

Report on the PhD thesis by Ms. Agnieszka Stańczak, M. Eng., with Supervisor Prof. Lubomír Rulíšek and Co-advisor Martin Srnec, submitted within the study programme “Modeling of Chemical Properties of Nano- and Biostructures”. Title of the thesis: “Theoretical Investigation of the Enzymatic Reactivity of Coupled Binuclear Copper System(s) “Strongly Correlated” with Experiments”

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This thesis uses quantum-chemical “first principles” techniques to provide further insight into the biochemical reactivity of some enzymes containing coupled binuclear copper cofactors within the active site. This work involves studying the electronic structure of systems with unpaired electrons on both metal sites, with the resulting spins being coupled to one another and hence experiencing so-called static or strong correlation. The work has been carried out in the computational research group of Prof. Rulíšek at IOCB, but is also situated in the context of the long-term collaboration with the experimental group of Prof. Ed Solomon at Stanford University. The present work is an excellent example of the quality of science that results when experiment and computation are performed in tight link with one another – what the title also refers to as “strong correlation”.

The thesis contains seven chapters: (1) An introduction to the biochemical context with previous suggestions about the mechanism; (2) A chapter on computational methods for studying bioinorganic systems; (3) A statement about the motivation for the work; (4) A list of the project goals; (5) An extended chapter on Results and Discussion, which essentially consists in an extended summary and discussion of a series of papers already published in international journals (papers I to IV) and of a manuscript which is due to be submitted in due course; (6) Some overall conclusions; and (7) A discussion of the overall impact of the work and an outlook towards possible future work.

The thesis is well presented and is overall of very high quality. The introductory chapters (1) and (2) provide excellent concise overviews of the experimental and theoretical context to the work. The motivation for the work and goals are well explained in Chapters (3) and (4). The work described in Chapter (5) and published in papers I to IV (and described in the manuscript to be submitted) is of very high quality, as shown among others by the high quality of the journals in which it has been published. Paper I is more focused on methodological quantum-chemical aspects, and is co-authored with the supervisor, and two other co-authors from the research group at IOCB. Papers II to IV are all co-authored with Ed. Solomon and contain experimental as well as computational results. The major role played by Ms. Stańczak in each of these collaborative works is shown by the fact that she is either the first author of the papers, or joint first author, or high in the order of authors. The overall conclusions in chapter (6) are clear if rather brief, and the outlook in chapter (7) is also clear but brief. The language used in the thesis is of very good quality, with minor errors relating e.g. to the use of articles (a/the/no article) as is common for writers with a Slavic language as mother tongue. There are very few typos or spelling mistakes. Most importantly, the thesis is very well written in the sense that the arguments are exposed in a clear and well-reasoned way throughout. My own research interests overlap considerably with the topics covered in the thesis, so there are many topics covered in the thesis that I look forward to discussing in the oral defence. However, I have not detected any topic where I strongly disagree with the conclusions reached, where I believe that the methods chosen were inappropriate for the problem being tackled,

or where I feel that there are obvious items of additional work that should have been performed. In short, I have very few or even no criticism of the work performed and instead congratulate the candidate on the excellent work performed.

I have two general comments about the thesis manuscripts with thoughts for future students. These are **not** criticisms but elements for reflection. Both comments relate to the structure of the manuscript. Nowadays, PhD theses in computational chemistry (and indeed in many scientific areas) in many countries are closely linked to co-authored scientific publications. The thesis can be presented in two ways: the first, like in the present case, involves a “top” that is a general introduction to the topic and the theoretical background, which is written by the candidate (with comments from the supervisor) specifically for the thesis, and a “tail” containing some general conclusions – here, respectively chapters (1) to (4), and chapters (6) and (7), and a “core” that is a summary and paraphrase of the published papers (here, chapter (5)), with the papers themselves as appendices. An other approach includes likewise a “top” and a “tail”, with a set of “Results” chapters that are simply the paper manuscripts. Both approaches are fine for demonstrating the skills and judgement expected for a doctoral candidate. My first comment, though, is that it is useful that the thesis should include a statement about the role of the candidate in the work performed in the published papers. In the present case, it is obvious that the candidate’s role was to perform most of the actual computations, and to help elaborate the conclusions and design the work following the “strongly correlated” interaction with experiment, as well as actively participating in drafting and revising the manuscripts. But I find it helpful to include a detailed statement on this topic – at present, there is only a general statement in chapter (4). In my opinion, it is good practice for the guidelines for doctoral theses to explicitly request such a detailed statement. A second comment is that in many current theses, the section or sections on overall conclusions and outlook is rather short and contains little beyond a repetition of the points made in the conclusions to the individual papers resulting from the work. This thesis is typical in that respect. While this is understandable (the conclusions of the papers have obviously involved quite a lot of thought from all co-authors, so they should contain the main outcome from the work), I feel doctoral candidates should be encouraged to try quite hard to include in their thesis a more general overview and discussion.

In summary, this thesis contains a large volume of work of excellent quality, which has for the most part already been published in peer-reviewed international scientific journals of very high quality. The thesis itself is very well written and presented, including the parts that have not previously been published. I accordingly strongly recommend that the thesis should be accepted to proceed to the defence.



Jeremy Harvey