REVIEW

from Prof. DSc Sonia Varbanova Ilieva,
Faculty of Chemistry and Pharmacy, Sofia University “St. Kl. Ohridski"
of the materials submitted for the competition for the academic position of **'Associate Professor'**
at the Laboratory of Chemistry and Biophysics of Proteins and Enzymes
Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP), BAS
in higher education professional field 4.2. Chemical Sciences (Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances)

In the competition for the academic position **'Associate Professor'** announced in the State Gazette, issue 43/31.05.2019, **Chief Assistant Dr Miroslav Angelov Rangelov** from the Laboratory of Chemistry and Biophysics of Proteins and Enzymes, IOCCP, BAS is the only candidate.

1. General presentation of the materials deposited

The electronic and hard copy materials submitted by Dr Miroslav Rangelov **meet all the requirements** of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the relevant regulations for its implementation (including those of BAS and IOCCP). The applicant meets the criteria (minimum requirements) of IOCCP-BAS for the academic position 'Associate Professor'.

For this competition, Dr Rangelov has presented **16 scientific articles and 1 chapter in a book** (a monograph). The publications presented do not repeat the articles for the doctoral thesis. The scientific articles have been published in reputed international journals with high impact factor. The papers are distributed in the respective quarters as follows: 9 - Q1; 4 - Q2; 3 - Q4. M. Rangelov is the leading author (corresponding author) in 4 publications.

An extended habilitation report on the applicant's scientific contributions in Bulgarian and English is presented. The main scientific contributions of Dr Rangelov are discussed in the report. The development of his scientific work is presented logically and consistently as a continuation and extension of the theoretical studies initiated at the beginning of his career and reflected in his dissertation. The applicant's view on the development of his research over the next 5 years is also briefly presented.

I would like to mention that when creating a list of publications, all publications should be written in the same manner. I would also recommend the leading author (corresponding author) to be marked (for example with a star symbol) as accepted in the scientific literature.

2. Brief biographical information

M. Rangelov graduated as a Master of Science in Organic and Analytical Chemistry at the Faculty of Chemistry, Sofia University “St. Kl. Ohridski" in 1997. After that he enrolled as a full-time doctoral student at IOCCP, BAS, and scientific specialty Bioorganic chemistry, chemistry of natural and physiologically active substances. He has continued his scientific work at the institute as a chemist, research associate and subsequently assistant (2011- to present).

In 2008, he defended his doctoral dissertation on *"Participation of a vicinal hydroxyl group in peptide bond biosynthesis in the ribosome - model studies"*. Therefore, the professional and scientific experience gained is fully linked to the announced competition. It is not clear from the documents (particularly the CV) whether M. Rangelov has held specializations in foreign scientific groups, but he has participated in a number of national and international scientific congresses / conferences and research projects.

3. General characterisation of the applicant's scientific activities

The scientific work of Dr Rangelov is in the field of computational modelling of biological systems, where the theoretical investigation of the peptide synthesis in the ribosome is the main part. The modelling of a ribosome is an extremely complex task and the work of Dr Rangelov and co-authors involves the following steps:

(i) theoretical studies of the mechanism of aminolysis as a process, responsible for the peptide bond formation, catalysed by the ribosome in vivo;

(ii) implementation of the methodologies developed for the theoretical calculations in software packages;

(iii) application of the established approaches and methodologies to other properties of the ribosome and other biological systems;

(iv) simulation of a complete ribosome model.

Through the application of quantum mechanical (QM) theoretical calculations, the reaction mechanism of the aminolysis process has been studied for several model systems, the choice of which is logically justified by the knowledge and experimental data for the real processes. The energy of the reaction and the influence of various factors have been evaluated. The molecular aspects of the catalytic mechanism in the ribosome have been investigated: the role of the vicinal hydroxyl group in the process of catalysis; the mechanism of acyl group migration between vicinal hydroxyl groups; the catalytic role of proton-donating and proton-accepting groups with different location to the reaction centre has also been analysed; the aminolysis process of diols has been modelled. As a result of these extensive studies, a methodology has been developed for constructing catalytic maps by thoroughly scanning the space around the reaction centre.

