

A Test of the Ligand Field Molecular Mechanics as an Efficient Alternative to QM/MM for Modelling Metalloproteins: The Structures of Oxidised Type I Copper Centres

Robert J Deeth

Computational details

Protein sequences were obtained where possible from the MOE database (MOE 2005.06), otherwise they were downloaded from the Protein Data Bank. The metal and any solvent molecules were removed and the structure carefully checked against the published sequence for missing or incorrect residues. Partial atomic charges were assigned according to AMBER94 rules within the following features applied. The C and N termini were assumed to be ionised as were all carboxylate-containing side chains. All lysines and arginines were assumed to be positively charged while histidines were made neutral apart from the two ligating histidines which were protonated. Neutral histidines carried the H atom at the delta position. The apo proteins were checked to ensure they carried an overall integer charge.

The copper was then inserted and the delta protons from the coordinating histidines plus the cysteine H removed. The copper was then joined to the relevant donor groups and assigned a charge of +0.9556. To ensure MOE automatically assigns the correct atom types, all donor atoms are assigned a HintLP.

The protein was then solvated with water molecules to a depth of 5 Å. In the vicinity of the solvent exposed histidine, the solvation layer was increased to 15 Å. This resulted in a droplet comprising 600 – 800 water molecules. The protein atoms were then fixed and the water shell minimised to a gradient of 0.05 followed by 10 – 20 ps of molecular dynamics (NVT ensemble, fixed water geometry). The water sheath was then reminimised to a gradient of 0.05. Finally, a complete LFMM geometry optimisation of protein plus water was carried out to a gradient of less than 0.01.

DFT calculations used the ADF 2005 package. Geometries were optimised in vacuo using the BP86 functional with TZP bases on the copper and the immediate donor atoms and DZP on all remaining non-hydrogen atoms. A DZ basis was used for H. Frozen cores up to 2p were used on Cu and S and up to 1s on C and N.