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Hybrid QC/MM potential simulations of iron-containing proteins

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INTRODUCTION

Theoretical studies of proteins containing transition metals require a proper description of the metal unpaired electrons. The reactivity of these metalloproteins is usually correlated with the metal open shell electronic configurations. In this work we simulated two classes of metalloproteins: Myeloperoxidase (MPO) catalysis of chloride to hypochlorite oxidation reaction; and various iron-sulfur proteins (ISP) on going a reduction reaction.

METHODS

Initial configurations for MPO and the ISP proteins rubredoxin, ferredoxin, Rieske and mitoNEET[1,2] were obtained from crystallographic structures. All protein models were built in a salt neutralized water box. Energies were calculated with either a pure MM force-field or a quantum chemical/molecular mechanical (QC/MM) hybrid potential with several different density functional theory (DFT) functionals. In particular, the OPBE functional and DZP basis set were used. MM parameters were developed for the iron prosthetic groups. In the QC/MM calculations for MPO, the active site equipped with a heme center and the groups covalently linked to heme were included in the QC region. For the ISPs, the iron-sulfur clusters and its coordinated residues were described in the QC region.

Molecular dynamics (MD) simulations were run with the pure MM potential. Geometry optimizations and single-point energy calculations were performed along selected structures obtained from these MD trajectories with the hybrid QC/MM potential. Redox free-energies were calculated using the linear response[3] approximation. The CHARMM36 force-field was used for all MM calculations. MD simulations were performed with GROMACS version 4.6.7. Hybrid potential calculations were done with the pDynamo library version 1.8 interfaced with ORCA version 3.0.1 for QC calculations.

RESULTS AND DISCUSSION

For MPO, the QC/MM calculations indicate an associative (An+Dn) mechanism for the chloride oxidation reaction. Other mechanisms were also tested but shown to be energetically unfeasible. High residence water sites near the heme group were detected in MD simulations and are in line with a possible hydration reaction of the heme group.

For the ISPs, redox potential calculations showed that pure MM force-fields are unable to distinguish among several tested mutants with measured redox potentials. However, QC/MM calculations are in reasonable agreement to the experimental data. The convergence of the redox potential calculations with varions DFT functionals, basis sets, and simulation details of the hybrid potential are analysed. Protein environment flexibility and polarization effects are found to be important for the calculation of redox potentials in these ISPs.

CONCLUSIONS

Modeling iron proteins is still a challenge. Hybrid potentials are useful in describing key elements of the electronic structure of these protein active metal centers. These hybrid potentials may also be used for the calculation of experimental observables and reaction mechanisms.

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