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Review report on the habilitation thesis of RNDr. Peter Košovan, Ph.D. entitled "Acid-base equilibria at the nanoscale"

The habilitation thesis of RNDr. Peter Košovan, Ph.D., presents the candidate's work concerning theoretical description and computational modeling of acid-base equilibria in complex, non-ideal systems at the nanoscale. The thesis is based on eight peer-reviewed papers co-authored by Dr. Košovan and published in the years 2015-2021 in scientific journals well-respected in the field. The candidate is the first author of one and a corresponding author of seven of the papers. These papers, constituting the core of the thesis, are already well-cited, with up to 47 citations in the case of the oldest one.

Acid-base reactions and their equilibria form one of the primary topics of chemistry. Under standard ideal conditions, they are relatively easy to describe and quantify. However, at the nanoscopic level and under conditions far from ideal, homogeneous, well-diluted cases, many aspects of acid-base reactions cannot be described by standard analytical approaches. Dr. Košovan developed a theoretical and computational approach that can be used to study acid-base equilibria under such conditions. The relevance of this work spans from studying conformations and properties of polymers, including proteins, to designing properties of novel materials.

The thesis opens with an introduction that outlines the main problems tackled by the author. The following chapter briefly describes two previously used approaches to deal with acid-base equilibria at the molecular scale: constant pH (cpH) and reaction ensemble Monte Carlo (RxMC) methods. Then, the novel method introduced by Dr. Košovan is presented. In his approach, named grand reaction ensemble Monte Carlo (G-RxMC), the acid-base equilibria of inhomogeneous polyelectrolytes are described taking into account the possibility of small ions transfer from the system of interest to a reservoir. The inclusion of the reservoir is the crucial element of the approach, allowing for describing acid-base reactions in such systems as proteins in a vicinity of biomembranes or polyelectrolytic hydrogel materials. Dr. Košovan's method is based on the RxMC technique, in which on the top of configurational MC moves, reaction MC moves are introduced, able to model acid-base equilibria. G-RxMC also includes exchanging small components (ions) with a reservoir, while bigger molecules

(polyelectrolytes) stay in the main system. In practice, on the simulation side, a coarse grain approach is used to model the molecules, with an implicit treatment of water solvent.

The main results obtained with the methodology proposed by the candidate and included in the selected papers are presented in the third and fourth chapters. Chapter three deals with acid-base equilibria in solutions. The author discusses the case of a weak acid attached to a polyelectrolyte and the behavior of weak polyampholytes. In particular, dependence between the conformation of selected polymers and system pH is analyzed. The studied polymers include charged polypeptides, such as Lys_5-Asp_5, which undergo significant conformational changes with varying pH; this example is essential for an overall understanding of protein conformations under locally varying conditions. The fourth chapter presents the results obtained for acid-base equilibria in two-phase systems. In practice, such systems represent, for instance, a solution of proteins in a dialysis bag or a polyelectrolyte gel material in solution. Here, particularly interesting are the results obtained for electrostatically crosslinked polymeric gel materials where pH was shown to control the phase separation; these findings are potentially important for designing new polymeric materials with tunable properties. It should be stressed that most of the presented results were confronted with experiments, and an excellent overall agreement was obtained. It proves that the G-RxMC method can reproduce experimental results and provide useful predictions and molecular-level interpretation of the investigated phenomena.

The habilitation thesis is summarized with the conclusions and outlook chapter. After a short summary of the significant methodological advances and their use, the author presents his future research plans. These plans are directly based on the methods described in the thesis and include two main research lines. First, mixed experimental and simulation studies of model systems, such as more complex oligopeptides. Second, application of the developed methods to guide the experimental design of specific materials. Worth noting, the theoretical and simulation work will be conducted in close collaboration with experimental research groups, both in Prague and abroad.

The text of the habilitation thesis is carefully prepared; it reads very well. This is also true for the chapters describing the theoretical foundations. All equations and figures are well presented and discussed. I found only a few typos and editing errors (e.g., typos in the Preface chapter; Fig. 4.3 is not mentioned in the text; Ref. [67] is not co-authored by the candidate). The literature is well-chosen and adequately cited.

The papers selected as a basis of the habilitation thesis are overall a good representation of the research work by Dr. Košovan. His work is very timely, connecting theory and simulations with experiments and having potential use in new material design. The author is active in his research field, as proven with his publication and citation record (over 40 impacted published papers; nearly 700 citations, h-index 17). The G-RxMC method introduced recently will undoubtedly strengthen his position in the field; this method is also available for use by the research community within one of the simulation software packages. Dr. Košovan has significant international collaboration, including experimental groups. His teaching and supervising activities are solid; for instance, he currently supervises four Ph.D. candidates.

I suggest that the following issues can be discussed during the defense:

1. What is the overall influence of the coarse-graining approach used by the author in the simulations of the acid-base equilibria with the G-RxMC method? Also, would an explicit inclusion of solvent qualitatively change the obtained results?

2. On page 10, short-range repulsive interactions between all involved components are mentioned but not explained. What is the physical basis/interpretation of such interactions? How were they modeled in simulations?

3. The thesis does not describe the details of the simulations that were performed. What practical issues/problems may be encountered while using the G-RxMC method?

Summary:

In my opinion, the overall scientific activity of RNDr. Peter Košovan, Ph.D., and the presented habilitation thesis fulfill the requirements of the habilitation procedure. Therefore, I support his candidacy for obtaining the docent appointment by the Scientific Council of the Faculty of Science, Charles University in Prague.

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