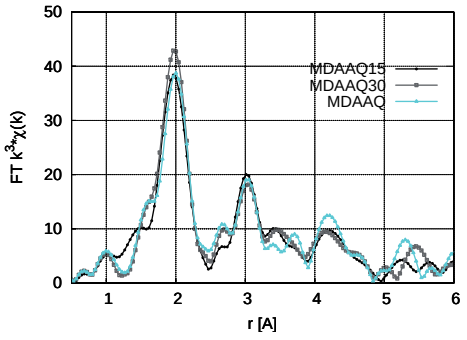

Figure 2. Comparison of Fourier transformed EXAFS oscillations of solved meso-hematin in chloroquine presence without (MDAAQ) and with (MDAAQ15, MDAAQ30) water addition.