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Characterization of Chloroquine-Ferriheme Solution Structure Using EXAFS and MD

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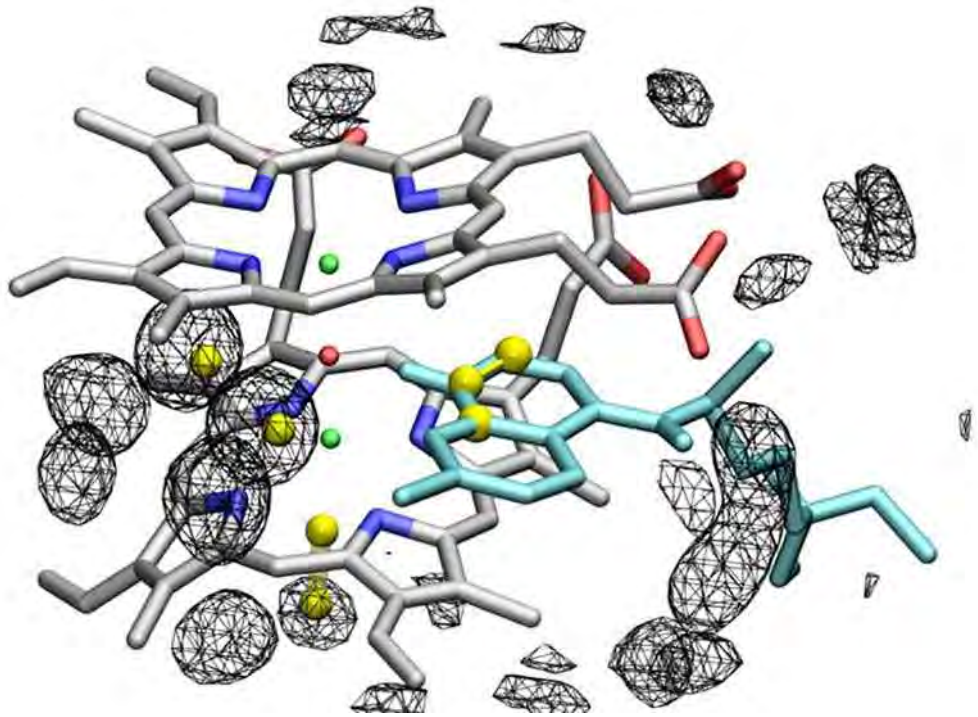
The complex formed between the antimalarial drug chloroquine (CQ) and its target iron(III)protoporphyrin IX (ferriheme) in aqueous solution is of considerable importance in understanding its mechanism of antimalarial activity. Recently, convincing evidence showed that CQ induces the μ-oxo dimeric form of ferriheme in aqueous solution, but the structure of this complex in solution is uncertain.[1] Molecular dynamics (MD) simulations in aqueous solution were used to model the structure of μ-oxo ferriheme and two possible conformations of the CQ-ferriheme complex, one in which CQ π-stacked with the unligated face of ferriheme and the other in which CQ was docked between the porphyrin rings. The EXAFS spectrum of μ-oxo ferriheme obtained from frozen solution strongly supported the hydrated structure determined from MD simulation where an excellent fit to the spectrum was only obtained when incorporating waters of hydration at regions identified by computation. On the other hand, the EXAFS spectrum recorded on the dried solid of μ-oxo ferriheme required no solvating waters to produce excellent agreement with the crystal structure of μ-oxo ferrihaem dimethyl ester.[2] The EXAFS spectrum recorded on a frozen aqueous solution of the CQ-ferriheme complex was able to distinguish between the two conformations modeled computationally. Fits to the EXAFS spectrum using the π-stacked structure produced poor agreement while those obtained using the docked conformation reproduced the spectrum well. This indicated that the latter is the most likely form of the CQ-ferriheme complex in aqueous solution.

[1] *D. Kuter, S.J. Benjamin and T.J. Egan, J. Inorg. Biochem., 2014, 133, 40-49.,* ***[2]*** *L. Chen, J. Lee, D.R. Powell and G.B. Richter-Addo, Acta Crystallogr., 2004, E60, m1340.*



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