

REVIEW

**Reviewer: Assoc. Prof. Dr. Nadezhda Markova,
Institute of Organic Chemistry with Centre of Phytochemistry,
Bulgarian Academy of Sciences**

of the materials submitted for participation in the competition for occupation of academic position
"Associate Professor"

**in Institute of Organic Chemistry with Centre of Phytochemistry,
Bulgarian Academy of Sciences**

in the professional field 4.2. "Chemical Sciences"
scientific specialty "Organic Chemistry",

In the competition for "Associate Professor", announced in the State Gazette, issue 9 of 30.01.2024 and on the website of IOCCP-BAS, the only candidate was the **Assistant Professor Dr. Vera Ventsislavova Deneva** from the Institute of Organic Chemistry with the Phytochemistry Center - BAS.

1. General presentation of the received materials

The set of materials submitted for participation in the competition is in full accordance with the requirements of the Law for the development of the academic staff in Republic of Bulgaria and the Regulations for its implementation, the Rules for the conditions and the order for acquiring scientific degrees and for occupying academic positions and meets the specific criteria of Institute of Organic Chemistry with a Center for Phytochemistry - BAS for taking the academic position (AP) of "Associate Professor". All materials on the competition are prepared very carefully, clearly and in detail, with relevant supporting materials and leave no doubt about as to their authenticity. The reference for the fulfillment of the minimum national requirements for a professional direction 4.2. "Chemical Sciences", when occupying AD "Associate Professor" showed that Ch. Dr. Vera Deneva 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 (of the applicant/s)

Ch. assistant Dr. Vera Deneva completed her higher education in 2009 at Sofia University "St. Kliment Ohridski", Faculty of Chemistry, where he graduated with the educational and qualification degree (EQD) "Master in Organic Chemistry". Immediately after that, she entered as a full-time doctoral student at the Institute of Organic Chemistry with a Center for Phytochemistry - BAS. In the period 2009-2013 the candidate is a PhD student in the scientific specialty "Organic Chemistry" under the supervision of Prof. DSc. Lyudmil Antonov. In 2013, after successfully defending a PhD thesis with title: "Experimental and theoretical studies of tautomeric systems based on azo-naphthols and their azomethine analogues", Vera Deneva obtained the educational and scientific degree "Doctor". From 2012 to 2017, she was appointed to the position of

"assistant" at IOHTCF-BAN, and in 2017 she was elected "Assistant Professor" at the same institute, where he continues to work until now. From 01.10.2011 to 15.06.2012, Dr. Deneva conducted a specialization at the University of Friborg, under a scholarship from a research program of the Swiss Confederation.

In 2012, she was the winner of the "Ivan Evstatiev Geshov" award of the BAS for a young scientist under 30 years old.

2. General characteristics of the applicant's activity

Evaluation of the candidate's scientific and scientific-applied activity

Dr. V. Deneva is the co-author of 26 scientific papers, 4 of which are included in the dissertation of the candidate for the educational and scientific degree "doctor". All publications are in *Scopus* and *Web of science*-refereed reputable journals falling in quartiles Q1-Q3. The total impact factor of the journals is 97. In 2 of the scientific articles with quartiles in refereed journals, Dr. Deneva is the corresponding author and in 8 he is the first author. The distribution of the 26 articles by quartiles of the magazines in which they were published is as follows: in magazines of the category Q1 – 20 items, in magazines Q2 – 4 items, in magazines Q3 – 2 items. The large number of articles in publications with quartile Q1 is impressive and speaks of the high scientific level at which the candidate works. The number of observed citations on the publications is 683 according to *Google scholar* (h-index = 12) and 391 according to *Scopus* (h-index = 10). This value is indicative of high scientific productivity combined with a wide response in the literature.

