Chapter 1

Introduction

In the last few years, the interest for theoretical approaches in biological and biochemical sciences increased a lot. This may be mainly due to the fact that a tremendous amount of experimental information exists on many different systems. A more general understanding is, however, often lacking. The use of powerful computers and new algorithms allow to understand and predict effects of protein mutations on for instance association constants, reaction rates, and structural parameters. Theoretical investigations can not only help experimentalist to interpret their results and to design new experiments. Joint efforts of theoretical and experimental research can provide deeper insights in complex biochemical processes.

Redox processes belong to the simplest chemical reactions. Nevertheless they are of outstanding importance in biological systems. Electron-transfer processes are involved in many bioenergetic reactions (respiration, photosynthesis, nitrate respiration), in the repair of damaged DNA, in the fixation of molecular nitrogen, in many detoxification processes, and in a large variety of other metabolic processes. Because electron transfer is involved in many biochemical key-reactions, much effort is spent to understand the detailed mechanism of these reactions in and between proteins. This research will obviously increase the fundamental understanding of biochemical systems. Moreover, research on electron transfer in proteins has also impact on medical science (Arkin *et al.*, 1996; Hall *et al.*, 1996; Dandliker *et al.*, 1997), on development of molecular electronic devices (Krätzschmar, 1996; Astruc, 1997), on improvement of agricultural technology (Duke, 1990), and on the usage of alternative energy sources (Barber & Andersson, 1995).

The most prominent physiological electron-transfer chains are the reactions involved in oxidative phosphorylation (respiration chain) and photosynthesis. Both reaction chains are intensively investigated. Recently a large amount of structural information of proteins involved in these reactions became available from X-ray crystallography and from electron microscopy. This knowledge increased the interest of experimentalist as well as of theoreticians in bioenergetic research. Oxidative phosphorylation and photosynthesis may be the first complex biochemical reaction systems bound to membranes for which a detailed knowledge based on structural information becomes available.

Electron transfer reactions within proteins or tightly-bound protein complexes are well studied. Much less is known about the electron transfer in protein complexes that are only loosely bound. Structural informations about such complexes are hard to obtain. For a long time, simulations (Northrup, 1994) or kinetic fitting of the ionic strength dependence of the second order electron transfer rates to van Leeuwen-Theory (van Leeuwen *et al.*, 1981; van Leeuwen, 1983) or to the parallel-plate model (Watkins *et al.*, 1994) were the only possibilities to relate

structural data to experimental results. The recent use of para- and diamagnetic NMR provides more direct insights in the structure and the structural dynamics of electron-transfer protein complexes (Ubbink & Bendall, 1997; Ubbink *et al.*, 1998). Investigations on electron-transfer protein complexes revealed that many of these protein complexes show a structural reorientation that is coupled to the electron-transfer process. The use of photoinduced electron-transfer reactions is suitable to obtain more detailed information about the dynamics of these complexes (Kostić, 1991; Kostić, 1996).

During my PhD work, I studied the dynamic of electron-transfer proteins, mainly of those proteins that are involved in photosynthetic electron transfer. In Chapter 2 of my PhD thesis, I describe some basic principles of protein association and a simulation method that I developed and applied during my PhD work. Furthermore, I describe a method to compare isofunctional, i. e., physiologically equivalent, proteins that have no common structural features. This method is based on approaches usually used in drug design (Hauswald, 1998). It was used for the first time to compare the structure of isofunctional proteins during my PhD work. In Chapter 3, I describe briefly the Marcus electron-transfer theory. I also give a short outline of the method to search for electron-transfer paths (Onuchic *et al.*, 1992). In Chapter 4, I describe the methodology to calculate protonation and oxidation probabilities of proteins that have many titratable residues and redox-active groups. There I introduce a newly-developed method to include structural variability of proteins in the calculation of titration curves. Furthermore, I describe a method to take into account the redox potential and the pH of the solution in the calculation of protonation and oxidation probabilities in proteins. In Chapter 5, the electron transfer in photosynthetic reactions are described. This is the main part of the thesis. First, I briefly summarize the basic principle of photosynthesis. Then I describe the reactions on which I did calculations during my PhD work in more detail. These reactions are the coupling of electron and proton transfer at the Q_B-site of the bacterial photosynthetic reaction center, the docking and electron-transfer reaction of plastocyanin or cytochrome c_6 with cytochrome f, the electron-transfer reaction of ferredoxin or flavodoxin with ferredoxin-NADH reductase. Finally, I summarize my results.