REVIEW

by prof. Vassil Borissov Delchev, DSc,
from the Department of Physical chemistry, University of Plovdiv
on the materials for the defence of a doctoral thesis
for the awarding of the academic degree *Doctor of philosophy* (PhD)
in the Institute of general and inorganic chemistry – Bulgarian academy of sciences
(IGIC - BAS)

Field of higher education: 4: Natural sciences, mathematics and informatics
Professional area: 4.2. Chemical sciences
Scientific field: Theoretical chemistry

PhD student (aspirant): assist. prof. Sofia Slavova, IGIC-BAS
Title of the doctoral thesis: „Mechanisms of prebiotic reactions based on formamide – an *ab initio* modeling"
Scientific supervisor: prof. Venelin Enchev, DSc

Director's order for the constitution of the Scientific jury: **РД-09-46/26.02.2021 г.**
Decision of the first meeting of the Scientific jury: **to write an academic review.**

The aspirant has presented in digital form the materials for the defence of the doctoral thesis for the awarding of the academic degree *Doctor of philosophy*. The documentation involves: 1) Director's orders for taking her as a PhD student (№ РД-09-77 / 28.06.2019 г.) and for the finishing of the PhD study (№ РД-09-173 / 30.10.2020 г.), 2) a certificate for passed examinations during the PhD study, 3) a standard *Curriculum Vitae*, 4) diplomas for higher education – bachelor and master, 5) a list of publications included in the PhD thesis, 6) a list of citations, 7) a list with participations in conferences, 8) a PhD thesis, 9) An abstract (summary) of the PhD thesis in Bulgarian and English.

Biographic information

Assoc. prof. Slavova has been born in the Russian federation, Samara district. In 2016 she has graduated the Institute of Chemistry of the Saint Petersburg State University, Russian federation. Two years later (2018) assist. prof. Slavova has graduated the same Institute with a master's diploma. Immediately after that she has been nominated to a position "researcher" in this Institute, department of General and Inorganic Chemistry. In the same year until 2019 she has held the academic position "assistant professor" at the Institute of Organic Chemistry with a Phytochemistry Center – BAS, Sofia; the Theoretical chemistry group of the laboratory Structural organic analysis. Since 2019 until now Sofia Slavova has been holding the academic position "assistant professor" at the Institute of General and Inorganic Chemistry – BAS, Sofia, Theoretical and Computational Chemistry laboratory. She has a command of the Russian language (native), Bulgarian and English, the last two languages at a B2 level. She has been introduced in deep to the quantum chemical software GAMESS-US and GAUSSIAN and declares solid computer skills.

The total number of all publications of assist. prof. Sofia Slavova is six, all of them published in specialized periodic issues with quartiles Q1 and Q2. For her short experience as a researcher the aspirant presents a notable scientific production with a total impact factor of the journals in which she has published papers equal to 23.12. According to the SCOPUS database the Hirsch index of the author is 2. The results from the investigations of Sofia Slavova have been cited in 20 scientific publications. The aspirant has participated in four national projects and two projects, funded by the Fund for fundamental investigations of the Russian federation. The results from her research have been popularized on four

international and fourteen national scientific forums. She has been awarded with three awards – by the Union of Scientists in Bulgaria, by the FameLab laboratory, and by the Nineteenth Russian conference of young scientists, Nizhni Novgorod, Russia. All mentioned achievements show that Sofia Slavova is a completed scientist who is able to propose scientific problems and to look for tools for their implementation.

Knowledge on the problem

The literature review in the dissertation comprises 23 pages, which are about 20 % of its volume. The review involves 189 references on the problem of the dissertation. The major part of the references is published after 2000, where about 4.8 % of them are from the last two years (2019-2020): four for 2019, four for 2020 and one for 2021 (reference No 128). The review is structured in three major sections: "Hypotheses for life origin", "Prebiotic synthesis of the building blocks of biomolecules" and "Application of quantum chemical computations for studying of prebiotic reactions". The literature review makes fascinating reading even to non-specialists in the professional area. Some fundamental questions are commented, such as when, how and where the life on Earth was sprung up. In this aspect the fundamental works of *Miller* have been cited. They concern the biosynthesis of the first organic compounds like amino acids etc. on primary Earth. In a separate section the author has described the major theoretical investigations in the area of prebiotic chemistry. They include clarifications of reaction mechanisms, which lead to the production of organic compounds, mostly from simple gas molecules, which were available in the primary hydrosphere and atmosphere on Earth. The detailed literature review shows that the aspirant is introduced in depth to the studied problem. From the literature survey it becomes clear that there are a lot of ambiguities on some mechanisms of prebiotic reactions, which are crucial to prove or reject existing hypotheses. Therefore the investigations in this area are actual and in a stage of their intensive progress. Obviously the aspirant has successfully found her research field. She has chosen to study some mechanisms of prebiotic reactions based on formamide as a starting molecular system. The current dissertation is a proof that she has successfully coped with the outlined tasks. Assist. prof. Slavova has studied the reaction mechanisms of synthesis of nucleobases and pterin from formamide.

