Michael Hoffmann, *Investigation of Bioenergetical Processes with Multiple-Length-Scale Approaches*. PhD Thesis (in English), Department of Physics, Faculty of Science, University of Paderborn, Germany (2006).

Abstract

The study of bioenergetics encompasses energy transformations in organisms. The most common manifestation of this is the ability of organisms to derive energy from its environment, to transform it into a biological useful form, and use it to grow, respond and reproduce. At a molecular and cellular level, a central issue is the coupling of energy-yielding to energy-consuming processes. Simulation of these processes often require the consideration of several length scales ranging from the electronic structure to continuum electrostatics. To handle the computational demands especially involved with conformational sampling, multiple-length-scale approaches that integrate different levels of length scale and theory are an attractive technique. In this work, multiple-length-scale techniques are used to investigate the problem of proton blockage in aquaporins and the phenomenon of color tuning in rhodopsins. Rhodopsins for instance transform light into a proton gradient (bacteriorhodopsin bR) or a photosensory response (phoborhodopsin ppR). The relation of aquaporins to bioenergetics is their to facilitate very efficiently the transmembrane flow of water but preventing dissipation of the energy stored in proton gradients across membranes by impeding proton transfer (PT) through the protein.

For characterizing the progress of long-range PT, first a new reaction coordinate (RC) is proposed and then used to simulate the PT in a model channel. The simulation suggests that this RC can be used efficiently for computing a meaningful potential of mean force. The new RC also eliminates the problems encountered by earlier suggestions and works without assuming a mechanism a priori. In addition, the effect of environments with variable electrostatic properties on the PT energetics demonstrates that the employed QM/MM/continuum electrostatics simulation protocol is capable of describing this aspect of heterogeneous environments found in biological systems.

Using these techniques, the aquaporin GlpF is investigated. The simulated water structure in the pore of GlpF is found to be consistent with previous experimental and theoretical studies. A simulation without proper treatment of long-range electrostatics, in contrast, lacks this pronounced water structure. For the PT through GlpF, a free energy barrier of $\sim$25 kcal/mol, sufficiently high to impede PT through the pore, is found. A perturbation analysis further indicates that the main contribution to the free energy barrier is the desolvation penalty for transferring a proton from bulk solvent to the single water file through the pore rather than distinct structural elements of the protein.

The mechanism of color tuning in the rhodopsin family of proteins is studied by comparing the optical properties of bR and ppR. Despite a high structural similarity, the absorption maximum $\lambda_{\max}$ is strongly shifted between them. Using a coupling of efficient methods, a wide variety of aspects including dynamical effects required for the calculation of absorption spectra are studied. The calculated shift $\Delta\lambda_{\max}$ and the magnitude of the band width agree well with experimental results. Using mutation studies and the analysis of vibrational properties allows the clear identification of two main and equally important factors that are responsible for about 90 % of the spectral shift: the counterion region at the extracellular side of retinal and the amino acid composition of the binding pocket. The good agreement between the theoretical and the experimental results shows that modern quantum mechanical methods can not only reproduce but also interpret spectral properties of photoproteins.