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Division of Student Affairs
Department of Doctoral Studies
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Re: Evaluation of PhD Thesis "*Chemical reactivity through the lens of traditional and non-traditional concepts*" **submitted by Priyam Bharadwaz**

I had a pleasure to read and evaluate the Ph.D. thesis of Priyam Bharadwaz (also referred to as the candidate) entitled "*Chemical reactivity through the lens of traditional and non-traditional concepts*" (in the following referred to as the thesis). The thesis summarizes candidates' efforts in the field of computer modeling and understanding the subtleties of enzymatic methanogenesis in Project I and quantitative description of bifurcation reactions for which the "classic" transition state theory is not enough and other approaches have to be used, in Project II. Overall, the thesis present solid interesting science at frontiers of the reaction mechanism studies, which is also documented by the high-impact publications presented.

From the formal point of view, the thesis comprises approximately 60 pages of text and is divided to two projects, that resulted in two publications, which is a thought minimum to present thesis, adding that the publications are of high-quality and well received by community. The candidate is the first author on the presented papers.

The overall structure of the thesis (Introduction, Methods, Models, Chemical Reactivity, Results) is acceptable but I do not see any logic in separating Sections 3 and 4 from the Methodology part and giving Section 4 after Section 3. The language of thesis is clear, concise, and easily comprehensible. I find information given well balanced and to the topic. I enjoyed most of the reading. I hardly found any typos and only occasionally unclear sentences. The ideas presented and scientific argumentation is rather clear. The text is well accompanied by Tables and Figures, however, some of the Figures are hardly readable in printed manuscript and even when enlarging in computer, e.g. Figures 3 and 12. The thesis are well supported by literature.

As to the scientific content of the thesis, the **Introduction** section briefly and clearly explains the proposed objectives and gives necessary info to understand the topic. Sections 2-4 (**Computational Methodology, Construction of structural models, Theory of chemical reactivity**) explain clearly and briefly the DFT, basis sets, reduction potentials, subtleties of calculations, and structural as well as theoretical models. Here, the transition from eq (14) to eq (16) is a bit unclear to non-initiated reader. Also, the AIM and solvent models could be discussed in a more detail here.
Q1: Can candidate explain the use of LAN2TZ basis set for Ni. I think using polarization function is critical here. Also, polarization functions and TZP-quality or even TZP+-quality basis sets were used for other atoms, so why not for Ni?

Section 5 presents results of Project I which is the study of the mechanism of methane production on native F430 catalytic center and its biosynthetic precursors and why they (do not) catalyze the process differently from the native F430. The discussion is very clear and it is seen that the overall project has been carefully considered. I particularly enjoyed the idea of splitting the overall process to subprocesses, such as electron transfer and bond formation (Figure 7) which brought deep understanding of chemistry behind differential catalytic properties of **A-E**.
Q2: It is not entirely clear to me, why simulations were done with protonated carboxyl groups and only later recalculated with deprotonated ones. Can candidate explain?

Q3: The candidate found the Step 2 barrierless unlike the Siegbahn et al. Indeed the barrier found is rather small. What could be the reasons for this discrepancy? Can candidate elaborate a few possible reasons?

On page 44, the procedure that explains the role of the ligand polarization is not clear. It should be probably accompanied by a Figure or a graph.

Q4: Can candidate explain again the topic at bottom of page 44?

Q5: What actually should one imagine under the delocalization index and how does it differ from the Wiberg bond index? I am not asking for mathematical derivation but for a chemical insight.

Section 6 presents the results of Project II which dealt with methodology and testing of methods for predictions of reaction product ratios for bifurcation reactions. The candidate has shown that in-house developed method RMCF analysis performs very well for series of bifurcation reactions and also provided critical analysis of the method in comparison with approaches available from other labs. The candidate herself developed protocol, how to use the RMCF approach for various reactions. The topic is clearly explained and results are well described and critically analyzed. The particular example of combining RMCF and TST on page 61 is beautiful. What is somehow hard to comprehend is example in Scheme 2B.

Q6: Can candidate enlighten, how is the partitioning done in Scheme 2B? Which parts of the product B are used for the formula 27?

The **Conclusions** section are clearly written, and summarize the results of the thesis. My overall impression from the presented work is positive. I particularly appreciate the insight, which theoretical calculations bring into the reaction mechanisms, even beyond the TST theory. Such calculations are not a mere reproduction of experimental numbers but give deeper understanding that can be sometimes hardly derived from experimental studies.

In summary, the presented thesis show good science carried out by the candidate throughout Ph.D. studies and therefore, I recommend thesis for the Ph.D. defense and ultimately for awarding the Ph.D. title.

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