# REVIEW

## by Assoc. Prof. Dr. Nadezhda Vasileva Markova
## Institute of Organic Chemistry with Centre of Phytochemistry-BAS

of the materials submitted for participation in the competition
for the academic position of ASSOCIATE PROFESSOR
at **the Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP), BAS**

professional field 4.2 Chemical Sciences
scientific specialty: "Organic Chemistry"

In the competition for "associate professor", announced in the State Gazette, issue 40 of 16.05.2025 and on the website of IOCCP -BAS, the only candidate is **Asst. Prof. Dr. Simeon Stoyanov Stoyanov** from the Institute of Organic Chemistry with Centre of Phytochemistry-BAS.

### 1. General presentation of the received materials

The set of materials submitted for participation in the competition is in full compliance with the requirements of the Act on the Development of Academic Staff in the Republic of Bulgaria (ADASRB) and the Regulations for its implementation and meets the criteria of the Institute of Organic Chemistry with a Centre of Phytochemistry-BAS for occupying the academic position (AD) “associate professor”. All materials for the competition have been prepared very carefully, clearly and in detail, with the relevant evidentiary materials and leave no doubt about their authenticity. The report on the fulfillment of the minimum national requirements for professional direction 4.2. “Chemical Sciences”, when occupying the AD “associate professor” showed that the Asst. Prof. Dr. Simeon Stoyanov fulfills and even exceeds the required minimum number of points. A detailed analysis of the scientometric indicators is given in Section 3.

### 2. Brief biographical data

Asst. Prof. Dr. Simeon Stoyanov completed his higher education at the Faculty of Chemistry and Pharmacy of Sofia University "St. Kliment Ohridski", where he graduated with the educational and qualification degree (EQD) "Master in Organic and Analytical Chemistry". Later, in 2004, he was appointed as a chemist at the Institute of Organic Chemistry with the Centre of Phytochemistry, Bulgarian Academy of Sciences and worked there for one year. In 2005, he was enrolled as a full-time doctoral student at the Institute of Organic Chemistry with the Center for Phytochemistry-BAS. Under the supervision of Assoc. Prof. Dr. Yordan Tsenov and Prof. DSc. Ivan Binev, in 2009, Dr. Stoyanov defended his PhD thesis with title: "IR-spectral and structural changes caused by the conversion of nitriles into anions and radicals". During the period 2008-2010, the candidate was again appointed successively to the positions of chemist and assistant at the Institute of Organic Chemistry. From 2011 to the present, Dr. Simeon Stoyanov holds the academic position of assistant professor at the same institute.

## 3. General characteristics of the candidate's activities

Dr. S. Stoyanov is a co-author of 32 scientific papers, 6 of which are included in the candidate's PhD thesis for the acquisition of the educational and scientific degree "doctor". The majority of the publications are in reputable journals referenced in Scopus and Web of Science, falling into quartiles Q1-Q4. In 8 of the scientific articles with quartiles in referenced journals, Dr. Stoyanov is a corresponding author, and in 12 he is the first author. The distribution of the 32 articles by quartiles of the journals in which they were published is as follows: in journals of the category Q1 - 6 issues, in journals Q2 - 9 issues, in journals Q3 - 3 issues, Q4 - 10 and 4 in journals without an impact factor, one of which is in the Journal of the Bulgarian Academy of Sciences. The relatively large number of articles in publications with quartiles Q1 and Q2 speaks of the good scientific level at which the candidate works. The number of citations noted on the publications is 105 according to Scopus (h-index = 6).

From 2004 to 2015, Asst. Prof. Stoyanov has conducted several specializations and courses: Summer School in Gas Chromatography-Mass Spectrometry at the University of Novi Sad, Serbia, courses on "Supercomputer Applications in Natural Sciences" in Sofia, work with the MOE (Molecular Operating Environment) software package in Amsterdam, the Netherlands, as well as work with the Leibniz Raman spectrometer at the Institute of Polymers, Dresden, Germany.

