Molecular simulations in electrochemistry

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

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1 Introduction

In this chapter, we give an overview about the main points of this thesis. First, we introduce the role of electron transfer reactions in chemistry based on Marcus' Theory. Then we give a short description of proton transfer mechanism and the background of molecular simulations. The chapter is followed by the explanation and advantages of the methods that were chosen for molecular simulations of the entire study. Finally, we give an overview of the method of electron and proton transfer we employed, explaining why it enables us to simulate flavins and the outline of thesis is defined.

1-1 Electron transfer in chemistry

As a multidisciplinary field, electron transfer is essential in chemistry, biology and physics [1–10]. Being the process by which electrons are transferred between or within molecules, it underlies many important chemical, physical, and biological phenomena including enzymatic reactions, semiconductor activity, photosynthesis and many others.

During electron transfer reactions in a chemical context, typically no chemical bond is broken or formed. Instead, only readjustments of bond geometry (distances and sometimes angles) in each reactant, and rearrangements of the configurations of the environment, such as solvent molecules around the reactants, are occurring. The fundamental notions of electron transfer have been elegantly captured in a simple analytical theory by Marcus. This theory has been crucial in interpreting experiments, as well as providing novel understanding and implications.

Many chemical reactions involve transfer of electrons from one molecule to another or from one molecule to the solvent. The key questions are as follows: What are molecular details of this commonly occurring reaction? How does it depend on the nature of the donor and acceptor molecule and what is the role of the environment.

With his own theory, Rudolph A. Marcus† explained the details of electron transfer coupling to physical idea to simple equations [1, 4–6]. This was the basis of a significant development in the field of theory and modeling of electron transfer. This theory has been applied to many kinds of different systems. The important enhancements have been pioneered by Warshel [11], Warshel and King [12] and more recently further developed using Density Functional Theory (DFT) based simulations by Sprik [13–24].

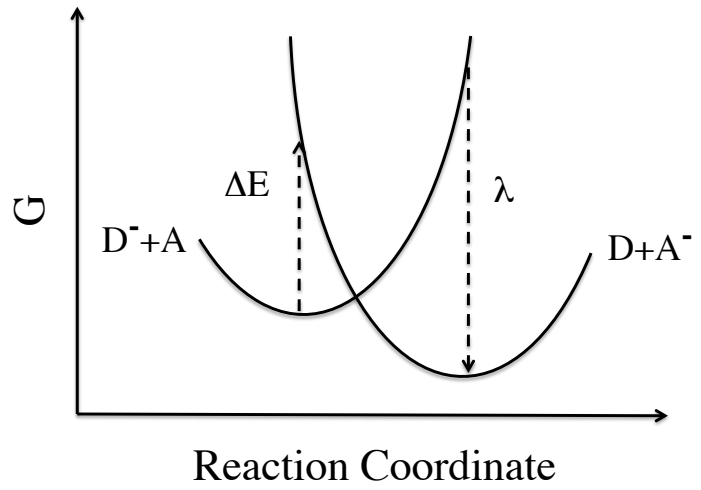

Figure 1.1: The potential energy surface of electron transfer according to Marcus' theory depicting the reorganization energy λ and the vertical excitation energy ΔE.

† The Nobel Prize in Chemistry 1992 was awarded to Rudolph A. Marcus

The Marcus theory makes a connection between the vertical excitation energy fluctuations and the solvent reorganization. This consulate is illustrated in the picture of intersecting parabolas (in Figure 1.1) in which the electron transfer activated state is reached at the intersection point. As a consequence of the Gaussian statistics of the energy fluctuations, the curvatures of the two parabolas are equal [25–27]. Still, the versatile role of solvent in electron transfer reactions is poorly understood on a microscopic level, which complicates the understanding of biological processes. In this thesis, we have investigated the role of solvent reorganization during electron transfer reaction used by Marcus' theory and molecular simulation techniques such as DFT based Molecular Dynamics (DFT–MD) and hybrid DFT/force field based MD simulations (QM/MM).

1-2 Proton transfer in chemistry

Proton transfer reactions are a ubiquitous example of charge-transfer processes, and they represent a classic example of the relevance of solvation dynamics to reactivity. Proton transfer reactions are strongly affected by the surrounding solvent. Protons, as positively charged hydrogen ions, move very quickly in water from one water molecule to another as shown in Figure 1.2. The principle of proton transfer in water has been known for 200 years and is named the Grotthuss mechanism. It was proposed by Theodor Grotthuss in 1806[†]. The mechanism is based on the assumption that there is not a single specific proton moving from one molecule to another; instead, there is a cleavage of bonds. One proton docks onto a molecule, which causes another proton to leave that molecule and bind to another neighboring molecule [28–31].

