ÚOCHB AV ČR
IOCB PRAGUE
Ústav organické chemie a biochemie
Akademie věd České republiky, v. v. i.
Institute of Organic Chemistry and Biochemistry
of the Czech Academy of Sciences

In Prague, April 7, 2022

Prof. Tomáš Polívka
Chairman of the Olga Dvořáčková Ph.D. Committee
University of South Bohemia
České Budějovice

Re: Olga Dvořáčková – Evaluation of the Ph.D. Thesis "*Acid/base properties and reactivity of square planar complexes".* **Original and Revised Version**

I had an opportunity to read and evaluate the doctoral thesis of the Ph.D. candidate Olga Dvořáčková, MSc. from the University of South Bohemia in České Budějovice entitled "*Acid/base properties and reactivity of square planar complexes*". The thesis comprises the main text (27 pages in the ***original*** and 33 pages in the ***revised*** version, excluding references) and three appendices – papers related to the topic of the thesis and published during Ph.D. studies.

First, I will focus on the material presented in the three attached papers that comprise the 'scientific content' of the thesis. Paper 1 – published in the top-tier specialized ACS journal *Inorganic Chemistry* - deals with the Lewis acid/base properties of neutral Pt(II) and Ir(I) complexes, exemplified by their interactions with the group 13 YX_3 halides (Y = B, Al, Ga) in which the central atom (Y) is electron-deficient. The calculations confirmed the Lewis basicity of the Pt and Ir metal centers. The phenomenon is quite untypical, though not entirely unprecedented, for metal ions which are typically best described as Lewis acids (=acceptors of the electron density). The calculations were executed with a great degree of expertise. DFT methods used throughout the study were first calibrated employing the "golden-standard" CCSD(T) calculations. One may issue a mild warning on the accuracy of the CCSD(T) methods for the d^8 metal ions and perhaps ask a question about the importance of the non-scalar

Doc. Dr. Lubomír Rulíšek, DSc.
Group Leader
Theoretical Bioinorganic Chemistry

lubomir.rulisek@uochb.cas.cz
M: +420 731 447 872
T: +420 220 183 263
rulisek.group.uochb.cz

ÚOCHB AV ČR / IOCB Prague
Flemingovo nám. 2
166 10 Praha 6
Czech Republic

relativistic effects, but I consider the computed data presented therein as quite solid. The issue with the Paper 1 is the contribution of the candidate. The first and corresponding author is the candidates' supervisor and the declared contribution of the candidate is 25%. As such, it is not, in my eyes, a key contribution to the thesis (main work of the candidate). However, the Paper 1 reports the work that I liked most (out of three attached appendices) and I have seen that the publication have already had a very healthy number of views and has received six citations (self-citations excluded).

Papers 2 and 3 are in my eyes more anecdotal. They are also more difficult and tedious to read, being mostly piled with excessive number of computed data. The titles of the two contributions are almost identical: "Tuning the Reactivity and Bonding Properties of Metal Square-Planar (*aka* Pt(II)) Complexes by the Substitution(s) on the Trans-Coordinated Pyridine Ring (Paper 2)/Non-Aromatic Amine Ligand (Paper 3)". Both were published in (what I would call) 'repository journals' (ACS Omega and Chemistry Select). In my opinion, they could have been combined into one more impactful paper, exploiting the opportunity to compare the similarities and differences of the two types of ligands in the *trans*- position to the chloride. The main aim of the two studies was the evaluation of the kinetic and thermodynamic stability of the Pt(II) complexes, perhaps providing some guidance into the design of new Pt(II) anticancer drugs. The opportunity of presenting the guidance principles has been slightly drowned in the excessive and tiresome reporting of many less important, less interesting, theoretical details, perhaps obliterating the main message from the two studies. On a positive note, both papers seem to have a decent number of views. It thus seems that they have attracted considerable attention.

