MUNI SCI National Centre for Biomolecular Research

Review of Doctoral Dissertation

Title: Theoretical studies on photoinduced charge and electron transfer processes in nucleobase pairs and their prebiotic precursors

Candidate: Kinga Szkaradek, Faculty of Chemistry, Wrocław University of Science and Technology

Kinga Szkaradek presents a doctoral thesis summarizing her scientific achievements using theoretical calculations to elucidate various photoinduced processes in nucleobases and their aggregates, including both canonical and non-canonical base pairs. The work features results from advanced ab initio calculations, spanning characterization of excited states, ionizations, intersystem crossings, and other phenomena, and, more importantly, accounting for various geometric changes during photodeactivation pathways. Although this approach is methodologically sophisticated and well-chosen for exploring the complex behaviour of nucleobases, some limitations remain, particularly due to the intricate nature of the systems and the computational challenges involved (for example, all calculations lack the impact of explicit [micro]solvations). Nevertheless, the results offer fresh perspectives on fundamental questions about the prebiotic era and bring new information into a puzzle of the origin of life.

The thesis provides a comprehensive report of the results obtained during her doctoral studies rather than a concise summary or critical discussion of published papers. This choice may limit some broader benefits of ongoing publication in peer-reviewed journals. Namely, external independent reviews during data publications could bring fresh ideas and perspectives from the scientific community.

Nevertheless, some results were published in scientific journals. Based on a Web of Science search, the candidate is listed as the author or co-author of probably six papers, including two that appear directly relevant to her doctoral research:

1. Szkaradek, K. E.; Stadlbauer, P.; Sponer, J.; Gora, R. W.; Szabla, R. UV-Induced Hydrogen Transfer in DNA Base Pairs Promoted by Dark nπ States.* Chem. Commun. 2020, 56 (2), 201–204. https://doi.org/10.1039/c9cc06180k
2. Szkaradek, K.; Gora, R. W. Theoretical Insight into Photodeactivation Mechanisms of Adenine-Uracil and Adenine-Thymine Nucleobase Pairs. Phys. Chem. Chem. Phys. 2024, 26 (43), 27807–27816. https://doi.org/10.1039/d4cp02817a

In both articles, the candidate is the first author, showcasing her ability to conduct independent research. The first paper is cited in the thesis on page 62 but without further information on how the thesis and published paper complement each other. In general, a short summary of these publications would be beneficial for the thesis, even though some papers were obviously in preparation at the stage of thesis submission.

The thesis is written in English. It comprises two main chapters, a brief summary including future perspectives, and extended Polish and Czech summaries.

The "Introduction" chapter (45 pages) provides in-depth motivation for the work and literature review. The photochemistry of the model and biological compounds is reviewed. The candidate also discusses their potential importance in the prebiotic era and the chemical origin of life. This literature review is detailed (based on about 226 references) and well-structured. In total, the thesis contains 288 references. Unusually, the references are provided in two places: as footnotes and listed separately at the end of the document. This way, I consider it slightly distracting as the footnotes do not allow for an efficient literature search or orientation in the text (neither titles nor DOI is included).

While the text is very readable and easy to follow, certain sections present information common to many textbooks. This is especially true for chapter 1.4 (Methodology) and, for example, the subsection "Hartree-Fock". By the way, the better title of this section would be "Hartree-Fock Method".

The "Discussion of results" chapter (64 pages) presents and discusses a large volume of data, highlighting the candidate's productivity. However, the text seems very long, and sometimes it is difficult to absorb all the described findings. The results are split only into two main subchapters: 2.1 Radiationless deactivation of the canonical nucleobase pairs (27 pages) and 2.2 Investigation of alternative base pairs (37 pages). These sections appear to form the basis of two already published papers. Perhaps a different organization with intermediate summaries would benefit from a better understanding of the main outcome.

Presented data are discussed concisely following the scientific standards. However, some imperfections can be found. From some moment, which seems to be the inclusion of the ring deformation coordinate, the x-axis in many graphs does not contain information about units of distances. In contrast, a unit of ring deformation is provided in captions. Also, the text does not explain the meaning of the ring deformation. Secondly, it would be beneficial if there were separate chapters describing computational details before each (sub)result section. While some description of the computational methodology is provided in Chapter 1.4, many details are scattered or repeated or, on the other hand, missing throughout the discussion of the results. In addition, Tables 9 and 10 captions do not indicate that the middle parts are related to the chloroform environment, which is mentioned in the text. Nevertheless, these are generally small issues.

The most important results of the thesis are summarised in the section "Final remarks and conclusion" (5 pages). In my opinion, the objectives presented in Chapter 1.3 have been successfully met.

I will skip comments to the Polish extended summary (8 pages) because I do not speak Polish.

The Czech extended summary (7 pages) summarizes the thesis. However, some additional proofreading would improve the quality. Some wording is odd or even incorrect. For example, "... popsaného v diplomové práci, .." should be „... popsaného v disertační práci, ..." (page 126).

In conclusion, the candidate demonstrated the ability to conduct modern academic research in theoretical photochemistry independently and successfully. The published work constitutes an original contribution to the resolution of scientific problems. The doctoral thesis meets the requirements set for doctoral theses in the field of fundamental and life sciences within the discipline of chemical sciences.

Hence, I confirm that the doctoral dissertation fulfils the following two conditions:

- "the doctoral dissertation demonstrates the candidates's general theoretical knowledge in a discipline (or disciplines) and the ability to conduct research or artistic work independently,"

and

- "the subject matter of the doctoral dissertation shall be an original solution to a scientific problem or in terms of the application of results of own scientific research."

Therefore, I unequivocally recommend this good scientific work for the defence.

In Brno, 7th January 2025

RNDr. Petr Kulhánek, Ph.D.
National Centre for Biomolecular Research
Masaryk University
Kamenice 5
625 00 Brno
Czech Republic

Questions:

1) Please describe a coordinate employed to quantify the ring deformation. How is this coordinate related to puckering coordinates defined by Cremer, D.; Pople, J. A. General Definition of Ring Puckering Coordinates. *J. Am. Chem. Soc.* **1975**, *97 (6)*, 1354–1358. https://doi.org/10.1021/ja00839a011?
2) There is no unique decomposition of the potential energy into easily interpretable components. Did you consider other decomposition schemes, such as SAPT, implemented in the Psi4 package or others alongside the employed HVPT-EDS?
3) The interpretation of decomposed energies usually depends on the decomposition scheme and the interpretation scale (quantum vs classical). For example, the electrostatic interaction is seemingly over-estimated due to short-range effects, such as penetration energy, see the introduction in Rackers, J. A.; Wang, Q.; Liu, C.; Piquemal, J.-P.; Ren, P.; Ponder, J. W. An Optimized Charge Penetration Model for Use with the AMOEBA Force Field. Phys. Chem. Chem. Phys. 2016, 19 (1), 276–291. https://doi.org/10.1039/C6CP06017J.). How does this effect impact your systems, which are hydrogen-bonded and thus might be susceptible to this phenomenon?
4) Truncation in the atom-centered basis set expansion leads to the basis-set superposition error (BSSE). In your case, the calculated interaction energies were corrected by the counter-poise method (page 41, ref 206), a straightforward approach for intermolecular interactions. However, the same effect can occur on an intramolecular scale due to conformation change or large electron density reorganization. I wonder how large this effect might be in your systems, especially between ground and excited states.
5) Why did you not consider a microhydrated environment in your calculations? Was it because of calculation demands or to simply keep the model as simple as possible because of the interpretation difficulties?