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Report on the doctoral thesis of **Ms Eva Pluhařová** entitled "*Solvent effects on ion pairing and photoionization in water*"

The PhD thesis manuscript presented by Ms Eva Pluhařová is devoted to a theoretical and computational study of solvent effects on a series of processes involving ions in aqueous solutions, including ion pairing and DNA photoionization.

The manuscript starts with a brief introduction highlighting the importance of the different systems that have been studied and a concise and pedagogical review of the broad range of computational techniques that have been employed. The following chapters then describe successively the different questions that have been addressed during this doctoral work and their main results. Ms Eva Pluhařová finally offers some concluding remarks and provides reprints of the nine publications in international peer-reviewed journals which have already resulted from this work.

The thesis manuscript is very well written, and the degree of detail provided in the text has been extremely well balanced to provide the reader with sufficient information to explain the key concepts and results without diluting these essential points in an unnecessarily long discussion. This is especially remarkable given the wide gamut of systems and of methodologies, both computational and experimental, that have been employed in the different projects, and this clearly shows that Ms Eva Pluhařová has acquired an excellent understanding of these aspects.

The different chapters of the thesis are now succinctly described.

Chapter 2 reviews the key theoretical concepts and simulation tools used during the thesis. These include classical molecular dynamics simulations with different treatments of the electronic polarizability, DFT-based ab initio molecular dynamics and mixed quantum/classical (QM/MM) simulations for the

calculation of photoelectron spectra. The respective strengths and limitations of the different techniques are clearly described.

Chapter 3 shows how one can improve standard classical molecular dynamics force fields for concentrated aqueous salt solutions, with an illustration for LiCl and Li₂SO₄ solutions. Classical force fields have indeed been parameterized on dilute solutions and they do not properly reproduce the structure of concentrated salt solutions measured experimentally. Ms Eva Pluhařová convincingly shows that together with a fine-tuning of Lennard-Jones parameters, the recently suggested “Electronic Continuum Correction” approach that scales the atomic partial charges leads to a dramatic improvement of the results of classical molecular dynamics simulations without using any expensive explicit description of electronic polarization.

Chapter 4 then discusses several aspects of ion pair formation, including their formation thermodynamics, their structure and their signature in infrared vibrational spectroscopy, illustrated on the cases of LiF and of pairs between a model peptide bond, N-methylacetamide (NMA), and Na⁺ and Ca²⁺ ions. Ms Eva Pluhařová shows that ion pairs between NMA and Na⁺ is less favorable than with Ca²⁺ but is still favorable, even though it cannot be observed in vibrational spectroscopy because the ionic perturbation on the C=O band is too weak. This result is very important to understand the behavior of proteins and ions in biochemical systems.

Chapter 5 finally focuses on the two studies of DNA damage that have been performed in collaboration with experimentalists. The first part elucidates the initial stage of the indirect damage mechanism, where the ionizing radiation ionizes water to form the OH. radical that will subsequently attack DNA. Ms Eva Pluhařová establishes that a delocalized cationic hole is formed and becomes localized in approximately 30 fs, before a fast dissociation leading to the OH. radical. The second part addresses the direct DNA ionization. Ms Eva Pluhařová presents the first rigorous determination of vertical ionization energies for the different DNA building blocks, which is a remarkable result. Ms Eva Pluhařová further shows that the hydration shell plays an important role in the value of these ionization energies, while the rest of the DNA structure is almost negligible, which paves the way for future efficient calculations of ionization energies of DNA bases.

This manuscript demonstrates the outstanding amplitude and quality of the doctoral work presented by Ms Eva Pluhařová, which is also apparent in the numerous publications that she has already coauthored. Ms Eva Pluhařová displays a remarkable scientific maturity, a great understanding of a broad range of scientific questions and theoretical methodologies and an excellent knowledge of the literature. I therefore strongly recommend her work to be defended to obtain the PhD degree.

While the manuscript is already very clear, I would like to mention a few questions and comments which might be further clarified during the oral discussion:

- 1 – Chap. 2 (p. 14): the nature of the different factors causing a broadening of the photoelectron absorption band might be specified: in particular, the difference between the factors causing a homogeneous vs an inhomogeneous broadening, and why nuclear quantum effects induce a broadening.

2 – Chap. 2 (p.10): what are the key limitations of the ECC approach ? How well is it expected to do in non-isotropic systems and for dynamics for example ?

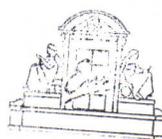
3 – Chap 4 (p. 38): The correlation between the number of hydrogen-bonds formed by the salt bridge and the location of the proton is very convincing. However, could this be generalized to a collective solvent coordinate used for example for proton transfer reactions in polar solvent ? In addition, does an increase in the number of hydrogen bonds systematically stabilize the zwitterion? If one considers a hydrogen-bond donated to the water molecule in the ClH...OH₂ pair, this does not seem to be universal.

4 – Chap 5 (p. 45): Photoelectron spectroscopy is presently not sufficiently sensitive to detect the H₂O⁺ radical that is formed. Would it be possible to detect it with vibrational spectroscopy?

5 – Chap 5: The results nicely show that the vertical ionization energy depends mostly on the neighboring water molecules and not on the rest of the DNA. What would be the impact of a typical ionic buffer on these ionization energies ?

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