The high conformational flexibility of the model compounds, containing a vicinal hydroxyl group, results in different (greater number) reaction coordinates of the aminolysis process. This is one of the reasons that has determined a necessity for developing automated algorithms for some steps in the process of theoretical analysis of the reaction path - for example, the selection of the computational method; conformational search (analysis) for stable structures and transition states, including elimination of conformationally equivalent structures; automatic generation of geometry parameters for unknown initial structures and transition states; IRC calculations - a comparative approach between intermediates and transition state geometries is applied to evaluate and fully build the reaction coordinate (the IRC procedure implemented in the Gaussian package is quite "demanding").

These new methodological developments have been implemented in the MolRan software package. Dr Rangelov is the main author of this software package. The development of the software began when he was a PhD student. Its development and refinement continued further for obtaining a graphical

environment for visualization and generation of molecular geometries, analysis of the electronic structure and chemical properties of molecules optimized with other QM programs (including Gaussian and GAMMES, as the most widely used). Besides qualitative visualization of structures and input-output formats from quantum-chemical calculations, the program also includes an algorithm for conformational search - a sequential procedure for varying dihedral angles with screening of structures identical in energy. With the help of this software, it is also possible to relate each transition state to its corresponding intermediate for a given reaction coordinate.

The developed methodologies and algorithms have been applied for studying other properties of the ribosome as well as for exploration of other biological systems.

The interactions of sodium and magnesium ions and phosphate groups of RNA were investigated using *ab initio molecular dynamics*. Metal ions play an important role in maintaining the configuration of DNA and RNA as a bridge in the interaction between different parts of the macromolecules or by neutralizing the negative charges of phosphate groups. For this process of neutralizing negative charges in the ribosome, a heuristic algorithm has been developed that adds the missing ions, optimizing their appearance and position. A review article is published on the studies of metal ion – nucleic acid interactions by experimental and theoretical methods.

The algorithms developed in the scientific work of M. Rangelov can be applied in the field of drug design; *in silico* evaluation of drug activity; studies of drug-receptor interactions.

From the publications presented, it can be concluded that M. Rangelov has established a fruitful cooperation with research groups from his institute as well as from the Faculty of Electrical Engineering, University of Niš, Serbia. As a result of these collaborative studies, M. Rangelov has expanded the scope of his scientific activities. Several papers on biological activity of different groups of organic compounds have been published. Studies have been conducted to establish the quantitative structure - activity relationship for biologically active compounds.

The 16 scientific articles submitted for the competition have been published in reputed international scientific journals, many of them with a high impact factor: 9 articles fall into quartile Q1. The average impact factor (IF) of the publications is 2.65, with IF ranging from 0.238 (Bulg. Chem. Commun. - 1 publ.) to 7.885 (JACS). In fact, articles on theoretical research that is M. Rangelov's main scientific field, have been published in renowned journals with high IF, thus proving the quality of the research. In my opinion, this is the strongest demonstration of the level of scientific work of M. Rangelov and therefore, the Associate Professor position is a natural result in his scientific career.

The research carried out and the results published have **scientific as well as applied contributions** in the relevant fields of science. These contributions can be formulated as: substantiations of significant new sides of already existing scientific fields, problems, theories, hypotheses by means of new methods and approaches; creating new methodologies for analysis; getting new facts.

The citation report provided is incomplete and rather vague - for instance, it does not contain citations after 2012. Probably the reason is that only citations for participating in this competition are

presented. A complete list of publications is not provided. According to the Web of Science data, 21 publications of M. Rangelov have a total of 157 citations, which determines an h index 8.

Dr Rangelov has participated in 17 national scientific projects, leading one of them, and in 5 international scientific projects. As a team leader in the PRACE project, he has been responsible for the development of a software package dedicated to computer aided drug design. In the framework of this project, MD simulations of a complete model of *E. coli* ribosome was developed, with the potential for application in drug design.

CONCLUSION

According to the submitted materials and scientific papers, the above analysis of their importance and scientific contributions, I am convinced in my **positive assessment** and firmly recommend to the Scientific Jury to prepare a report-proposal to the Scientific Board of IOCCP-BAS for the selection of **Dr Miroslav Angelov Rangelov**, for the academic position of **'Associate Professor'** at IOCCP-BAS in the professional field 4.2. Chemical Sciences (Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances).

09/09/2019 Reviewer:

Prof. Sonia Ilieva