Determination of Force Field Parameters for the Octahedral Iron Complex in Lipoxygenase

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1 Introduction

Lipoxygenases catalyze the position- and stereospecific dioxygenation of fatty acids and lipids to chiral conjugated hydroperoxy fatty acids. They are found in all higher organisms. Their products are the precursors of a number of physiological effectors. Some details of the catalytic mechanisms of these enzymes are still not known. In particular, it is unclear how molecular oxygen penetrates deep into the binding pocket and how the fatty acid substrate is aligned to the active site containing an octahedral iron complex. To address these important points we plan to perform extensive molecular dynamics (MD) simulations. A necessary prerequisite for these calculations is to determine the force field parameters used in MD describing the molecular interactions regarding the iron complex in a physically reliable manner. In this complex, the iron is coordinated with four histidines, the C-terminal carboxy group and one hydroxy anion pointing into the binding pocket. During the reaction Fe$^{3+}$ is reduced to Fe$^{2+}$, consuming one electron which resulted from the abstraction of a hydrogen atom from the lipid substrate. The corresponding proton is taken up by the hydroxide.

$$[\text{Fe}^{\text{III}}(\text{LOX})(\text{OH})]^+ + \text{H} - \text{R} \rightarrow [\text{Fe}^{\text{II}}(\text{LOX})(\text{H}_2\text{O})]^+ + \cdot\text{R}$$

Commonly used force fields like CHARMm [4] describe the molecular interactions as follows: The bonds and bond angle potentials are approximated with harmonic potentials in terms of bond length or bond angle, respectively, dihedral rotation is subjected to a periodic potential that is a linear combination of cosine functions. Van der Waals interaction is summarized by a potential well with an attractive branch $\sim r^{-6}$ and a repulsive component $\sim r^{-12}$ and each atoms sees the electrostatic field arising from partial point charges assigned to the atoms. While Van der Waals parameters are available for all atoms and the equilibrium bond lengths can be obtained from crystallography, the force constants and charge distributions have to be derived from quantum mechanical calculations. These calculations are explained in the following.

2 Methods and Results

To save computation time the cluster was modelled in a simplified manner following the lines shown in [3] for soybean LOX. The histidines are replaced by ammonia, the C-terminal carboxyl group was modeled as formiate while the sixth ligand is the hydroxy anion (Fig. 2).

All simulations were performed on an IBM pSeries 690 Supercomputer with the QM package Gaussian [2] as DFT calculations using the B3LYP functional [1]. First the geometry was optimized. Assuming a locally harmonic potential surface the eigenvalues of the Hessian matrix (second derivative of potential energy with respect to the coordinates) represent the normal modes of molecular
vibrations. These were projected onto the internal coordinates such as bonds and angles and the force constants determined from the according frequencies.

The partial charges for the atoms were obtained using electrostatic potential fitting (ESP) where the set of atom based point charges is searched whose electrostatic potential fits best the one arising from the electron density distribution at equilibrium geometry. The sum of the partial charges have to equal the net charge of the molecule.

3 Discussion

According to crystal field theory ligand binding in coordination compounds is due to electrostatic attraction while ligand field theory also includes bonding by formation of molecular orbitals. In most cases both approaches yield the same qualitative results. Indeed the delocalization of ligand electrons into the empty 4s and the half filled d orbitals of the iron in our model is rather weak compared to a covalent bond. Thus it may simply be considered to model the binding by Coulomb interaction using a formal charge of +3 for the iron atom. Nevertheless we expect the bond and angle parameters to result in a better, more stable cluster geometry. Currently we are comparing both parameterization strategies in MD simulations.

References


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