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REPORT

on the dissertation entitled *"Computer Simulations of Polymer-Enzyme Complexes and Chelate Structures of Heavy Metal Ions"* submitted by **Halyna Butovych** in partial fulfilment of the requirements for the degree of **Doctor of Philosophy**

The dissertation deals with the molecular-level complexation phenomenon - a prominent problem in physics and chemistry that has far-reaching implications in technology. Two specific examples are considered: (i) self-assembly of functionalized polymers with catalytic enzymes, and (ii) chelation of certain heavy metal ions by short linear polyethyleneimine (PEI) polymers and ethylenediaminetetraacetic acid (EDTA) molecules. Modern theoretical tools such as Langevin dynamics, classical molecular dynamics and quantum chemical calculations based on density functional theory are employed to gain microscopic insights into the structural and thermodynamic features of intermolecular interactions, which are of both fundamental and practical interest. The work has been carried out at a high professional level with most reported results published in reputable scientific journals.

The dissertation includes an introduction, a thematic review, three research chapters with original results, concluding remarks, references and supplementary appendices.

In the Introduction, the subjects and objectives of the study are outlined, while the Review section discusses existing studies addressing similar problems and approaches.

In Chapter 2, a coarse-grained model is proposed to describe the self-assembly of polymer-enzyme mixtures into complexes, where polymers are represented as chains with patchy segments and enzymes are modelled as patchy spherical monomers. To investigate complexation and predict the binding degree between polymers and monomers, a modified version of Wertheim's first-order thermodynamic perturbation theory (TPT1) was developed. This modification consists in the improved treatment of the contact values of terminal and intermediate polymer segments with monomers in the reference system, which is a key element in perturbative approaches of this kind. Computer simulations using Langevin dynamics performed in this study confirm the high accuracy of the theoretical results, while also revealing their limitations in the case of dense functionalization of polymer chains.

Chapter 3 presents a study of the chelation of Hg^{2+} ions by PEI chains of different lengths. The results of atomistic molecular dynamics and quantum chemical calculations shows that a chain containing five nitrogen-bearing units exhibits optimal coordination of a single Hg^{2+} cation, combining high donor atom availability with minimal steric hindrance. It is also demonstrated that longer chains, containing ten nitrogen atoms, can coordinate up to four Hg^{2+} ions, although the binding energy per ion decreases due to electrostatic repulsion between the ions and reduced flexibility of the polymer backbone. These findings establish important trends that determine the selectivity and stability of PEI complexes, which may be exploited in the rational design of sorbents for heavy metal ions.

Chapter 4 focuses on the mechanisms of chelation of Hg^{2+}, Cd^{2+}, and Pb^{2+} ions by EDTA, with particular attention to different protonation states of this ligand. It is shown that fully deprotonated EDTA forms the most stable complexes, especially with Hg^{2+} ions, whereas partial protonation reduces the number of available donor groups and thereby decreases the chelating capacity. Similar to Chapter 3, this study combines two methods – molecular dynamics and density functional theory, allowing the estimation of the main structural characteristics of the observed complexes as well as the adsorption or binding energy between the ions and the EDTA molecule. In addition, the author provides a detailed analysis of the hydration shells of the studied ions, highlighting the peculiarities of Pb^{2+}, which present specific challenges for modelling. The use of multiple computational protocols enabled the successful reproduction of key trends and confirmed their consistency with experimental data.

The dissertation makes an important contribution to the development of the theory and practice of molecular modelling of complex multicomponent systems. For the first time, TPT1 has been adapted to describe polymer-enzyme complexes with taking into account the distribution of functional groups along the polymer chains. A thorough analysis of PEI-Hg^{2+} systems based on MD and DFT calculations has revealed optimal conditions for selective ion binding, and the EDTA studies have shed light on the mechanisms governing protonation-dependent chelation. The obtained results are of practical significance for environmental engineering (wastewater treatment from toxic metals) and biotechnology (enhancing biocatalytic efficiency in biofuel production from cellulosic biomass).

The thesis is well written. However, I have some concerns which the author may consider addressing in order to make it even better.

Comments:

1) Page 3, sentence containing “приєднуються атоми водню” (hydrogen atoms are attached). I doubt these are “hydrogen atoms”, rather their nuclei.

2) In the notations of Fig 2.5 symbols mTPT and TPT should be replaced with mTPT1 and TPT1 respectively. Symbol “MC” should be defined.

3) Table 3.1 lists non-bonded parameters for the PEI and mercury ions used in the simulations. It should be updated to include the parameters of counterions.

4) I’m confused about the data shown in Tab. 3.2. The caption shows G_{cmpx} suggesting that it is Gibbs free energy of complexation. Yet columns 2 and 3 are marked as “MD” and “Binding energy, MD” implying that they both contain data generated by MD. However, it’s never been explained how Gibbs free energy was estimated in MD. The quantity introduced for that method is “adsorption energy”. Is this what is shown in Tab 3.2? If so, why is there 2 columns instead of one? Finally, what is “complexation energy” referenced in Fig. 3.17? These issues have to be clarified. All used terms and quantities have to be clearly defined.

5) Scale should be added to the vertical axis in Figs. 4.5-4.7

6) What does the lgβ symbol mean in Tab. 4.2. It’s never defined. What are the units of free energy in that table?

In conclusion, Halyna Butovych's thesis *"Computer Simulations of Polymer-Enzyme Complexes and Chelate Structures of Heavy Metal Ions"* constitutes a carefully executed and complete scientific study that reports important new results. In this work, the author has demonstrated a considerable proficiency at using methods of theoretical physics, such as computer simulations and analytical theory. Based on the totality of the evidence that I have seen, I conclude that Halyna Butovych meets the requirements of, and should be awarded the title **"Doctor of Philosophy"** in natural sciences (104 – Physics and Astronomy).

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