STANDPOINT

by Ivelina Mircheva Georgieva, Assoc. Prof. Dr.
Institute of General and Inorganic Chemistry – Bulgarian Academy of Sciences
of PhD Thesis for conferment of the educational and scientific degree "**Doctor**"
field of higher education **4. Natural Sciences, Mathematics, Informatics**
professional field **4.2. Chemical Sciences (Theoretical chemistry)**

Name of the Candidate: **Assist. Prof. Sofia Olegovna Slavova** – PhD student in independent training at Institute of General and Inorganic Chemistry (IGIC) – BAS, Laboratory "Theoretical and computational chemistry"
Scientific supervisor: Prof. DSc Venelin Enchev
Title of the PhD Thesis: **„Mechanisms of prebiotic reactions based on the formamide – *ab initio* modelling"**

The subject of review: By order № РД-09-46/26.02.2021 of the Director of IGIC-BAS, I am appointed as a member of the scientific jury under a procedure for the defence of dissertation work for conferment of educational and scientific degree "Doctor". The set of materials presented by the PhD student in paper and electronic form is in agreement with the Law for the development of the academic staff of the Republic of Bulgaria and to the corresponding implementing Regulations for BAS and IGIC.

Information about the PhD student: Sofia Slavova graduated with an excellent diploma from her higher education, speciality "Chemistry" at the Institute of Chemistry of St. Petersburg State University (Russia), bachelor's degree (in 2016) and master's degree (in 2018). The themes of her Diplom theses are in the field of Theoretical Chemistry. For a short time, she worked as a researcher in the Transition Metal Cluster Chemistry Group at the Institute of Chemistry (Russia) and as an assistant professor in the Theoretical Chemistry Group at IOC-CF-BAS. In March 2019 she joined the Laboratory of Theoretical and Computational Chemistry at IGIC-BAS and in July 2019 she enrolled in a PhD program in the scientific speciality "Theoretical Chemistry".

The PhD thesis of Sofia Slavova contains a thorough theoretical study of the most likely mechanisms of autocatalytic reactions based on formamide for the formation of purine and pyrimidine nucleobases, and pterin, which are important biomolecules for the origin of life on Earth. The model reactions in which formamide is a reagent, catalyst and medium occur as a result only of thermal processes. The topic and research approach are relevant and based: 1) on the most realistic theory (according to accumulated experimental evidence) about the extra-terrestrial origin of life, assuming that one of the most common molecules in the universe, formamide is a starting molecule in prebiotic synthesis and 2) of experimentally obtained over 10 basic products (nucleobases) from formamide in liquid phase after heating at 100-180 ° C. To clarify the chemical evolution, quantum-chemical computational approaches have been skillfully applied, which, unlike the experiment, can predict the most rational reaction pathways for obtaining experimentally established or possible biomolecules. The theoretical studies are performed using the Møller-Plesset method at the MP2/cc-pVDZ//SCS-MP2/cc-pVDZ level and a solvation model based on density (SMD), which are validated for reliable simulation of the geometry, weak interactions, and energy of the model reagents,

