
I had a pleasure to read and evaluate the Ph.D. thesis of Filip Šebesta (also referred to as the candidate) entitled “Computational Study of Organometallic Interactions with Models of DNA/RNA and Proteins Using Tools of Quantum Chemistry and Molecular Mechanics” (in the following referred to as the thesis). The thesis nicely summarizes candidates’ efforts in the field of computer modeling of various smaller inorganic complexes – mostly derivatives of the anticancer agent cisplatin – and their interactions with the biological counterparts: such as RNA/DNA, proteins, and small molecules such as the ascorbic acid. Employing state-of-the-art techniques of quantum chemistry (wave function/DFT methods and various solvation models) and molecular modeling (molecular mechanics, molecular dynamics, advanced free energy protocols) or a combination of both, such as QM/MM, the candidate attempts to find correlation between physicochemical properties of the studied compounds and their biological activity.

Formally, the thesis comprises approximately 50 pages of text which includes synopsis of nine research articles (8 original, 1 review) attached as appendices. The submitted manuscripts (4) or published papers (5) then represent the scientific part of the thesis. The candidate’s contribution to the presented work is significant; he is the first author of all eight original contributions. The thesis is written in a good English: the theoretical background and the attached papers are at the very good level whereas the synopsis (section Results, pp. 37-52) has been apparently written in a bit hasty manner with typographical errors here and there and a certain lack of streamlined logic. It is difficult to appreciate the scientific content of the thesis fromthis section only: one has to read the attached papers or manuscripts. This does not, though, preclude the fact that the reported work is scientifically sound (vide infra). I also assume that most of the manuscripts were written by the candidate himself. They are, in general, relatively easy to read and the scientific argumentation is mostly clear. This is, in my eyes, one of the important criteria to be fulfilled by a Ph.D. candidate.

Concerning the scientific content of the thesis, most of the work reported deals with the
Pt(II) or Pt(IV) complexes which are of potential pharmaceutical use (*corollary note: I am not sure whether the word organometallic is appropriate here; since these are defined as compounds containing at least one metal-carbon bond which is usually not the case here). The candidate attempts to compute four important physico-chemical characteristics of these systems: reduction potentials, bond dissociation energies, activation energies, and thermodynamic stabilities (incl. pKa values). Some of them are assumed to be related to the interaction of the compounds with the DNA/RNA bases which might be the origin of their antitumor activity. The numerical values are often satisfactory and attempts are made to explain the trends in the computed data by employing various qualitative concepts of quantum chemistry (Bader’s atoms-in-molecules analysis, reaction force concept of Michalak, reaction electronic flux concept of Toro-Labbe, frontier orbitals, etc.). In the second part of the thesis (papers VI-VIII), the candidate broadens the scope of the thesis to other metal ions, such as mercury and also extends the work methodologically: by using umbrella sampling methodology to obtain free energy reaction profile of the proton transfer coupled the interaction of mercury with thymine. In addition, the candidate attempted to derive force field parameters for the second (Ru, Rh) and third (Hg, Pt) row atoms and tested their performance in the MM/MD simulations which might be considered as quite useful. The work presented in the thesis is then “concluded” by the comprehensive review on metal interactions with nucleobases summarizing more than two decades of various efforts in the field (i.e., original work reported in ~200 references cited therein).

My overall impression from the presented work is positive. The studies are methodologically and technically sound, the Burda’s group belongs to renowned experts in the field and some of the presented results might be of an interest to (bio)inorganic and coordination chemists. If I would need to be *deliberately* critical, I would suggest a slightly better organization of the presented work. Some of the results might have been better grouped since some of the papers attached are more a collection of the computed results than a developing and exciting scientific story to tell to the reader. I miss, to a certain point, a greater aim to which all these efforts may lead to: perhaps this can be the topic raised in the discussion upon the defense of the thesis (see below). Concerning the massive amount of the work presented, I might have several tens of technical questions and minor issues; this fact demonstrates the great interest the thesis aroused in me. Below, I tried to select the most important issues and I would be happy to hear the candidates’ opinion on those topics.

In summary, the presented thesis summarizes a high-level science carried out by the candidate throughout his Ph.D. studies and therefore, I recommend it is accepted as the material for the Ph.D. defense and ultimately for awarding the Ph.D. title.
Questions:

1/ The Wertz’s entropic contribution is quite new to me. Can the candidate compare it with standard rigid-rotor-harmonic-oscillator (RRHO) model or with its “free-rotor” (RRFRHO) extension?

2/ The development of force fields is quite intricate problem and often includes the simultaneous (multidimensional) optimization of various parameters. To me, it seems that in paper VIII, the parameters were developed rather independently on each other which may not guarantee the best set of parameters for the overall performance?

3/ As mentioned above, can the candidate speculate how the bioinorganic chemistry and (potentially) medicinal chemistry may utilize the massive amount of computed data for further development and Pt anticancer drugs?

4/ The VTHA method of Srnec and Bim to compute reduction potentials of highly charged species has been reported recently. Did the candidate attempt to use it? Also, it is not clear whether the computed data denoted as “CT” (cosmotherm) are the COSMO-RS solvation energies? If so, there are many computational details missing.

5/ Is there experimental evidence for the loss of both ligands in Pt(IV) to Pt(II) reductions. Are these potentials reversible?

6/ Most of geometry optimizations reported in the thesis were done employing \( \omega B97XD \) DFT functional. This is not the most common functional to be used in bioinorganic chemistry. Did the candidate carry out a calibration study on its performance for the studied complexes?

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