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Prof. Dr. Tomáš Polívka.
Head of the Committee for PhD studies in Biophysics
University of South Bohemia.

Dear Prof. Polívka ,

This is the evaluation of the PhD dissertation by Olga Dvořáčková, PhD research scholar of the University of South Bohemia in České Budějovice Faculty of Health and Social Sciences, which is entitled '*Acid/base properties and reactivity of square planar complexes*'.

The present PhD thesis has been conducted under the supervision of Doc. Zdeněk Chval, who holds a consolidated experience on the field of the computational chemistry and its application to resolve complex chemical problems. As stated in my evaluation (see below) the performed theoretical work by the scholar reaches all the required standards of quality for a PhD dissertation.

It should be highlighted the number of associated publications in indexed international journals. These peer-reviewed works ensure the accuracy of the reported results in the present dissertation, which includes a significant effort to benchmark a reliable protocol to assess the activation and reactivity of metal coordination compounds based on Pt(II) and Ir(I) centers. These kinds of studies are strongly connected to pharmacokinetics, a critical step for designing novel drugs. This is particularly true in such drugs with Pt(II) centers, as the latter mechanism is key for a successfully attack to malignant DNA. It is remarkable the solid description of geometrical parameter and energies when compared with available experimental data. This thesis also deals with the topological analysis, a complementary approach that helps to complete the picture of the chemistry behind the biological activity exhorted by that family of metallodrugs.

My revision is based on my own experience in the use of theoretical tools to resolve organometallic systems, including mono and bi-valent anticancer drugs. However, the reported data need to be evaluated in terms of the more practical consequences, so that I wish to point out here the most possible 'medical' conclusions of the reported in that PhD work.

After careful evaluation and reading all text, my main comments are as follow:

1. Introduction (Chapter 1) is written in a very efficient and clear way, where the main topic of the PhD work, e.g., metallodrugs with a focus on Pt-centers, is nicely summarized. The theoretical background of the used schemes is briefly discussed. As correctly stated by the scholar, Pt is a very reactive center in 2+ oxidation state. Indeed, cisplatin-like drugs might attack not only to nuclear DNA or RNA, but also to mitochondrial DNA. Such high reactivity leads to the known undesirable side effects of chemotherapy, as correctly introduced in that dissertation.

2. Chapter 2 might be seen as a short but concise description of the used levels of theory, which are based on density functional theory (DFT) calculations. Even if condensed, the extension is not an issue as more details are available in the attached papers. Theoretical background correctly addresses the core of DFT, including both functionals, basis set, pseudopotentials to mimic relativistic effects and solvent approaches. The use of 17 DFT combinations with the comparison to CCSD(T) is in all respects sufficient for benchmarking the proposed protocol.

3. One of the brightest points of that PhD work is that results (Chapter 3) follow a very logical strategy, with an early study of the reactivity of Pt(II) complexes upon decoration at trans-site. Next, after benchmarking of the methodology, hydrolysis of pyriplatin and cis-amminedichloro pyridineplatinum are reported. With the increase of the available functionals, one can now select among a wide panel of methods. Highly parametrized functionals, as the ones developed in Minnesota, are very popular nowadays because they might provide very accurate description of chemical reactivity (i.e., thermodynamic and kinetic parameters).

I am not sure if M06-2X-D3 is the best-placed candidate, as Pt-derivatives were not included during the parametrization of parent M06-2X (prior D3 correction). However, it is possible to find such level of theory with metallodrugs, so that their use during the PhD thesis is not particularly problematic, as illustrated by the correlation with CCSD(T) outcomes in two of the published papers.

4. I would like to stress the devoted effort for mimicking the hydrolysis phenomena. The comparison of energetics with decoration on the trans-coordinated non-aromatic amine ligand in both gas and water solvent allows to extract a general conclusion about the impact of such structural changes. I am positive that this first computational step could be use in the future to increase the accuracy of these chemical models, e.g. In my opinion, the reached conclusions herein will help to define next models, e.g., by including dynamic effects and/or explicit/implicit solvent models.

Suggested questions to be answered by the student during the defense:

1. The discussion of the basis theoretical background of the highly parametrized functionals developed in Minnesota, with main pros and cons when applied to metallodrugs.

2. The reasoning of the possible impact of explicit water molecules during the simulation of hydrolysis phenomena.

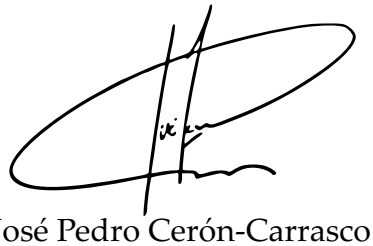
3. The description of the impact of such decoration in subsequent attack to biological target, e.g., DNA.

4. The correlation of Lewis acidity/basicity of the metal center in the framework of tumoral tissues.

In short, this Examiner feels the conducted work follows a state-of-the-art computational protocol, which is particularly important when one deals with complex systems as metallodrugs and if conclusions in solution are looked for. The performed calculations back up all reported data. As stated above, this examiner finds particularly useful the provided energies for hydrolysis as it allows to set up efficient protocols to monitor the activation of novel Pt-based drugs as well as to predict their stability and possible reactivity with third-party molecules, e.g., trihydrides and trihalides motifs, which complete the characterization of the acid/base properties of the selected drugs, as promised in the title of the dissertation.

Consequently, the present PhD work by Olga Dvořáčková satisfies all requirements to be publicly defended in the current form.

Kind regards,



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