1. Introduction

Enzymes catalyze most chemical reactions in living systems. To understand the biochemical processes in a cell, it is necessary to know by which properties an enzyme is enabled to control the rate of a chemical reaction.

In principle, all properties of an enzyme are encoded in the sequence of amino acids that constitute the enzyme. The amount of known sequences is growing very fast due to automated sequencing procedures and rapid data analysis. The work attaining the largest public interest is done by groups connected via the Human Genome Project. The databases containing the genetic code of humans and other livings are accessible in principle for every interested person nowadays via the internet. However, the therein provided information as such does not permit insight into biological processes or functions of enzymes. Only the correlation of the amino acid sequence with the function of the translated enzyme will make it possible to explain the data in the sequence databases leading to a better understanding of the action of enzymes. This knowledge can be applied *e. g.* for medical purposes like the development of new drugs or the treatment of diseases by gene therapy.

The activity and function of an enzyme can partly be understood from its three dimensional structure, which itself is a function of the amino acid sequence. The elucidation of a protein structure is prerequisite to learn more about its enzymatic activity and mechanism.

However, with the knowledge of the structure alone it is not possible to explain how an enzyme works. The structure itself does not show completely which mechanism is applied by an enzyme to catalyze a chemical reaction and why the chosen mechanism is so effective. To gain further insight into the catalytic power of enzymes it is necessary to quantify the relationships between structure and activity of an enzyme. To accomplish this, kinetic assays together with mutation experiments are major contributions.

To support the experimental strategies and to go even beyond the possibilities of experiments it is necessary to apply computational methods that can give quantitative informations about the interactions that are relevant for enzyme function.

Electrostatic interactions in macromolecules are most relevant for their structure and function. Any attempt to correlate the structure of a protein with its function quantitatively, has to include the calculation of intra- and intermolecular electrostatic energies. Electrostatic energies have a large influence on processes like solvation, ligand binding, protein-protein association, pk_a values of ionizable amino acid side chains, redox potentials and enzyme catalysis.[1,2,3,4,5,6,7,8,9]

During my PhD work, I applied theoretical methods on two enzymes: acetylcholinesterase and arylsulfatase A. In both systems the role of electrostatic contributions on the properties of the enzymes gained major attention. In chapter 2 I will describe the basic theory that helps to account for the electrostatic energies inside and between macromolecules. A very important aspect is the elucidation of a protein's protonation pattern on the basis of its electrostatic properties.

The first part of the 3. chapter introduces the theory of enzyme kinetics and catalysis. The catalytic power of enzymes can be investigated by computer simulations of the catalyzed reactions. The theories that make it possible to simulate chemical reactions within large molecules like enzymes are outlined in the remaining part of chapter 3.

In chapter 4 computer simulation techniques are applied to the enzyme acetylcholinesterase. For the first time the protonation pattern of an enzyme was established prior to the simulation of a catalyzed reaction.

In chapter 5 the electrostatic properties of arylsulfatase A are investigated and the association between the subunits of this octameric enzyme is investigated. In chapter 6 I suggest a procedure, how theoretical methods can be applied to elucidate the mechanism of a part of the catalytic cycle of arylsulfatase A.