Review of Doctoral Dissertation

Title: Theoretical studies of the influence of environment on photochemical and photophysical properties of selected heterocyclic compounds

Candidate: Mikołaj J. Janicki, Faculty of Chemistry, Wrocław University of Science and Technology

Mikołaj J. Janicki presents a doctoral thesis summarizing his pioneering scientific achievements from applying theoretical calculations to elucidate the photochemical behaviour of heterocyclic compounds. He selected 2-aminoimidazole, 2-thiocytosine, and oxazoline derivatives, which are related to the prebiotic era. To adequately describe their behaviour, he had to model the impact of the environment, which is not an easy task. He tested an explicitly microhydrated environment combined with implicit solvent and how the attached saccharides change photochemical behaviour. Obtained results were published in four papers in impacted journals (Faraday Discussions, Chemical Physics, Chemical Communications, and the Journal of Chemical Physics Letters), where the candidate is the first author. In addition, the candidate is also co-author of the other seven papers, one of them being a paper in Nature. Altogether eleven papers published in about five years is an outstanding achievement.

The thesis is written in English. It consists of two major chapters accompanied by a short summary including future perspectives and extended Polish and Czech summaries.

The "Introduction" chapter (31 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 120 references) and well structured. Sadly, many statements are cited by several references; thus, it is difficult to track the origin of the statement. In the following subsection, theoretical methods are summarized. In my opinion, this part is too short. I would expect a more elaborated summary providing a critical assessment of the employed computational method and techniques, their abilities and especially limitations.

The "Published scientific articles" section (43 pages) presents four published papers. Each paper is accompanied by a short summary. These works are as follows: a) electron-driven proton transfer in microhydrated 2-aminoimidazole; b) solvation effects on the photochemistry of 2-thiocytosine; c) photostability of oxazoline RNA-precursors; and d) impact of ribose on photochemical properties in thionated nucleosides. Even though these works underwent a peer-review process in the journals, I will fulfil my role as a thesis reviewer to provide an additional critical assessment. Thus, some comments and questions about the published works are raised at the end of this review. Here I will only criticize the usage of some abbreviations such as AIM (aminoimidazole) and NAMD (non-adiabatic molecular dynamics), which were very confusing for me, as they are more often used in conjunction with the Atoms-In-Molecules concept (AIM) and the name of well-known software for classical molecular dynamics (Nanoscale Molecular Dynamics - NAMD).

In section "Summary" (5 pages) the most important results are concisely summarised.

As I do not speak Polish, I will skip comments to the Polish extended summary (11 pages).

The Czech extended summary (10 pages) nicely summarizes the thesis. However, some additional proofreading would improve the quality. For example, the word "sířený" (page 104) usually means applying sulfur dioxide to preserve wine or fruits and not substitution by sulphur.

Even though the thesis and articles were prepared with care, I found some errors, for example, page 84 and 96, "... milisekund (10^{-6})" should be "... milisekund (10^{-3})"; page 4, Figure 1, middle figure, "π^* orbital" should be "π orbital"; page 6, Figure 2, "... the occupied π^* and ..." should be "... the occupied π and ..."; page 48, Reference 49 is incorrect, "*Theor. Chem. Acc.*, 2012, **131**, 1-14." should be "*Theor. Chem. Acc.*, 2012, **131** (6), 1237."; page 62 (Article 3), "oxazolidinone thione" should be "oxazolidinethione".

In conclusion, Mikołaj J. Janicki demonstrates that he can independently and successfully pursue modern academic research in the field of theoretical photochemistry. The published work represents an original solution to scientific problems. The doctoral thesis of Mikołaj J. Janicki meets the requirements for doctoral theses in the field of fundamental and life sciences in the discipline of chemical sciences. Therefore, I unequivocally recommend this excellent scientific work for the defence with high distinction.

In Brno, 13th July 2022

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Additional comments and questions:

1) In both the thesis and the articles, some essential information about the used computational methods is not provided. Can the candidate elaborate on how the semi-classical non-adiabatic molecular dynamics simulations were performed? In particular, what were the initial atom velocities and how they were controlled in the course of the dynamics?
2) Follow-up question. No-adiabatic transitions were allowed only between the excited states (page 38), but the ground state was observed in the dynamics. How did the transition to the ground state happen?
3) Was microhydration tested for the other side of 2-aminoimidazole (site with the nitrogen atom with a lone pair)? I can imagine a process in which the amino group is deprotonated, but the proton is returned to this nitrogen atom, providing a tautomer of 2-aminoimidazole.
4) Can the rate of electron transfer between 2-aminoimidazole and water molecules be determined from non-adiabatic molecular dynamics simulations?
5) It is not clear how the COSMO model was employed in all studies. Can you elaborate on how the fast and slow solvent responses were handled in vertical excitations and relaxed structures of excited states?
6) In QM calculations, the inclusion of explicit solvent molecules is a challenging task full of compromises. In the published studies, only a limited number of water molecules were added. Then, geometries were fully optimized. However, at this step, the orientation of water molecules becomes incorrect, especially at the boundary of microhydrated volume. This reorientation of water molecules can cause severe artefacts, and I wonder how this approximation was justified or verified. Also, it is quite risky to use a single configuration for such flexible systems. I believe molecular dynamics simulations on QM(solute+explicit hydration)/MM level(rest of the solvent) could provide more valid structures.