Abstract

Proton transfer (PT) is essential for the working of metabolic processes in organisms from bacteria to humans. Short- and long-range PT are an integral part of reactions for instance in bioenergetics and enzymatic reactions in general. For the understanding of processes in cells on an atomistic level of detail, PT plays a central role. In this work, motivated by the goal of describing long-range PT, methodological developments for atomistic simulations were made, which were then applied to the bacterial reaction center (BRC).

First, for multiscale simulations, quantum mechanical/molecular mechanical (QM/MM) techniques were investigated for the CHARMM/SCC-DFTB framework. An issue of discussion in the recent literature is the description of electrostatics at the QM/MM boundary. In addition to previous suggestions for the QM/MM treatment of electrostatic interactions at the QM/MM boundary, a new approach, the divided frontier charge (DIV), was introduced and implemented. The performance of these schemes is evaluated based on properties including proton affinities, deprotonation energies, dipole moments, and energetics of proton transfer reactions. Similar to previous work, it is found that calculated proton affinities and deprotonation energies are very sensitive to the link atom scheme. Errors on the order of 15 to 20 kcal/mol are observed for less suitable models. Other schemes give better and, on average, mutually comparable results. For short-ranged proton transfer reactions, encouragingly, both activation barriers and reaction energies are fairly insensitive (within a typical range of 2-4 kcal/mol) to the link atom scheme due to error cancellation, and this was observed for both gas-phase and enzyme systems.

Another development presented here makes potential of mean force (PMF) calculations possible for long-range proton transfer. For this purpose, a set of collective reaction coordinates is proposed for characterizing the progress of long-range proton transfers. The modified center of excess charge (mCEC) overcomes some of the problems associated with previous suggestions. The mCEC can be used to define a new set of collective coordinates, which describe PT along highly nonlinear three-dimensional pathways, without specifying the mechanism or pathway *a priori*. The approaches of other authors were limited to linear pathways. Calculations on a realistic model of carbonic anhydrase demonstrate that adiabatic mapping using these collective coordinates gives reliable energetics and critical geometrical parameters similar to minimum energy path calculations. This suggests that the new coordinates can be effectively used as reaction coordinate in potential of mean force calculations for long-range PT in complex systems. Indeed, aside from the use in this project, the reaction coordinates presented here, are now in use by collaborators for a number of projects investigating PT.

As an application of the techniques developed here, the PMFs for proton transfer along a curved, $\sim$20 Å long pathway between Asp210(L) and Glu212(L) in the bacterial reaction center (BRC) were computed. The proton donor and acceptor are connected by a bifilar chain of eight water molecules and are 10 Å apart. Depending on the charge state of the quinones, the barrier for PT is 15-17 kcal/mol. This is slightly higher than what is expected from experiment. For the Q_B^- charge states, the transition state is earlier than the highest transition state found for the Q_B^0 charge states. Despite these phenomenological differences, the results for this model suggest that the sequence of events for proton transfer cannot solely be understood from direct electrostatic interaction with the quinones. Instead, the foundation may lay in an electrostatic domino effect, i.e. the rearrangement of salt-bridges between Q_A and the proton wire. In addition, the results show that the solvent structure changes significantly during the reaction, stressing again the importance of dynamical approaches to long-range proton transfer, which were made possible through the work presented here.