transition states, intermediates and products in the studied chemical reactions, as well as for the calculation of energy barriers. The influence of the solvent, the entropy factor and the temperature on the activation barriers and the relative energies between reactants and products has been evaluated. The theoretical search for the most probable mechanisms of prebiotic reactions is a very complex task and for its implementation, Slavova demonstrates deep knowledge and skills in the field of quantum chemistry and chemical kinetics. As a result of the theoretical study, the most preferred energy pathways of reactions are proposed for the initial preparation (from formamide) of basic reagent-precursors and intermediates - formimidic acid, water, hydrogen cyanide, ammonia, formic acid, 2-imino-acetonitrile, 2-aminoacetonitrile, 2-aminomalononitrile, isocyanic acid, urea, guanidine, glyoxal and 3-hydroxyacrylonitrile, needed for further formation of nucleobases. The main prebiotic precursors (2-aminomalononitrile, 2-aminoacetonitrile and urea) are identified and the possible reaction pathways for the production of purine nucleobases (adenine, hypoxanthine, guanine, isoguanine, xanthine and 2,6-diaminopurine) and pterine as some reactions take place through intermediate compounds N'-(1H-imidazol-5-yl)formamidine and N'-(1H-imidazol-4-cyanide-5-yl)formamidine. A favourable reaction pathway for the preparation of pyrimidine nucleobases (cytosine, uracil, 2,4-diaminopyrimidine and isocytosine) is found using a basic precursor 3-hydroxyacrylonitrile. The proposed network of interconnected autocatalytic reactions for nucleobases formation is based on the calculated energy-preferred reaction pathways from a thermodynamic and kinetic point of view under thermal conditions up to 180 ° C, where the permissible energy barrier is up to 40 kcal/mol. The investigation of more than 300 model reactions of varying degrees of complexity is pioneering and for the first time, the mechanisms of prebiotic autocatalytic reactions for the formation of adenine, hypoxanthine, 2,6-diaminopurine, guanine, xanthine, isoguanine, pterin, 3-hydroxyacrylonitrile and urea from formamide are proposed. A theoretical model for obtaining guanine, isoguanine and xanthine has also been suggested, which is yet to be experimentally proven.

The volume, content and structure of the dissertation work meet all requirements of the Law for the development of the academic staff of the Republic of Bulgaria and to the corresponding implementing regulations for BAS and IGIC. The PhD thesis is presented into 118 pages, includes 3 tables and is richly illustrated with 58 figures, containing mainly schemes of autocatalytic reactions. It is structured in 3 Chapters: Literature review, Computational Methods and Results, and in addition there are separate Sections: Conclusions, Contributions and Literature with 218 cited references. The present thesis is characterized by precise style, language and completeness. In consequence of research on dissertation work, original and significant results are obtained with fundamental impact and they are summarized into 3 papers: two in *International Journal of Quantum Chemistry (IF = 2.25, Q2, 40 points)* and one in *Journal of Biomolecular Structure and Dynamics (IF = 3.31, Q2, 20 points).* Four citations have

already been found in the literature. The collected 60 points for published papers exceed the minimum criteria under indicator G (30 points) for the acquisition of the educational and scientific degree "Doctor" at IGIC-BAS. The results obtained are personally presented by the PhD student at 6 national conferences with oral reports and 3 scientific forums – with poster participations. The content of the synopsis of the Doctoral thesis accurately reflects the goals, tasks, main results and conclusions of the dissertation work. An excellent impression is made by the precise scientific style, the skilful systematization of the huge number of data about the model reactions and the exhaustive presentation of the results in the dissertation. The PhD student has managed to develop the topic in a relatively short period of time, has mastered the quantum-chemical approach for kinetic and thermodynamic characterization of reactions in the field of prebiotic chemistry and is already showing abilities for independent research.

Comments: On page 42, Fig. 3.4 (above); page 44, Fig. 3.5c; page 65, Fig. 3.22 (step 29) the level of the energy barrier of the product relative to that of the reagent does not correspond to the specified relative energies. If the Table's numbering in the thesis is followed in the Synopsis (of doctoral thesis), then Table 1 on page 20 should be Table 2 and Table 2 on p. 21 and p. 22 should be Table 3.

In summary: The PhD thesis contains fundamental scientific results that represent an original contribution in the field of theoretical chemistry, prebiotic chemistry and chemical kinetics. The research work is well planned and successfully fulfilled both in quality and quantity. Due to the said above, I confidently give my positive assessment of the research, the results achieved and contributions presented in the Dissertation and I vote "**yes**" for conferment of the **educational and scientific degree "Doctor"** to **Sofia Slavova** in the field of higher education 4. Natural Sciences, Mathematics and Informatics, Professional field 4.2. Chemical Sciences (Theoretical Chemistry).

12.05.2021
Sofia

Member of scientific jury:
Assoc. Prof. Dr. Ivelina Georgieva