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Study of Chemical Reaction under Oriented External Electric Fields; Application to electrostatic enzymatic catalysis

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Abstract:

The effects of external electric fields upon matter is a long-standing object of studies and it has always given rise to the development of new concepts. For instance, in the very early days of chemistry as a science, Berzelius was already investigating the influence of electricity on chemicals. Thus, he laid the basis of the concept of electronegativity. This synergy between electricity and matter is certainly due to the electric nature of the subatomic particles. As such it is now well known that electric fields induce modifications of the electron structure of atomic and molecular systems and can give rise to a wide range of phenomena. For instance, the shifting and splitting of spectral lines of atoms and molecules is well known and coined as the Stark effect. Another example is the fact that the local electric fields seem to be of utmost importance in catalysis, be it homogeneous, heterogeneous or enzymatic. For instance, Warshel argued that enzymatic evolution is guided by the design of the OEEF that fit best the catalysis of a specific chemical reaction. More recently, Head-Gordon imagined creating protein mutant design to create the best OEEF for catalysing a specific reaction. The main objective of this thesis is to understand the effect of Oriented External Electric Fields (OEEF) upon chemical reactivity, regio and stereo selectivity, and eventually catalysis. The work plan is two folds.

WP1: prototypical enzymatic reactions will be studied first in gas phase and then in solvent without electrostatic fields. The early stages of an enzymatic catalysis will be modelled by the influence of a local OEEF created by point charges (liken the OEEF within the active site) upon a specific ligand. The flexibility and allosteric effects of the enzymes will be modelled by classical mechanics and analyzed through the computation of free-energy landscapes methods¹⁸. QM/MM methods will be used. To this aim, advanced multiscale methods will be considered, including not only mechanical embedding, but also electronic and polarizable embeddings to accurately describe the mutual interactions between the QM and MM parts.

WP2: Will consist in NMR investigation of the enzyme dynamics and how it affects the kinetics of the catalysis. One of the most useful NMR observables is the chemical shift that is directly linked to the local electronic environment of a nucleus. As a consequence, any interaction gives rise to a subtle perturbation of the chemical shift. Until now, the quantification of this effect rest on the use of proteins databases. The goal of the current project is to develop and extend the concept of electric field to model molecular interaction and understand its direct link with chemical shifts. If possible, this new concept will be included in molecular dynamics as new collective variables to accurately model catalysis.