Next, I will evaluate the main text of the thesis and here, I must be more critical. My prevailing impression from the ***original version*** was: *unenthusiastic, bleak, inaccurate, and insufficient*. Chapter 1 is (was) an overview of the platinum as an element, usage of platinum complexes in cancer treatment, and Lewis theory of acids and bases. It is easy to read, with a bit of a historical tinge, but insufficient for the purpose of a good-level Ph.D. thesis. Instead of repeating introductory chapters from the textbooks, I expected high-quality, up-to-date review of recent advances in computations of Pt(II) complexes and demonstration how calculations helped to the experimental design or how they were directly correlated with the experimental data. In other words, a motivation for doing the work presented later. Such a text could have

Doc. Dr. Lubomír Rulíšek, DSc.
Group Leader
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lubomir.rulisek@uochb.cas.cz
M: +420 731 447 872
T: +420 220 183 263
rulisek.group.uochb.cz

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Flemingovo nám. 2
166 10 Praha 6
Czech Republic

been (for example) published as the 'minireview' in the *Journal of Biological Inorganic Chemistry*, or the *Journal of Inorganic Biochemistry*. There have been hundreds of papers reporting quantum chemical calculations of Pt(II) complexes (dozens are coming from Czechia, early work of Sponer and Burda in 90's and later of the Burda's group in 2000's and 2010's, including the work of the Ph.D. supervisor). Such chapter might have clearly shown how the field would benefit and advance from the work of the candidate presented in the thesis.

The chapter Methods lacked the neat flow of the text and logic, it was a bit 'bumpy' and not always accurate.

In Chapter 3 of the ***original version*** (Results and Discussion), the candidate failed to provide a succinct report of the results presented in the attached papers (let us say 4-5 pages per paper), clearly formulating the scientific question to be answered and (repeated from above) how a particular study advanced the field. One may spot several mistakes and inconsistencies in figures (e.g. Figure 5b does not seem to depict $Pt(Cl)_2(NH_3)_2 \cdot GaF_3$; in Figure 6, I can see more than one CH_3 group, in Figure 8, I find it confusing that the charge is depicted on the Pt whereas it is obviously a molecular charge of the whole complex; in Figure 9 I do not fully grasp what are **R**, **R_w**, etc…; moreover these energy profiles are not mentioned in any of the attached papers, including the accompanying SI – if I have not overlooked something). Last but not least, the attempt to compare the computed data with experiment is rather weak and unconvincing.

Most of my original criticism have been appropriately addressed in the ***revised version***. There is a new chapter 1.2.5 summarizing contributions of computational chemistry to development of 'bioinorganic drugs' such as cisplatin and its derivatives. It shows that computations may, indeed, contribute to mechanistic understanding of the biological action(s) of the (mostly) Pt(II)-related drugs. The section Methods is now more accurate, easier to read and it is a standard description of methods used, at least for the purpose of an application-oriented computational chemistry Ph.D. thesis.

Most importantly, Chapter 3 (Results and Discussion) now provides a succinct report of the results presented in the attached papers. It has improved, in comparison with the original version.

In summary, I ***recommend the presented thesis*** to be considered as the sufficient material for awarding the Ph.D. title.

Doc. Dr. Lubomír Rulíšek, DSc.
Group Leader
Theoretical Bioinorganic Chemistry

lubomir.rulisek@uochb.cas.cz
M: +420 731 447 872
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I might have two questions that the candidate may answer during the Ph.D. defense:

1) Could the computed barriers (chapter 3.1, Fig. 6) be somehow correlated with experimental data, either directly (i.e.: are some rate constants known for the Cl^- hydrolysis?) or to the biological activity of some of these compounds? It is not entirely clear to me what would be the optimal ratio/balance between the leaving ligand stability/lability.
2) Can the data presented in the paper OD1 lead to further 'optimization' of the Lewis basicity/acidity and to a formulation of the general, easy to understand, intuitive rules valid 'across the periodic table' to predict donor-acceptor characteristics of various $\{YZ_n \ldots ML_m\}$ Lewis pairs? Can their existence (and 'optimal tuning') be ultimately used for the chemical reactivity/catalysis in a similar way that 'frustrated Lewis pairs' (typically boron…phosphorus pairs) are used?

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