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RIJKSUNIVERSITEIT GRONINGEN

DENSITY FUNCTIONAL THEORY APPLIED TO COPPER PROTEINS

Proefschrift

ter verkrijging van het doctoraat in de
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door

Marcel Swart

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te Zutphen

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voor Elvira

in lieve herinnering aan papa en mama

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Preface

In November 1996, the Netherlands Foundation for Chemical Research (SON, now NWO/CW) and Unilever decided to initiate a joint research program called *Computational chemistry of biosystems*, as this field was considered scientifically challenging and promising.

In the early years of biotechnological research, attention focused on obtaining molecules with new properties, while more recently this has shifted towards optimization of a molecule in relation to its application. Therefore, insight is needed in the requirements for the application, as well as the properties of the biomolecules; this often necessitates a multidisciplinary approach.

Enzymes that catalyze redox reactions are of interest for industrial applications like the (trans)formation of coloring and flavoring agents. The chemistry of such transformations is complex and enzyme mechanism is not always easily understood. Quantum chemical calculations on model complexes can then be helpful for understanding which factors of the redox system contribute to the catalytic process. Until recently the presence of transition metals prohibited the computational treatment of large molecules. And as the interactions of transition metals are difficult to treat properly with simplified classical force fields, semi-empirical methods have also been of limited use. With the recent success of Density Functional Theory (DFT) in treating large systems in an efficient and accurate manner, the calculations have gained importance over the last few years.

One of the projects within the *Computational chemistry of biosystems* program is the *Modeling of metal-based redox reactions*, which involves two PhD-positions (Marieke van den Bosch in Leiden, Marcel Swart in Groningen) under the supervision of the professors G.W. Canters (Universiteit van Leiden), H.J.C. Berendsen and J.G. Snijders (Rijks*universiteit* Groningen). In this project, a combined approach of DFT calculations and Molecular Dynamics (MD) simulations is applied to the copper protein azurin, in an attempt to get a good description of the active site of the protein. The project involves the creation of a copper force field, including the development of two methods to extract force field parameters from the DFT calculations that can be used in the MD simulations; the geometry optimization of the active site in the presence of the protein; the calculation of magnetic, redox and UV/Vis properties that characterize the protein, as well as the application of DFT to two transition metal catalyzed chemical reactions, one of which takes place in a copper-containing enzyme. This thesis is the first one resulting from this project.

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