To participate in the competition for “associate professor”, Dr. Stoyanov has selected 26 scientific papers, all on the topic of the current competition. Nine of them, equivalent to a habilitation thesis, are included in Group of indicators “B”. In eight of these articles, the candidate is the first author, and in seven he is a corresponding author and the main executor of the research. In one of the publications, Dr. Stoyanov is even the sole author. This speaks of the ability of Asst. Prof. Simeon Stoyanov to independently conduct research and form them as scientific communications. The articles, equivalent to a habilitation thesis, have been published in renowned international journals, three of which are in Q1 journals, two are in Q2 journals, one is in Q3 journal, three – in Q4. With these publications, the candidate fully satisfies and even exceeds the requirements of Art. 2b of the ADASRB and the regulations of the IOCCP-BAS for its application. The remaining 17 publications, which met the requirements of Group of Indicators “G”, are also on the topic of the competition and present research related to the synthesis, isolation, characterization and biological (including antioxidant) activity of morpholine diones, arylcinnamic acids, benzimidazoles, etc. These publications combine experimental techniques (IR, UV spectroscopy) with quantum-chemical calculations (DFT, TD-DFT) to elucidate the structure and properties of both bioactive and pharmaceutical compounds, as well as mural pigments. These studies are of particular importance for medicinal chemistry and for the study and preservation of cultural heritage. The distribution of the articles included in Group of indicators “D” by quartiles of the journals in which they were published is as follows: three publications are in Q1 journals, 6 publications are in Q2 journals, 2 are in Q3 journals, 4 publications are in Q4 journals and 2 are in journals without impact factor and impact rank. With these publications, the requirements for a minimum of 220 points are met and exceeded (273 points are achieved). In the materials for the competition (Group of indicators “D”) a list of 119 citations is presented, according to the Sonix system of works for participation in the competition, with which 238 points are achieved and thus, the requirements for a minimum of 70 points for this group of indicators are more than three times exceeded. I accept for review all 26 scientific publications submitted by Assistant Professor Dr. Simeon Stoyanov for participation in this competition.

Dr. Stoyanov has presented sufficient data and convincing evidence for 32 participations in scientific forums in our country and abroad.

Simultaneously with his scientific activity, Asst. Prof. Simeon Stoyanov is an active participant in the development and implementation of scientific projects. He is a participant in eight projects at the National Science Foundation, four at the Bulgarian Technical University and one at the Bulgarian Academy of Sciences. Dr. Stoyanov has also taken part in the INFRAMAT consortium – "Distributed infrastructure of centers for production and research of new materials and their applications for conservation, access and e-storage of artifacts (archaeological, folklore) at the Ministry of Education and Science.

**4. Assessment of the candidate's personal contribution**

*Main contributions to the candidate's scientific and applied scientific activities*

The scientific works of Assistant Professor Dr. Simeon Stoyanov are of a high scientific level, correspond to the topic of the competition and are in the field of organic chemistry. In most of the scientific publications, combined experimental (IR and Raman spectroscopy) and theoretical methods for the characterization and study of organic compounds have been used. The conducted studies can be attributed to the categories of novelty for science, as well as enrichment of scientific knowledge, by clarifying the preparation and structure of anionic derivatives of organic compounds, representing drugs, strong poisons or new compounds with potential biological activity. The main contribution of the candidate is related to the interpretation of vibrational spectra and methods for their simulation.

The habilitation thesis is well structured, written carefully and clearly. The research in *publication **1[4B]*** of the habilitation thesis is related to the derivation of special scaling factors and equations in the interpretation of the valence vibrations and intensities of the C≡N bond in uncharged molecules, anions and radicals of various cyano compounds. The calculations were performed using Density Functional Theory (DFT) and the Hartree-Fock method, in combination with different doubly and triply split basis sets: 3-21G, 6-31G, 6-311G, 6-31G*, 6-311G*, 6-31+G, 6-311+G, 6-31G**, 6-31+G*, 6-311+G*, 6-31++G**, 6-311++G** and aug-cc-pVDZ. It was found that the average deviations between the scaled calculated and experimentally found spectroscopic features depend on both the type of the feature itself (whether it is a vibration or intensity) and the type of the molecule itself (whether it is neutral, radical or anion). The use of scaling equations instead of scaling factors does not give good results for frequencies, unlike for intensities.

Using a combined approach, including experimental (IR spectroscopy) and computational methods, both the formation of adducts of 2-{5,5-dimethyl-3-[(2-phenyl)vinyl]cyclohex-2-enylidene}-malononitrile with potassium cyanide and sodium methoxide, as well as the possibility of controlling the isomerization of the different adducts, is demonstrated. The IR spectral data show the practically complete conversion of the β-carbanion adduct via δ- to ζ-adduct within 3 hours (*publication **2[6B]***). The increase in the area of delocalization of the carbanion charge during the isomerization leads to a slight but measurable increase in the vibrations in the nitrile group by about 10 $cm^{-1}$. On the basis of quantum-chemical calculations, the most significant changes in the bond lengths, valence angles and electronic charges of the resulting isomers have been determined. It has been found that δ-adducts have a lower total energy, i.e. are much more stable compared to β-adducts, and ζ-adducts are more stable than δ-adducts.

