Abstract

The common theme of the thesis is the understanding of chemical reactivity in the field of bioinorganic and (bio)organic chemistry from the perspective of traditional transition state theory (TST) as well as approaches going beyond. Specifically, I present two studies in this thesis – one focused on reactivity factors shaping methanogenesis mostly using TST and one exemplifying a non-TST case in chemical reactivity, which I solved using a new tool that I co-develop during my PhD studies.

For the first thesis project based on TST, we took on the task of understanding catalytic efficiency of the F430 coenzyme in methanogenesis as compared to its four bio-synthetic precursors, providing a plausible view of how the evolutionary driving force shapes the biocatalytic proficiency of F430 towards CH_4 formation. In nature, production of methane is facilitated by a key enzyme known as methyl coenzyme M reductase (MCR). MCR catalyzes the final step in the conversion of coenzymes M ($H_3C–SCoM$) and B (CoBS–H) to methane and heterodisulfidic product. The active site of the enzyme hosts an Ni-containing cofactor F430. The catalytic mechanism can be then explained as F430-mediated reductive cleavage of the $H_3C–S$ bond in coenzyme M, yielding a transient CH_3 radical capable of extracting a hydrogen atom from the S–H bond of coenzyme B. Despite this, the key reactivity factor contributing to catalytic efficiency of MCR is still in its nascent phase. In this work, I am trying to understand the driving force behind the methanogenesis. I performed computational investigation to explore whether and why F430 is unique for methanogenesis in comparison to four identified precursors formed consecutively during its biosynthesis. Indeed, I obtained the native F430 cofactor as most competent for methane bioproduction compared to all precursors. In fact, there is a sequential improvement of catalytic efficiency at each enzymatic step towards F430 maturation. Unexpectedly, the native F430 cofactor possesses the highest reduction potential, which suggests that F430 would be the least proficient reductant for the cleavage of the $S–CH_3$ bond of coenzyme M. I found out that a key contributing factor that dominates the reactivity for reductive cleavage of the $S–CH_3$ bond is actually the formation of Ni–S bond. The native F430 appeared as the weakest electron donor along the series and consequently, possessed the most covalent Ni–S bond and hence the most stable rate-determining transition state leading to the highest reaction rate.

In the second part of this thesis, I explore reactions for which TST is inappropriate method of understanding their chemical reactivity. According to TST, transition state is the highest-energy, short-lived state along the minimum energy pathway that the reactants must have to overcome to form the products. These types of reactions can be described within the TST framework because a major product is determined by the lowest energy barrier. However, in addition to these reactions, there is now an increasing number of reactions in which a single transition state may be responsible for the formation of multiple intermediates or products simultaneously. These types of reactions are known as multi-furcating reactions. Bifurcating reactions produce two distinct products channels originating from a solitary transition state. Therefore, they represent paradigmatic examples that defy explanation within TST. Therefore, with the increasing amount and importance of these reactions in both organic and bioinorganic chemistry, there is a growing demand for a suitable theoretical tool that can precisely quantify the outcome of products at a minimal cost. Till date, there are only a few computational methods that are reported for prediction and quantification of the product outcome for such reactions. In this thesis, I computationally proposed a simple approach that satisfies these criteria, by evaluating the energy distribution within the reactive mode of the key transition state. This method was first introduced by our group and relies on the kinetic energy distribution (KED) within the reactive mode of the key transition state. Our KED-calculated product selectivity within the reactive mode yields an excellent agreement with experimentally reported product ratios and predicts the correct selectivity for 89% of studied cases. I consider 60 different types of bifurcating reactions, which includes pericyclic reactions, rearrangements, fragmentations and metal-catalyzed processes as well as a few trifurcating reactions. Given its predictive power, the procedure makes reaction design feasible even in the presence of complex non-TST chemical steps.

Later, I also extended the application of KED analysis in studying the nature of generated transient methyl-radical in the first catalytic step of methane production by methyl coenzyme M reductase. KED analysis reveals that kinetic energy in the reactive mode is concentrated in the motion of the nascent methyl radical.