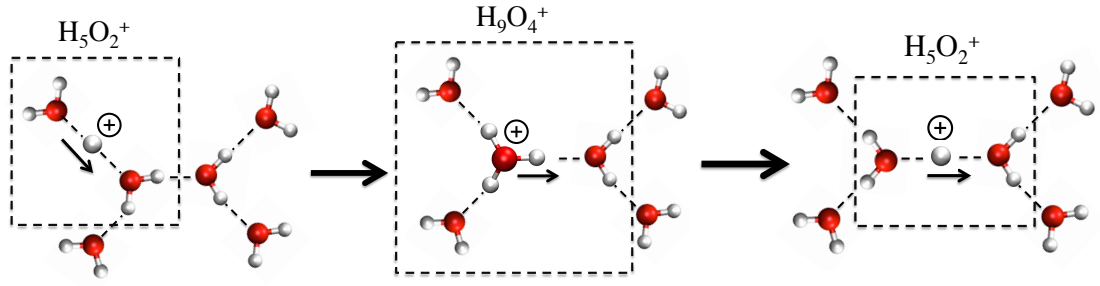

Figure 1.2: Grotthuss mechanism of proton conduction in liquid water. Note that in order to move the proton charge, only permutations of covalent and hydrogen bonds are required.

Computational studies have the advantage that the electron and proton transfer processes can be decoupled by computing the reaction free energy of the proton (or electron) transfer reaction at a fixed oxidation (or protonation) state.

[†] Theory of de-composition of liquids by electrical currents, T. Grotthuss, 1806 [28]

1-3 Flavins in chemistry

Flavins (7,8-dimethyl-10-alkylisoalloxazines, Figure 1.3) catalyze a wide variety of reactions, due to tuning of their reduction potentials by the flavoenzymes that bind them. Flavins can be electronically photo-excited by blue light, which, in a receptor protein, starts a cascade of molecular changes known as a photocycle. Many chromophores undergo a cis-trans isomerization reaction upon adsorbing a photon. Flavins however, have a different, unique, mode of action. They undergo a change in redox potential, which results in an electron transfer from a nearby protein residue to the flavin. Apart from their role as chromophores, flavins are also key in a wide range of biological (ground-state) oxidation and reduction reactions.

Flavoproteins have been classified based upon their biological function, stabilization of the flavin semiquinone, and the reactivity of the oxidized and reduced flavins toward sulfite and oxygen, respectively [32–35]. These classifications based on reactivity also correlate to some degree with structural motifs, such as the flavin butterfly bend angle [32, 33]. Additionally, some enzymes possess covalently bound flavins, and these linkages represent substitutions on the flavin ring that can have substantial affects on reactivity.

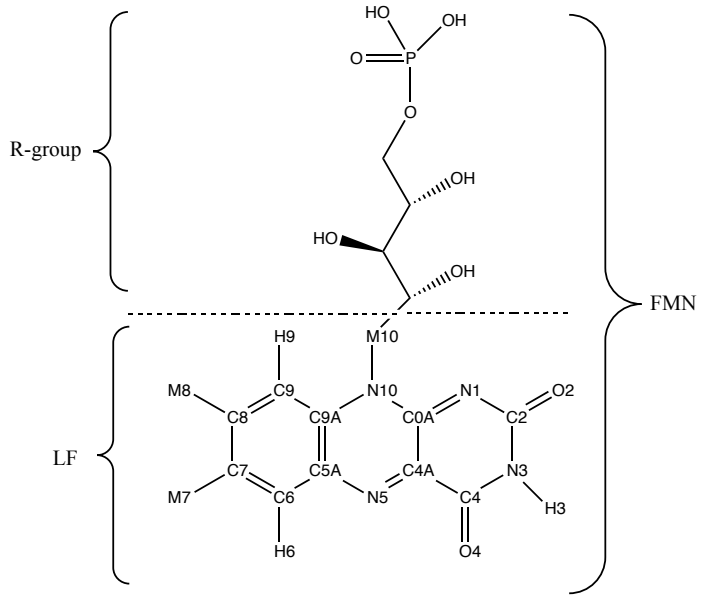

Figure 1.3: Molecular structure of flavins. Flavin derivatives with substituents at the M7 and M8 positions as well as on Lumiflavin (LF: M7 = M8 = M10 = CH_3), which shares the reactivity of the biological cofactors Flavin mononucleotide (FMN: M7 = M8 = CH_3, R = $CH_2(CHOH)_3CH_2OH_2PO_3$), and Flavin adenine dinucleotide (FAD: R7 = R8 = CH_3, R = $CH_2(CHOH)_3CH_2OH_2(PO_3)_2$-adenosine).

1-4 Molecular simulation

Studying molecular system by simulation is important to understand many key concepts in the physics, chemistry and biology. A fundamental goal of scientific research is to learn how things work, which at the microscopic level primarily means how atoms, molecules and electrons are involved in processes such as electron transfer, proton transfer, photosynthesis, and enzymatic reactions.

Molecular simulation started as a tool to exploit the electronic computing machines that had been developed during and after the Second World War. After a while, molecular simulation techniques, the level of theory, and computational resources have increased exponentially, and today we can simulate complicated systems with many sophisticated theories.

