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Electron and proton transfer reactions mediated by flavins in different molecular environments

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Summary

Molecular simulations are essential tools in order to understand such fundamental electrochemistry phenomena as electron and proton transfer mechanisms. In this context, there are many practical examples about these particular chemical processes in daily life. Electrons and protons can be transferred within a very short time from one molecule to another or from the molecule to the solute. They can be easily transferred thanks to their small masses whenever a suitable condition is set. Although these mechanisms can take place quite fast, the reaction proceeds experimental techniques taken from the state of the art theories. But there are still missing gaps when it comes to fully understand the detailed mechanisms of experimental observations. One of these issues is the exact role of solvent structure in electron and proton transfer reactions. The related question in this context is how solvent reorganization tunes the redox potential.

Either as a experimentalist or as a computational scientist, before going to laboratory or starting computational analysis, it can be argued that the solvent environments affect these light particles very strongly. In other words, the solvent controls the conductivity by surrounding the solute. The molecular environment structure fluctuates around the target molecule during the electron and proton transfer reactions.

In this thesis, we have studied electron and proton transfer mechanisms of flavins in the gas phase, aqueous solution, BLUF domain and LOV domain environments using contemporary molecular simulation techniques and Marcus Theory. Flavin has been chosen for a sample chemical structure for this thesis because of their ubiquitous redox properties in nature. These molecules can be found in many oxidation and reduction processes in biological systems. Its molecular environment largely modulates the redox potential of flavin molecules so that a change of the environment will lead to a different redox potential. However, a detailed molecular picture for reorganization of flavins' environment upon reduction is still unclear.

For this aim, we have calculated the reduction free energy curves of the redox half reactions of flavin in different environments as a function of the instantaneous gap energy (ΔE) using density functional theory based molecular dynamics simulations (DFT-MD) and hybrid quantum mechanics / molecular mechanics (QM/MM) simulations. Furthermore, we have compared DFT-MD and QM/MM results for the same system in order to understand the long range effect on redox properties.

Additionally, we have computed the free energy profiles of the de-protonation reactions of flavin in the semiquinone and fully reduced oxidation states using constrained

DFT–MD simulations. We have found, in agreement with the experiment, that the N5 site is the predominant proton acceptor, although the computed pK_a value is somewhat smaller than the experimental number. The computed pK_a for the N1 protonation in the fully reduced state is in agreement with the experimental number. We have employed two different, commonly used; reaction coordinates based on the distances between the proton and the donor and acceptor atoms. Further improvement of the accuracy of this type of pK_a calculations may require development of more advanced reaction coordinates that go beyond the description of only the proton transfer from a donor atom a first solvation shell water molecule.

As a conclusion of electron transfer parts of the thesis, we have found that the reduction potential of flavin in aqueous phase, which is calculated using free energy perturbation simulations, has the typical parabolic shape as predicted by Marcus’ theory of electron transfer. The water solvent structure undergoes significant changes within the first coordination shell upon flavin reduction. These structural changes account largely for the reorganization free energy term in the measured redox potential. However, in the second reduction reaction, from semiquinone to fully reduced lumiflavin, the inner-sphere reorganization contributes significantly via the increased ‘butterfly’ bending of the flavin. This butterfly bending causes a deviation from the linear response approximation that underlies Marcus’ theory of electron transfer.

Comparing the QM/MM simulations, in which the solvent is modeled with an empirical forcefield, with the (full) DFT–MD simulations, we have found that the response through electronic polarization plays a significant role in the latter case.

Also, a small charge transfer between flavin and solvent is observed in the full DFT treatment. As a result, we find only in the case of the QM/MM model a strong correlation between ΔE and the (pair-wise computed) electrostatic potential (ESP) at the flavin due to the solvent. By analyzing the contribution of the ESP at the flavin per solvent molecule, we can not only distinguish between the different modes of hydration by solvent molecules that coordinate at the hydrophilic and hydrophobic sides of the flavin molecule, but also quantify their contribution to the reorganization free energy by measuring the ESP fluctuations per solvent molecule.

As a conclusion of electron transfer in proteins part, by mapping the changes in electrostatic potential and solvent structure, we gain insight in how specific polarization of the flavin by its environment tunes the reduction potential. Our molecular pictures of the reorganization of the protein environment upon flavin reduction allow us to understand the different redox potentials of flavoproteins found in nature.