

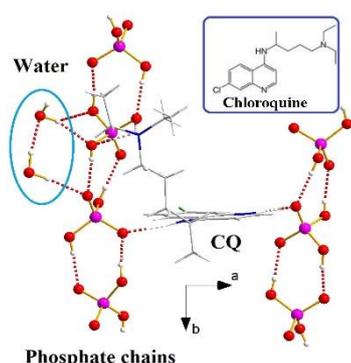
Understanding self-recognition in the antimalarial drug chloroquine: an experimental and theoretical charge density study

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Malaria is the topmost world parasitic disease, with hundred of thousand deaths for year, most of which being children with less than 6 years of age. The infection is due to Plasmodium protozoa and is transmitted through the bite of Anopheles mosquitoes. When the parasites enter in the circulatory system, it infects human erythrocytes and digest the haemoglobin, releasing haeme (Fe(II)-protoporphyrin-IX). Since free haeme is toxic to the parasite, it deactivate the iron-containing scaffold by promoting its dimerization and consequently the crystallization of dimeric haeme as β -haematin, a pale yellow insoluble crystal.

Chloroquine (CQ) is an aminoquinoline type drug used widely in the past for the treatment of malaria until resistant strains of *P. Falciparum* appeared. However, neither the mechanism of action nor the mechanism of action have been fully elucidated. The final purpose of this project is to understand the mechanism of interaction between CQ and haeme studying the self-recognition in this antimalarial drug. In this context, the present work focuses on the experimental and theoretical characterization of chemical bonds and intermolecular interactions in crystalline CQ [Karle & Karle, *Acta Cryst.* (1988). C44, 1605].



Chloroquine diphosphate salt was crystallized by various methods, including sol-gel techniques. Single-crystal X-Ray data collections were performed among room temperature (RT) and 100 K, using a Mo K α source. CQ is a dication with protonated basic functions on quinolone. In the solid-state, complex patterns of hydrogen bonds (HBs) involving both the phosphate groups and co-crystallized water molecules are set up. Phosphate ions form infinite chains parallel to the monoclinic *b* axis, while CQ molecules keep their fused ring system orthogonal to the chains (see the Figure), setting in the free space among them through allegedly strong N–H \cdots O HBs. The role of the two water molecules is less clear, even though they should help to coordinate phosphate ions. Even at 100 K, the X-ray data were not able to unequivocally determine the exact position of the H atoms. We therefore

complemented the X-ray model by solid-state DFT simulations, but at least one water hydrogen has no obvious close acceptors and some kind of disorder cannot be excluded.

On the basis of the solid-state DFT model, we applied the Hansen-Coppens multipolar approach [Hansen & Coppens, *Acta Crystallogr.*, Sect. A 1978, 34, 909] to study the experimental charge density in CQ diphosphate. The effect of the crystal field on the molecular conformation and the self-recognition energetics were investigated by both topological and quantum mechanical approaches. The importance of different intermolecular interaction patterns in setting up a stable crystal field is discussed.