The structural and spectral changes occurring upon the conversion of a series of benzophenones into ketyls have been studied (*publ. **4[2B]***). For this purpose, a series of quantum-chemical calculations based on standard DFT methods have been carried out, using different functionals and basis sets, in the presence and absence of solvent (DMSO). In order to assess the adequacy of the theoretical approach, the theoretically predicted frequencies of

the carbonyl bond have been compared with the experimentally observed frequencies. Very good agreement between experiment and theory is achieved when combining the IEFPCM and ONIOM methods with the basis set 6-311+G(2df,p) for the high layer and 6-311+G for the low layer. This shows the strong influence of the high-order polarization functions in the basis set of the high layer and the solvent effect. The chosen theoretical level ONIOM[B3LYP/6-311+G(2df,p)//6-311+G]-IEFPCM was applied to analyze the vibrational spectra, geometry and distribution of electron density in the C=O groups of substituted benzophenones and ketyl radicals. This distribution of electron density in the C=O groups of ketyls correlates well with the reduction of the vibrational oscillations of the C=O bond and turns out to be the dominant factor for the differences in the frequency spectrum.

In *publ.* ***8[1B],*** the possibility of converting flutamide into an azanion or radical anion was considered by spectroscopic and theoretical methods. Flutamide is a nonsteroidal competitive inhibitor of dihydrotestosterone and is used as an antiandrogenic drug for prostate cancer. The flutamide azanion was generated in a solution of DMSO-d6 by treatment with sodium methoxide and the possibility of electrochemical reduction of flutamide was studied by IR spectroscopy. At the theoretical level B3LYP/6–311++G and IEF-PCM/B3LYP/6–311++G in a solution of DMSO, the structures of the different conformers of flutamide, its anions and radical-anions were optimized, the geometric parameters of the molecules and the expected spectral changes associated with the formation of anionic particles were calculated. The structure, electronic charge and electron density distribution of the azanion and protonated/deprotonated radical-anion species were evaluated by correlating the experimentally observed with the predicted changes in the IR spectrum and based on the calculated geometric parameters. When comparing the spectra, it was found that the electrochemical reduction leads to the formation of the azanion, and not the radical-dianion, in contrast to the result observed for nimesulide (a nonsteroidal anti-inflammatory drug) in *publ.* ***5[9B]***. According to the data on the reduction potential and electron density, the propensity for nitroreduction of flutamide is lower than that of nimesulide, but higher than that of nitrobenzene. The information obtained may improve the understanding of the possible pathways for metabolism and interaction of flutamide and nimesulide with biomolecules related to its therapeutic action.

The spectral and structural changes due to the conversion of salophene into oxyanion and dianion were studied in *publ.* ***6[7B]*** using IR spectroscopy and quantum chemical methods at the B3LYP/6-311++G** level. Due to its antimicrobial function, salophene is used as an ingredient in cosmetic products, pharmaceutical ingredients, surgical materials, etc. Its IR spectra are included in many databases, but there are no studies of its anions. The geometric optimization in the study was performed in the gas phase and DMSO solution, with the solvent effect being simulated with the self-consistent field model (IEFPCM). Good agreement was found between the theoretical and experimental vibrational characteristics of the studied particles. The theoretical method used gives a good description of the strong spectral changes caused by the conversion of salophene into anion and dianion, which is associated with significant structural changes. Analysis of the changes in atomic charges shows that the first (oxyanion) charge remains localized mainly in the oxyphenylene fragment, while the second (nitranion) charge is distributed mainly over the acetanilide fragment.

Similar studies were conducted in *publ.* ***3[5B]***, again using a combination of experimental (IR spectroscopy) and theoretical methods to track the spectral and structural changes due to the conversion of 1,1,3,3-tetracyanopropane into mono-, di- and trianion. The conversion of the neutral molecule into a carbanion has a weak effect on the stretching vibration ν(C≡N) in nitrile groups distant from the anionic center (up to 13 $cm^{-1}$) and a strong effect on the cyano stretching vibration ν(C≡N) in nitrile groups directly connected to the anionic center (up to

140 $cm^{-1}$). The carbanion charge is distributed mainly in the anionic center and the cyano groups directly connected to it (total 0.85 e-). The transformation of the neutral molecule into a di- and trianion occurs with a stronger decrease in the stretching vibration ν(C≡N) to 300 $cm^{-1}$. Very good agreement between the experimental and theoretical data has been established. According to the calculations, the anionic charge formed by the second and third deprotonation steps is distributed almost evenly over all fragments.

