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Evaluation of the thesis
"Metal-Ion Selectivity from Quantum-Chemical Perspective"
by Ondrej Gutten

Dear Committee,

I have read the doctoral thesis of Ondrej Gutten entitled "Metal-Ion Selectivity from Quantum-Chemical Perspective", which was prepared in the framework of the Graduate Program Modelling of Chemical Properties on Nano- and Biostructures at Charles University of Prague and IOCB. Aim of the project work, which is summarized in the present thesis, was to develop and to validate computational protocols to predict the metal-ion selectivity of metal-binding systems based on first-principles calculations that employ wave-function theory (WFT) and density-functional theory (DFT) calculations. Free-energy contributions were considered in the 'static' harmonic approximation and solvent effects were described by explicit interaction of water ligands in the first ligand shell and beyond that by continuum solvent models. The proposed methodology was applied in cooperation with an experimental group and also used to investigate the effect of truncating peptide ligands with respect to hybrid quantum mechanical/molecular mechanical (QM/MM) simulations.

The thesis represents a self-standing scientific work that advances our knowledge on metal-cation interactions and details about approaches and pitfalls when simulating metal ion-ligand interactions from first principles. The scientific work is sound and I can fully recommend the acceptance of the thesis and granting of the desired title.

The thesis contains a synopsis to introduce the reader to the broader field of research, including basic aspects of metal-ion binding, a biological motivation, as well as a brief methodological summary. A fifth chapter of the synopsis briefly summarizes the 4 peer-reviewed articles that represent the scientific part of the thesis. This initial part has a length of about 50 pages. Overall, the thesis appears to be written under some time pressure. The language is clear, but contains several slips in the language and moreover also some incomplete sentences, for example on pages 5 and 14. Overall, the textual form of the introduction is acceptable. Some important concepts are only

mentioned and not properly discussed/explained, e.g. Jahn-Teller distortion and allostery. In particular, the discussion of correlated methods (MP2 and CCSD(T)) and the involved technicalities (e.g. basis sets) is a bit short, given that these methods play an important role as production and reference methods in papers 1 and 2 of the thesis.

The research part consists of 4 articles; Ondrej Gutten is the first author of three of them:

1. Interaction of Metal Ions with Biomolecular Ligands: How Accurate Are Calculated Free Energies Associated with Metal Ion Complexation? *J. Phys. Chem. A* 2011 (27 times cited)
2. Predicting the Stability Constants of Metal-Ion Complexes from First Principles. *Inorg. Chem.* 2013 (17 times cited)
3. Cyclam Derivatives with a Bis(phosphinate) or a Phosphinato-Phosphonate Pendant Arm: Ligands for Fast and Efficient Copper(II) Complexation for Nuclear Medical Applications. *Inorg. Chem.* 2015 (8 times cited)
4. How simple is too simple? Computational perspective on importance of second-shell environment for metal-ion selectivity. *Phys. Chem. Chem. Phys.* 2015 (5 times cited)

All four papers have been published in well-renowned journals in the field and are frequently cited, in particular paper 1.

Papers 1 and 2 discuss a protocol to describe the energetics of metal-ligand interactions and the accuracy and applicability of several electronic-structure theory methods (DFT and WFT). Mr. Gutten gives a profound and detailed view on the collected data and the results are indeed useful and informative. I particular enjoyed the honest introducing sentence to the conclusion section of the 2011 JPCA paper. The authors point-out the problems and the applicability of the methods in an accurate way, but I am missing a bit of discussion of approaches and routes that go beyond the static models that have been applied here, for good reasons by the way. Paper 3 is an application of the introduced methodology to a study of the complexation of a copper radio-nucleotide by cyclam derivatives. In combination with experimental work, the simulations by Mr. Gutten helped to elucidate the mechanism of copper complexation by phosphorylated forms of cyclam. In the field of biomolecular simulations, the question how much a model system can be simplified by means of simple potentials or by truncating the system is crucial to judge the quality of the predictions. The latter aspect has been investigated for metal cation-peptide interactions in paper 4 of the present thesis where Mr. Gutten finds, for example, a dependence of the possible magnitude of truncation (functional group *vs.* side chain *vs.* full system) on the hardness/softness of the ligand.

Overall, I have enjoyed reading the thesis, with the core of the thesis, the research papers, being of very good quality. I am looking forward to the defense presentation and to answers to some of my questions on the next page.

With best wishes from Berlin,

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Questions to the candidate:

1. In the introductory section, I feel that the methods part is a bit too short. In particular, I would like short statements or explanations on:
    a. Jahn-Teller distortion
    b. Basis sets for correlated methods like MP2 and CCSD(T)
    c. Allosteric regulation in protein receptors

2. In the Inorg. Chem. 2013 article you state "the exact hydrogen-bonding network around the complex is not known" referring to the cation-ligands complex in water. How well defined is the H-bonding network, maybe speculate a bit?

3. Structures for the complexes in this paper seem to be prepared based on chemical intuition, which appears to be reasonable. For some of them though, in particular the complexes with 4 water molecules and Cys/His or the $[M(CH_3COO)(H_2O)_5]^+$ complex (systems e, f, i in Figure 1 of Inorg Chem 2013), there might be a bit more structural flexibility. Would it eventually be necessary to perform global structure searches for these systems? Which methodological options would there be to predict such structures?

4. The application presented in paper 3 is very interesting and important. How would a computational protocol to design/screen radio-nucleotide ligands look? Which aspects of the ligands would have to be tested and what are the open points to be developed from a theorist's perspective?

5. In the synopsis to paper 4 (p. 47), I read the statement that "water as a solvent is extensively studied and chemically rather simple". How is it that simulations of water phase diagrams, for example, are still a challenge? What are aspects of water structure and dynamics that are challenging with respect to the present work?