In this context, molecular simulation techniques are used at an increasing pace to study chemical and physical phenomena as a complement to the experiment. It can simulate states that are very difficult to be reached or be used to probe and measure properties that are difficult to obtain experimentally. Molecular simulation techniques can give insight in the mechanisms of chemical reactions at microscopic level. However, as an important restriction, molecular simulation techniques can only be as good as the underlying theory and is validated if there is no programming error affecting the results. Other restrictions can be given as the finite system size and the length of simulation time.

1-5 Model and methods

The method of choice for this thesis are the DFT–MD and QM/MM simulation techniques. We have used the CP2K package [36] in order to perform these two simulation techniques because it has many sophisticated tools with extremely fast algorithms [37].

In DFT–MD, the atomic interactions are obtained from electronic structure calculations using DFT and –simultaneously– classical Newtonian equation of motion is employed to generate molecular dynamics trajectories a method also referred to as *ab initio* Molecular Dynamics (AIMD). The main advantages of DFT–MD for electron and proton application are as follows:
1) DFT–MD can produce a molecular force field from electronic structure calculations without experimental data.
2) We can obtain statistical analytical details of electron and proton transfer processes by accessing the electronic structure in a certain time period.
3) In our simulations, we have used explicit solvent (water and protein environment), so we can get details about solvent behavior during electron and proton processes.

However, the method is not perfect and there are many restrictions for this method. First of all, the accuracy of molecular interactions in DFT–MD is controlled by DFT. The main problem of DFT comes from the current exchange and correlation functionals that are still under development. Computational demands of DFT–MD are

very high as a second restriction. At the time of this research, the limit for length and time scales is around 1000 atoms and the trajectory lengths 20–100 picoseconds. However, in our case, DFT–MD method has been sufficiently fast to work for the smaller systems that we studied.

To understand microscopic picture of protein systems, we use the QM/MM method. QM/MM combines the strength of both QM and MM calculations, thus allowing for the study of chemical processes in relatively large systems. An important advantage of QM/MM methods is the efficiency. To overcome the limitation, on the other hand, a small part of the system that is of major interest is treated quantum-mechanically (in this thesis; flavin) and the remaining system is treated classically.

1-6 This thesis

The aim of this thesis is to address specific questions about the role of solvent reorganization on electron transfer in different environments and about the calculation of acidity constant, as well. Particularly, we focus on molecular simulation of flavin in water and different protein (BLUF and LOV) environments using DFT–MD and QM/MM techniques following Marcus' theory. On the proton transfer part of the research, we employed two different reaction coordinates in the constrained simulations to compute the deprotonation free energy profiles and to calculate the acidity constant using DFT–MD.

In Chapter–I & Chapter–II, we give an overview of the theoretical background of electron and proton transfer reactions. In this context, the applied techniques and detailed explanations of molecular simulations are also described.

In Chapter–III, we discuss the relationship of the chemical structure of lumiflavin and its redox properties, which plays an important role in biochemical oxidation-reduction reactions. The reduction potential of the flavin is largely modulated by its molecular environment. Although the redox potential of flavins in various media has been experimentally studied, a detailed molecular picture of the environment effect on the flavins' redox properties and the reorganization of the environment upon flavin reduction is still missing. The chapter describes the calculations of lumiflavin in the gas phase, then the characterization of the water solvent structure around lumiflavin is articulated and finally, the first and second reduction processes of lumiflavin in water are calculated by using DFT–MD.

In Chapter–IV, we focus our attention on a detailed analysis of the aqueous solvent response upon flavin reduction. In addition to our previous DFT–MD simulations of lumiflavin in the oxidized, singly reduced and fully reduced states, we perform simulations at intermediate, fractionally charged states to assess the solvent reorganization in smaller steps. Moreover, QM/MM simulations, which allows for larger systems and thus for analysis of the longer-range solvent response, are compared to DFT–MD. By comparing the QM/MM results to those from the DFT model, we can assess the electronic solvent response, which is only present in the latter.

Apart from the active role of flavins in electron transfer reactions, they can also act as proton donors or acceptors. The electron and proton transfer reactions are coupled: the acidity constants depend on the redox state of the flavin and, vice versa, the reduction potentials are a function of the pH. In Chapter–V, we compute the free energy profiles of the deprotonation reactions of lumiflavin in the semiquinone and fully reduced oxidation states using constrained DFT–MD. The pK_a of the protonation sites depends strongly on the oxidation state of the flavin, and further, the semiquinone radical state is rather unstable in water solution, which makes a direct measurement of the pK_a in this singly reduced state very difficult. Using DFT–MD simulations, we can study the proton transfer reactions of lumiflavin in each oxidation state separately. We briefly review the calculation of pK_a and constrained DFT–MD with the dynamics and solvation structure of lumiflavin in the aqueous phase and their interaction with the solvent.

Finally in Chapter–VI, by using QM/MM simulation techniques, we study the redox properties of flavin in different protein environments (BLUF and LOV proteins). By mapping the changes in electrostatic potential and solvent structure, we understand how specific polarization of the flavin by its environment tunes the reduction potential. Additionally, the separated electrostatic potential calculations are performed for water and protein to explain the different effect of the water environment in BLUF and LOV proteins.