Chemical reactivity through the lens of traditional and non-traditional concepts

Summary

The common theme of this 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.

Methanogenesis represents a distinctive form of anaerobic respiration that has been refined by evolution for maximum efficiency. The key enzyme that catalyzes the terminal and rate-determining step in biological methanogenesis is 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 biosynthesis pathway of cofactor F430 is complex and involves several convoluted enzymatic steps. Warren and co-workers elucidated that the late-stage bio-modification of F430 comprises of four enzymatically controlled steps. The first step involves the transformation of sirohydrochlorin to coenzyme-F430 by insertion of a nickel atom in the center of tetrapyroole ring. After that the overall process is followed by stepwise modifications: chelation, amidation, reduction by six electrons with addition of seven protons, lactamization, and closure of a propionate side chain coupled to water extrusion. To date, numerous studies have been conducted to unravel the mechanistic details of methane production by MCR. The mechanism considered in this thesis consists of three consecutive steps: (i) the H_3C–SCoM bond undergoes reductive cleavage, releasing the transient methyl radical and leading to the oxidation of nickel center from +I to +II with the concomitant formation of a Ni–S bond between NiII and SCoM; (ii) the H–S bond in HS–CoB undergoes an attack by the transient methyl radical, leading to the liberation of CH_4 and the generation of •SCoB radical; finally (iii) the Ni–bound SCoM couples with CoBS• radical to generate Ni(II)–disulfide anionic radical complex.

In this thesis, I leveraged the insights gained from four recently identified biosynthetic precursors of F430, and investigated their reactivity in comparison to the native F430. My findings revealed that F430 is optimally best suited for catalysis, exhibiting the lowest reaction barrier for the rate-determining step involving the reductive breakage of the thioether S–CH_3 bond by the Ni^I center. Interestingly, F430 has the highest reduction potential and is therefore the least effective reductant for breaking the S–CH_3 bond. However, another crucial factor in favor of native F430 is the

strength of the Ni–S bond formed in the reductive cleavage of S–CH_3, which actually eliminates the possibility of an inappropriate reduction potential. This bond emerges as the strongest for native active-site models anchoring F430 among its four biosynthetic precursors. The enhanced strength of the Ni–S bond is attributed to the highest covalent character, result of the weakest electron-donation ability of the native porphyrin-like F430 skeleton, a consequence of the complex chemical modifications occurring in the biosynthetic route of F430, particularly in the native porphyrin-like F430 skeleton.

In the second part of this thesis, I demonstrate the adoption and application of the KED-based analysis to predict the product ratios for a range of diverse set of bifurcating reactions. This type of reaction is now increasingly in demand, but predicting accurate product selectivities is quite challenging in terms of experimental cost and time. Bifurcating reactions are archetypal examples of reactions that fall outside the scope of traditional Eyring's TST. These reactions by nature follow one common ambimodal transition state TS_1, responsible for the formation of two products at the same time, once potential energy surface (PES) bifurcates after reaching valley-ridge inflection point (VRI) without the presence of any additional transition state. Therefore, they can not be studied within the framework of TST. Here, I explore the scope of computational approach that relies on KED within the reactive mode of ambimodal TS_1 to quantify the product selectivities for a diverse set of furcating reactions. I use the advantage of this recently developed computational method by our group to study selectivity of these reactions, since only very few computational techniques are reported so far in literture, in addition, a number of tested reactions are very limited. Some computational tools to study these types of reactions are conventional ab initio molecular dynamics (MD) simulations, Houk's bond order analysis, Carpenter's dynamic match analysis and very recently developed Goodman's method. In this thesis, I consider the different set of bifurcating reactions (almost 60 bifurcating reactions) , which includes organic pericyclic reactions, nucleophile substitution *vs*. addition in α-haloketones, Beckmann and Schmidt rearrangements *vs*. fragmentation, and isomeric Pummerer rearrangements and also trifurcating reactions, to predict product ratios from KED using the reactive mode composition factor (RMCF) analysis. This is achieved by partitioning the kinetic energy distribution (KED) of the reactive mode at the shared transition state into chemically meaningful and well-defined fragments. The strength of the RMCF analysis becomes apparent when compared to existing computational protocols designed for predicting branching ratios. It consistently outperforms all tested alternatives, excelling in predicting major products. Our method yields comparable results to the most successful method reported to date, requiring only a single transition state connecting the reactant complex with available product channels, supplemented by qualitative information about the bifurcation products. Importantly, the method can be seamlessly integrated with traditional transition state theory, making it applicable to reactions involving sequential TST and non-TST steps. The results show excellent agreement with experimental and molecular dynamics (MD) outcomes, highlighting the versatility and reliability of our approach. In its entirety, the RMCF protocol stands as a versatile and sophisticated approach for the prediction and comprehension of bifurcating and multifurcating reactions. Its excellent ability to flawlessly

participate into the analysis of chemical reactions, together with its flexible involvement in TST and accurate quantification of kinetic energy distributions across reaction regimes, positions this method as a user-friendly approach to better understand complex reaction mechanisms.