Another scientific area in which Dr. Stoyanov has made significant contributions is related to spectroscopic and quantum-chemical studies on the conversion of 5-nitrobenzimidazole derivatives into anions and radical-anions (*publications **7[8B]** and **9[3B]***). Benzimidazole derivatives have shown a wide spectrum of biological activity such as antineoplastic, anti-inflammatory, antibacterial, antifungal, anthelmintic, antiviral and antioxidant properties. The electrochemical conversion of N,N′-disubstituted hydrazone derivatives of 5-nitrobenzimidazole-2-thione into radical-anions and dianions is the subject of the combined experimental/theoretical study in *publ. **7[8B]***. Theoretical calculations were performed at the B3LYP/6-311++G** level for the ester and B3LYP/6-311+G(d) for the hydrazones, and the solvent effect was simulated using the self-consistent field model (IEFPCM) in DMSO solution. The electrochemical reduction of 3,3′-(5-nitro-2-thioxo-1H-benzo[d]imidazole-1,3(2H)-diyl)bis(N′-(2-methoxybenzylidene))propanehydrazide showed that the compound readily and reversibly generates radical-anion products in aprotic medium (DMSO). To clarify whether the reduction leads to the generation of a radical anion or a deprotonated radical dianion, a second spectroscopic experiment was performed, in which the deprotonation was achieved by treatment with sodium methoxide. Both experiments show distinctly different spectral characteristics, indicating that the reduction to radical anion is not accompanied by deprotonation. Based on the estimated electronic parameters, it was shown that the type of side chains (ester, hydrazone, etc.) attached to the nitrogen atoms in nitrobenzimidazole derivatives does not significantly change the propensity of the compounds to nitroreduction, but nevertheless the generated radical anions are characterized by different reactivity, which explains the different hepatotoxicity.

The bioreductive potential of 1-alkylated 5(6)-nitro-1H-benzimidazoles was investigated using electrochemical and quantum-chemical methods, as benzimidazoles are a suitable basis for the development of drugs exhibiting selective cytotoxicity through hypoxia activation or enzymatic activation of the nitro group (*publication **9[3B]***). Analysis of the frontier molecular orbitals of the compounds shows that upon reduction the unpaired electron is mainly accepted by the nitro group. The deprotonation of 1-alkylated 5(6)-nitro-1H-benzimidazoles was also characterized by IR spectroscopy and theoretical methods. The calculated electron affinities indicate that the propensity of 1-alkylated 5(6)-nitro-1H-benzimidazoles to undergo nitroreduction is higher than that of the structurally related 1-methyl-2-methyl-4-nitroimidazole and slightly lower than that of nitrobenzene and the radiosensitizer misonidazole. The studied 1-alkylated 5(6)-nitro-1H-benzimidazoles show potential for use as bioreductive agents and the discovered relationships can be used to prepare nitrobenzimidazole derivatives with increased electron affinities.

## 5. Critical remarks and recommendations

Overall, the Habilitation thesis is well and carefully written. It is made according to the requirements of the ADASRB and the Regulations of the IOCCP-BAS and mainly includes the candidate's scientific contributions in the works of the Habilitation thesis, i.e. those under Indicator B, but is not limited to the results of the submitted equivalent number of articles. It very clearly and in detail describes the specific original scientific contributions with which Asst. Prof. Stoyanov applies to the competition. I also have some minor remarks on the

materials submitted to me for review, related to the style of writing the Habilitation thesis and admitted technical and terminological inaccuracies, which, however, do not spoil the good impression of the candidate's work.

I would encourage the future Associate Professor Dr. Simeon Stoyanov to participate as a leader of a scientific project, since he has a clearly outlined topic and professional qualities for this.

**6. Personal Impressions**

My personal impressions of Dr. Simeon Stoyanov are very good. I have known him since he was a PhD student. He is a very good specialist in the field of IR spectroscopy and computational chemistry and there is no doubt that most of the contributions in these areas from his publications are his own. He is a respected colleague who knows how to work in a team. This, together with the high level of his scientific research activity, proves in an indisputable way his competence and makes him a well-established scientist in the field of Chemical Sciences.

**CONCLUSION**

In the competition for the position of Associate Professor, Asst. Prof. Dr. Simeon Stoyanov has presented a sufficient number of scientific papers published in refereed international journals with an impact factor and impact rank, which fully correspond to the topic of the competition, the ADASRB and the specific requirements of the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences for its application. The scientific production presented proves in an indisputable way the competence of the candidate to conduct and lead valuable research in the future. The results achieved in his scientific research activity, as well as his participation in a number of scientific projects and forums, outline the profile of a talented and thorough scientist, with clearly formed research interests and achievements in the field of organic chemistry. After analyzing the materials presented in the competition and based on my personal impressions, I find it reasonable to give my positive assessment and confidently vote "yes" for the election of Asst. Prof. Dr. Simeon Stoyanov of academic position "Associate Professor" in Professional Direction 4.2. "Chemical Sciences", Scientific Specialty "Organic Chemistry".

24.09.2025

Reviewer: .....
Assoc. Prof. Dr. Nadezhda Markova