The logic and the validity of the investigations based on formamide are explained in two paragraphs on page 17. They give a clear motivation for the research stepping on known facts cited in the literature review. The formulated by the author aim of the dissertation is in accord with the literature survey either.

Methods of research

The theoretical computations have been carried out with *ab initio* methods, which are described in Chapter 2 of the dissertation. The ground-state equilibrium geometries of the systems have been studied by means of the perturbation method of *Møller-Plesset* in the variants MP2, SCS-MP2 and SMD/SCS-MP2. The applied basis set is cc-pVDZ. It could be noted that from the stand point of the methodology a high theoretical level has been applied. In this manner the results obtained are comparable with experimental data and last but not least they are publishable in specialized issues with a deep impact factor. In Chapter 2 the author has given the major equations of the perturbation theory. However there is no information on the basis set applied, which should be given in Chapter 2 either. Therefore it is not clear why the aspirant has chosen this base set. In the scientific literature there are a lot of investigations, which compare structural and energy parameters obtained with different basis functions and their experimental values. Such researches have to be cited in the text of the dissertation, because they could motivate the choice of the basis set from the author.

In a separate section in Chapter 2 the author has given the more important moments of the theories of potential energy surfaces and the solvation model that is applied for the study of the reaction mechanisms.

Analysis of the results in the thesis

The results from the theoretical research are described on 62 pages of the dissertation. They include the ground-state reaction pathways of the formation mechanisms of pterin, purine and pyrimidine nucleobases from formamide. Reaction pathways for the synthesis of some basic precursors like glyoxal, glycinamide, urea, guanidine etc. have been also proposed.

A nice impression makes the large number of the studied mechanisms. Obviously an enormous piece of work has been done, which I have no doubt, is a personal achievement of the aspirant, supported by her supervisor. The studied mechanisms in the dissertation are illustrated in 40 figures. A detailed description in the text for each mechanism is given – which atoms reshuffle. Although in the text the transition states are commonly commented as first order saddle points I think that the author had to indicate the values of the imaginary frequencies of the parallel vibrations of these structures. The form of the parallel vibration is decisive for the assignment of one transition state to a concrete reaction mechanism. I suppose that the arrows in the pictures with the transition states (in figures) describing the motion of the corresponding atoms and fragments are actually the vectors of the imaginary vibrations!

Some energy quantities like heats at 0 K, standard Gibbs potentials, activation thermodynamic quantities and rate constants (estimated by the Eyring equation) of the transformations at standard temperature are summarized in Table 3 (page 92). In the discussion of the results the author has explained the possibility for the occurrence of a given mechanism by the height of the energy barrier and the thermodynamic functions (mostly the heat effect). When talking about kinetics of one reaction this usually happens on the basis of its rate constant. It would be better to give the values of the rate constants in the text for bearing out the conclusions quantitatively.

The solvent influence has been predicted by the SMD model for formamide surroundings. It has been shown that the inclusion of solvent leads to the reduction of the energy barriers up to 55 %. The reduction of energy barriers has been given in percents for different types of reactions.

The dissertation thesis contains science valuable results which open the door for the processes occurring on primary Earth. They support some hypotheses which have been proposed by other authors and described in the literature survey.

Contributions and significance of the research

The results from the theoretical computations are summarized in seven conclusions on page 99. They are in accordance with the described in Chapter 3 investigations and with the aim of the dissertation.

The contributions of the dissertation thesis are in the field of fundamental scientific investigations of reaction mechanisms of prebiotic reactions. A unified scheme of the reactions leading to the production of purine and pyrimidine nucleobases from formamide has been proposed. For the first time the author has proposed a mechanism for the synthesis of pterin. In my opinion the author could give on page 100 more detailed information for the contributions of the research. Additional contributions would be pointed out, for example such as the clarification of the mechanisms for the production of main prebiotic precursors etc.

