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The effect of protein structure on O_2 binding to heme: the hybrid QM/MM study

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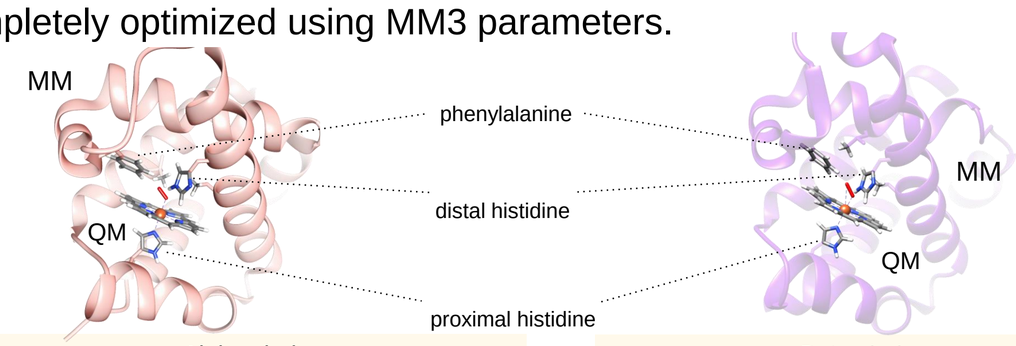
Motivation

The mechanism of the photodissociation of oxyhemoglobin is debated for years due to its exceptional biologically importance. The binding of oxygen to the Fe-porphyrin complex involves structural changes in the protein. The effect of proximal histidines has been well established for the heme oxygen affinity. In contrast, the impact of peripheral residues, heme isomers and structure distortions on oxygen binding is still being actively investigated. The existence of a hydrogen bond between distal histidine and dioxygen has been established by experiment [1].

1. Kepp K.P., Dasmeh P. Effect of distal interactions on O_2 binding to heme // Phys. Chem. B.-2013.-117, N 14.-P. 3755–3770.

Methodology

We simulated the effect of hemoprotein structure on oxygen binding using a hybrid quantum mechanical-molecular mechanical (QM/MM) method and embedded clusters - SIMOMM (Surface Integrated Molecular Orbital Molecular Mechanics) with GAMESS/TINKER software. Density functional theory method and all-electron 6-31G(p,d) basis set with p, d polarization functions were used for the QM region. The MM region was completely optimized using MM3 parameters.

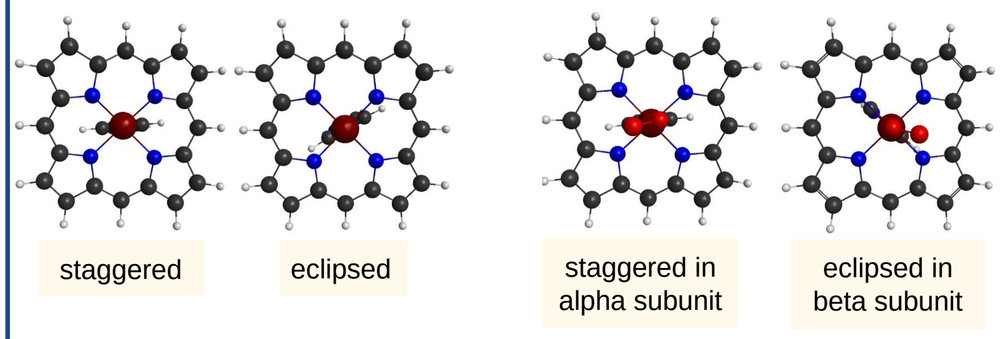


Alpha chain
QM: B3LYP/6-31G(p,d), O_2-$Fe_1N_8C_{34}H_{34}$
MM: MM3 Force Field, 2201 atoms of the alpha chain, from 2dn1.pdb (RCSB PDB)

Beta chain
QM: B3LYP/6-31G(p,d), O_2-$Fe_1N_8C_{32}H_{26}$
MM: MM3 Force Field, 2290 atoms of the beta chain, from 2dn1.pdb (RCSB PDB)

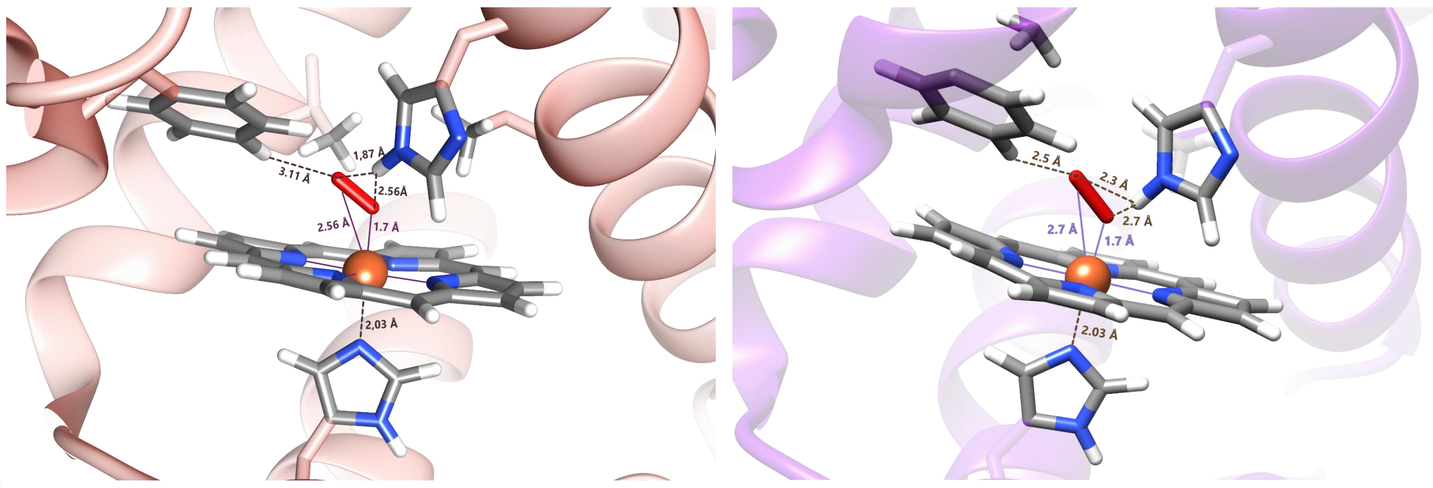
QM regions are shown by ball-and-stick models

Proximal histidine positions



- The staggered position of the proximal histidine is preferred for both heme and oxyheme in an alpha subunit, while the eclipsed position is preferred for the proximal histidine in the beta subunit have been revealed using QM/MM simulations;
- The energy gain of the staggered position of the proximal histidine is about 4.62 kcal/mol has been obtained using pure QM modelling.

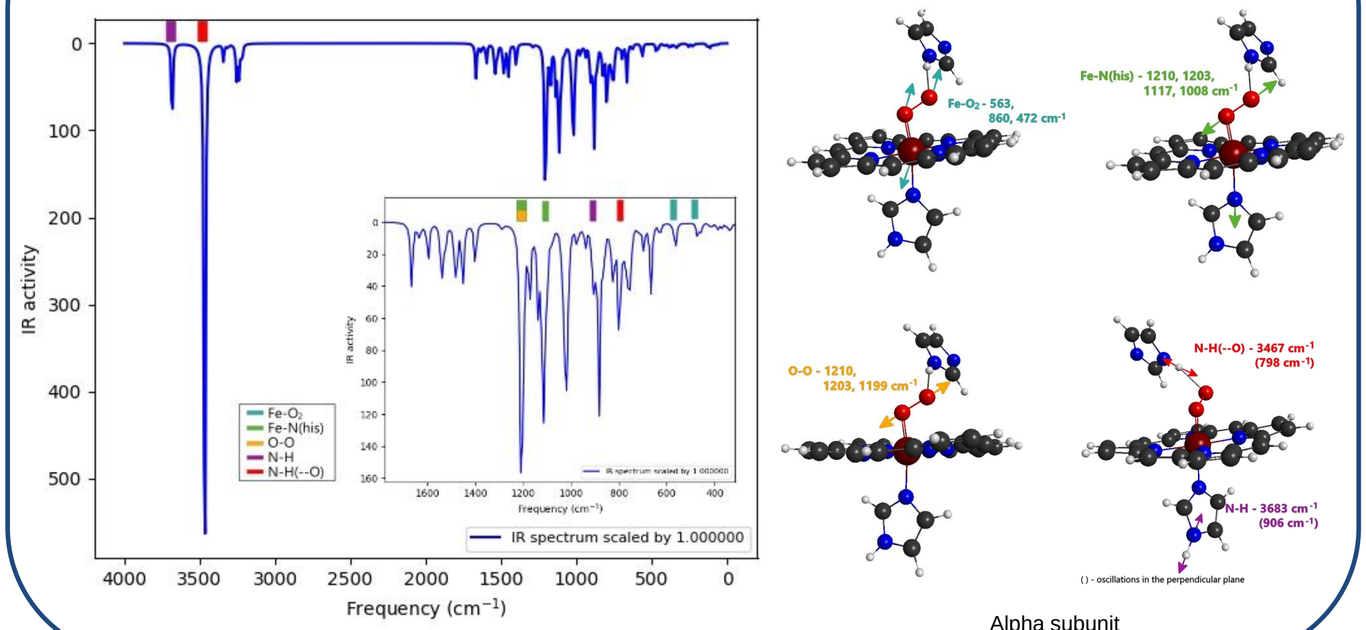
Oxyhemoglobin structures



Alpha subunit

Beta subunit

Vibrational Spectrum of the oxyhemoglobin



Alpha subunit

- Hydrogen bonds are formed between oxygen molecule and peripheral residues, both distal histidine and/or phenylalanine;
- A hydrogen bond between oxygen molecule and distal histidine is more robust in an alpha chain;
- A hydrogen bond between oxygen molecule and phenylalanine residue is more substantial in a beta chain;
- Shortening Fe-N(his) distance and curving structure of heme due to oxygen molecule binding;
- More curved structures of oxyheme has been obtained using hybrid QM/MM simulations than using pure QM models;
- The binding energies of O_2 molecule to iron in heme are in the range 4-14 kcal/mol for different models of the active site for oxyhemoglobin in different environments.

Conclusions

The binding energies of O_2 to the Fe atom in heme were calculated for different models of active sites. The obtained binding energies of Fe-O_2 is about 4 kcal/mol using hybrid QM/MM simulation. Higher values of 10 and 14 kcal/mol of the affinity of the oxygen molecule to the Fe atom were obtained using pure QM simulations in vacuum and solvent, respectively;
Hybrid QM/MM studies have shown the hydrogen bonds existence between oxygen molecule and peripheral residues (distal histidine and phenylalanine) in the oxyhemoglobin.
Calculated vibrational spectra are in agreement with the experiment.