UNIVERSITY OF CHEMISTRY AND TECHNOLOGY, PRAGUE
Faculty of Chemical Engineering
Department of Physical Chemistry

Oponentský posudek disertační práce

Priyam Bharadwaz: Chemical reactivity through the lens of traditional and non-traditional concepts

The PhD thesis of Priyam Bharadwaz focuses on advanced computational aspects of chemical reactivity/selectivity utilizing two case studies, namely metalloenzyme and organic chemistry. The thesis is based on two publications in esteemed *peer-review* journals, namely Introduction of Reactive Mode Composition Factor (RMCF) analysis published as an Edge Article in *Chemical Science* **(RSC)** in **2021**, and full article about "Reactivity Factors in Catalytic Methanogenesis and Their Tuning upon Coenzyme F430 Biosynthesis" in *Journal of the American Chemical Society* **(ACS)** in **2023**. The contribution of the candidate to those two publications is apparently dominant. The Result section of the thesis (denoted as Essential results of Project I and Project II) very closely follows these publications.

The thesis is rather concise, with a length of about 60 pages (without references), it is written in a very good English and the text is well structured. However, the proportionality of the extent (and detail) of some sections is not ideal, in my opinion.

In the introductory sections, for example, the standard textbook texts about DFT and basis sets are presented on 7 pages, while the advanced topics, which are of the real interest of the curious reader are very short, e.g., system construction (whole Chapter 3 is only 1 page) or Reactive mode composition factor analysis (Section 4.2) is slightly more than 1 page.

Within approx. 30 pages dedicated to results, the text of the thesis only marginally extends the data, figures, or information of the two publications. This is pity in my opinion.

Unlike in the concise form of a high impact publication, some sections of this thesis, could have been used to more scholar (illustrative) introduction of the newly developed approaches/methods. Instead, e.g., the section "6.5. Advantages and limitations of RMCF" suggests that some qualitative and quantitative analysis with some graphics and description is provided, but on a single page it keeps the statements from "Advantages and limitations of RMCF section" from *Chemical Science* paper. I believe that the excellent performance of the novel method (RMCF) deserves a space and promotion, and the thesis is ideal place for this purpose (apart of, e.g., Supporting Information in the publication).

At several place, there are some trivial typographical errors (indexes J vs. j, italics / roman, *ln* vs. ln, *d* vs. d, $\Delta G^{\neq}$ vs. $\Delta G^{\ddagger}$) or typo on rhs of equation (16). Some graphics are of poor(er) quality, such as Figure 3 (black background – in pdf and in printout) or the text (A-D) in Figure 11 is blurred. These issues could have been eliminated by an additional careful reading through.

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On a more positive note, it should be appreciated that the candidate is a **first or second author in another 7 publications** in the field of quantum chemistry, showing her broader scientific scope and keeping/establishing/building contacts in the scientific community. Finally, although not explicitly acknowledged in the thesis, it is evident that the candidate benefited from being involved in stimulating GAČR projects of the supervisor.

To summarize, this thesis is backed by two publications in international peer-reviewed journals of top quality (*Chemical Science, Journal of the American Chemical Society*). Despite my criticism in this report, **I must clearly state that Priyam Bharadwaz conducted very good theoretical research**. Her thesis and scientific work fulfills all criteria for obtaining PhD degree. **I am thus happy to recommend the candidate being awarded the PhD degree**.

Prague, September 11, 2024

doc. RNDr. Mgr. Jan Heyda, Ph.D. 

Questions for the defence that should be addressed by the candidate:

1. Questions to Project I. What are the kinetic constants of native F430 and of its biosynthetic precursors? The ΔG of TS_1 vary between 38.2kcal/mol (A) to 19.6kcal/mol (E), which is a factor of ~10^{14} difference in kinetic constants. Would such a slow reaction rate be beneficial for any early organisms, which were using (A) precursor? In other words, could these organisms be evolving *something* which does not "practically" catalyze at all?

2. Questions to Project I. Could the candidate estimate (or is it already known), how big is the difference between energetics (PES) in the cluster model vs. in fully atomistic MM-described protein environment (including solvent, i.e., in full QM-MM model), for the native F430 and its precursors? Could the presence of an explicit environment (partially) counter-compensate the large differences e.g., in TS_1 ΔG observed for the native F430 and its precursors?

3. Questions to Project II. The RMCF method is superior to the other established methods, highlighting its (low) computational demands and (extraordinary) selectivity and accuracy. I wonder:

1) How is the heuristic-insight into partitioning of "key" bond-forming/breaking atoms related to the understanding/knowledge of the (electronic) structure of TS_1 and of products?

2) What are (quantitatively) computational demands of ab-initio MD (e.g., of the used ADMP approach) vs. of compared theoretical methods (which require TS_1, P_A, P_B, TS_{AB} states)?

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