Publications included in the doctoral thesis

The PhD thesis involves three scientific papers – two of them published in the *International Journal of Quantum Chemistry* (2020 and 2021) and one in the *Journal of Biomolecular Structure and Dynamics* (2021). The two journals have quartiles Q2. The impact factor is 7.83. Therefore according to indicator Г of the minimal national requirements assist. prof. Sofia Slavova collects 60 points. It is double as high as the required number of points. With the current thesis the authors collects 50 points for indicator A. My search in the

SCOPUS database showed that the very recent publication in the *Journal of Biomolecular Structure and Dynamics* has two citations and one in *Google Scholar*. The last database shows also one citation of the work published in *International Journal of Quantum Chemistry* 2021.

The results of the investigations have been presented on 12 scientific forums: 9 oral and 3 poster presentations. They have been awarded with two prizes.

PhD thesis summary

The volume of the enclosed herewith PhD thesis summary in Bulgarian is 30 pages. It describes the major achievements of the dissertation thesis, and includes: introduction, aim, results, conclusions, contributions and lists of publications, citations and participations in scientific forums. In the summary are presented only the generalized figures of the mechanisms from the dissertation. In the thesis summary the author has given two citations of the publications, which should be pointed out in the PhD thesis as well! A PhD thesis in English is also available (30 pages).

Critical notes and recommendations

The experiments described in the beginning of the chapter "Results" have been carried out with samples of pure formamide and the investigated mechanisms in the dissertation are based on them. In this aspect the logical question arises: how the hydrolysis processes are referred to the completely waterless medium of the experiments.

The hydrolysis process of the proton transfer in Fig. 3.3e (page 41) has been determined as an autocatalytic reaction, but in my opinion it is not! Furthermore in the discussion the author states that formimidic acid is the catalyst of the transformation, but it is seen that this compound is not among the reaction products. The water molecule is also assigned to be a catalyst, which is not correct for a process of hydrolysis. I think that forimidic acid is not a catalyst also for the mechanism in Fig. 3.3f. The same comment could be done for the mechanism in Fig. 3.4 – the formation of formylcyanide. According to the structures from the figure the catalyst must be formamide rather than formimidic acid. There are other mechanisms for which I cannot accept that the assigned molecules for catalysts serve really as catalysts.

From the meeting for the preliminary assessment of the dissertation and the opening of the official procedure for the defence I left with the impression that the aspirant accepted my idea to give the values of IRC along the X-axis in the figures with the reaction curves. In the final variant of the thesis such values are not available!

At the the meeting for the preliminary assessment of the dissertation I have the possibility to comment the Y-axis of the figures with the ground-state energy curves. I think that the caption of the axes should be H and not ΔH. In my opinion those are the relative enthalpies rather than their changes since they are referred to the enthalpy of the reactant. As known the symbol Δ has a specific meaning in chemical thermodynamics. For example the heat effects in figures are ΔH.

The aforementioned critical notes do not depreciate the contributions of the dissertation, which has its scientific achievements that should be judged on merits. The author is a young, perspective researcher and I have no doubt that she will go on with her investigations in the filed of prebiotic chemistry in future. The aim of the critical notes is rather to help her in future scientific initiatives. I recommend the author to involve the excited states in the future research. According to the literature review a large part of reactions on primary Earth occur under UV irradiation.

I don't know personally assist. prof. Slavova but I have excellent impressions for her from the procedures in which I was invited as a member of the extended colloquia of the Institute: the procedure for the opening of a PhD position of S. Slavova and the procedure for the preliminary assessment of the dissertation. I wish her greater scientific success in future!

CONCLUSION

The provided materials for the current procedure are in agreement with the Law for development of the academic staff in Republic of Bulgaria, the Rules for its application as well as with the minimal national requirements in the professional filed. I consider that assist. prof. Slavova is a complete scientist in her area of research and despite the short research experience she shows considerable scientific achievements. All this and the aforementioned facts drive me to give my **positive vote** for the awarding of the academic degree *Doctor of philosophy* (PhD) of assistant professor Sofia Slavova in the field of higher education: 4: Natural sciences, mathematics and informatics; professional area 4.2. Chemical sciences; scientific field: Theoretical chemistry.

10.05.2021 г.
Plovdiv Reviewer: