PhD Thesis Review

Accurate Quantum Mechanical Calculations on Noncovalent Interactions: Rationalization of X-ray Crystal Geometries by Quantum Chemistry Tools

by Jiří Hostaš

In his thesis, Mgr. Jiří Hostaš focused on the methodology of QM and semiempirical calculations and their application to biomolecular systems and host.guest complexes. Large part of the thesis is dedicated to extensive comparisons of accuracy of various methods and their systematic assessment. In addition to this, the candidate applied theoretical tools to evaluation of interaction energies in strongly bound host.gues complexes and validated the theoretical methodology against experiment.

One of the directions in which the studied methodologies are applied is interactions of nucleic acids with proteins. The complexity of the protein/NA complexes is reduced by considering only pairwise interactions of nucleic acid bases and amino acids, mostly in vacuum. Then, the wealth of crystallographic data is organized in clusters, for which interaction energies are calculated and discussed in regard to predictability of interaction geometries. In the second part of his thesis he focuses on the host.guest complexes. Various QM methods are used to predict binding energies and Gibbs energies, which requires inclusion of solvation effects and temperature effects estimated from the rigid rotor-harmonic oscillator analysis. The results are compared with experimental stability constants where available. This part clearly demonstrates shortcomings of the current QM based approaches where especially the solvation terms still represent a serious limitation for accurate comparison with experiment.

The thesis itself is essentially a shortened version of the published works. The text is well structured and easy to understand and follow, and it is written in very good English with only a few typos and omissions due to adaptation from published articles. Most of

the references to literature are well chosen. From the formal point of view, this thesis is complete and well written.

Among the most important results presented are those concerning the accuracy and reliability of several efficient QM and SQM methods for various biomolecular systems. The reparameterization of the Grimme's DFT-D3 dispersion correction for use with small basis sets may find wide practical applications in calculations on large biomolecular complexes. Of practical importance are also extensive tests of semiempirical methods for noncovalent interactions, which carried out not only on the standard test sets but also for the nucleic acid/amino acid complexes. The only weaker point is the comparison with force field results which was carried out for motifs taken from the protein/nucleic acid complexes. It is rather common to compare the force field calculations with the QM results and it may be quite useful when properly interpreted. However, it should always be mentioned that the additive force fields are effective potentials parameterized to work well in solution. They are not designed to reproduce accurate interaction energies in vacuum. This fact should always be mentioned or discussed when such comparisons are made. Perhaps some of the observations presented in Figure 10 of section 3.3.2 could be explained considering this fact. Except for this, all comparisons and assessments are carried out carefully and properly interpreted.

Interesting are also the results concerning theoretical predictions of binding energies and structures of the host.guest complexes. Although accurate binding Gibbs energies are still inaccessible using this type of methodology, it is important to see that some of the features of binding can be reproduced and theoretical calculations may be helpful in rationalizing binding preferences of similar ligands.

Mgr. Jiří Hostaš has authored 8 articles in impacted journals, including high quality journals such as Chemistry – A European Journal and he is the first author of four of these works. In the collaborative efforts with experimental groups he is the main author of the theoretical parts of the works. This is a rather strong publication record which demonstrates candidate's interest in scientific work and his scientific potential.

In conclusion, in my opinion this is a very good thesis that presents insightful and important research and demonstrates the candidate's ability to conduct independent scientific work. Therefore, I recommend that the candidate be awarded the PhD degree.

Doplněk v českém jazyce: Mgr. Jiří Hostaš prokázal tvůrčí schopnosti v dané oblasti výzkumu a jeho práce splňuje požadavky kladené na dizertační práce v daném oboru. Práci proto doporučuji k obhajobě.

Questions for the defense:

1) In Eq. 18. on page 28, the total solvation Gibbs energy is a sum of the cavitation, hydrophobic and electrostatic components. Where does this equation come from? (it is not cited) What is the difference between the cavitation and hydrophobic terms? Is there any consensual way of decomposing solvation energy in the field of theoretical chemistry and implicit solvation models in particular?
2) The interaction Gibbs energies calculated according to Eq. 21 on page 76 are strongly overestimated with respect to the experimental values. Why is that? Which term is likely responsible? Are there any experimental data for entropies and enthalpies of binding of the studied ligands? Perhaps separate comparison of entropic and enthalpic terms could help to identify sources of inaccuracies in the theoretical estimates.

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