To participate in the competition for "docent", Dr. Deneva has chosen 16 scientific papers, all on the topic of the current competition. They have not been used in competitions under other procedures. Six of them, equivalent to habilitation work, are included in Group "B" indicators. In one of these articles, the candidate is the first author and is one of the main performers of the research. The articles equated to the Habilitation thesis have been published in reputed international journals, all of which are in Q1 journals. With these publications, the candidate fully satisfies and even exceeds the requirements of Art. 2b of the Law for the development of the academic staff in Republic of Bulgaria and the regulations of IOCCP-BAS for its application. The remaining 10 publications, with which the requirements of the Group of indicators "G" are fulfilled, are also on the topic of the competition and present research in the UV-VIS field on the tautomeric conversion of nitrogen-containing organic compounds (mainly azo dyes and Schiff bases), their ability to complex and their potential applications as molecular switches. Two of the publications in this group are related to vibrational spectral analysis of herbs and wine. Most of these studies are of particular importance to applied organic chemistry and can be evaluated as novel in science. The distribution of the articles included in Indicator Group "G" by quartiles of the journals in which they were published is as follows: eight publications are in Q1 journals and 2 publications in Q2 journals. With these publications, the requirements for a minimum of 220 points have been met and exceeded (235 points have been reached). A list of 118 items is presented in the competition materials (Group of indicators "D"). citations extracted from the Sonix system of the works for participation in the competition, with which 236 points were achieved and thus more than three times exceeded the requirements for a minimum of 70 points for this group of indicators. For review, I accept all 16 scientific publications presented by Dr. Vera Deneva for participating in the current competition.

Dr. Deneva has presented sufficient data and convincing evidence for 8 participations in scientific forums and 5 participations in summer schools at home and abroad.

Simultaneously with his scientific activity Assoc. Prof. Vera Deneva is an active participant in the development and implementation of scientific projects. She is a project manager in the Young Scientists 2016 competition at the Scientific Research Fund (SRF) of the Ministry of Education and Science. He is a participant in nine projects at SRF and two scientific networks on supramolecular chemistry (SUPRACHEM@BALKANS.EU and SUPRAMEDCHEM@BALKANS.NET), funded by the Swiss National Science Foundation.

Main contributions in the candidate's scientific and scientific-applied activity

The scientific works of Dr. Vera Deneva are at a very high scientific level, correspond to the theme of the competition and are in the field of organic chemistry. Most of the scientific publications used combined experimental (spectrometric and chromatographic) and theoretical methods to characterize and study organic compounds. The conducted studies can be attributed to the categories of novelty for science, as well as enrichment of scientific knowledge, by elucidating the structure and processes of tautomeric conversion in many nitrogen-containing aromatic organic molecules.

Dr. Deneva's **scientific contributions** can be grouped into the following two directions:

A. *Experimental and theoretical studies of tautomerism in nitrogen-containing aromatic organic compounds - azo dyes, Schiff bases and others.*

B. *Analysis and determination of active components in herbs and wine using spectral and chromatographic methods.*

In the first direction, the research is related to the tautomeric conversion in: azonaphthol dyes; pyrazole Schiff bases containing an azo group; coumarin derivatives; 4-substituted phthalimide Schiff bases, 7-hydroxy quinoline Schiff bases; benzothiazopyridine/isonicotinamide Schiff bases; 10-hydroxybenzoquinoline; rotary switches with a pyridyl ring and a carboxyl group; 5,6-pinene-bipyridine derivatives; favipiravir and compounds with a 1,3,5-triazine core linked to various substituents.

Three scientific publications (publ. 1-3 of the Habilitation reference) are devoted to the possibility of tautomeric conversion in azonaphthol dyes, as well as to the possibility of changing and controlling its direction. Using UV-VIS and NMR spectroscopy, quantum chemical calculations, and crystallographic analysis, proton transfer in three 1-(phenyldiazenyl)naphthalen-2-ols derived from Sudan I (1), an aza dye known to that it exists as a tautomeric mixture (publ. 1). By modifying the structure of the reference compound (addition of an additional –OH group or a piperidine residue) it is shown that the tautomeric process can be controlled in solution. In the case of 1-(phenyldiazenyl)naphthalene-2,6-diol (2) the equilibrium shift can be achieved by deprotonation of the additional hydroxyl group, whereas in 1-(phenyldiazenyl)-3-(1-piperidinylmethyl)naphthalene-2-ol (3) protonation of the nitrogen atom of the piperidine residue promotes the shift to the keto tautomer. It is concluded that compound 3 is more suitable as a tautomeric switch because the piperidine moiety is not close to the site where the transfer takes place and the protonation process does not directly affect the absorption spectra. In other compounds derived from 4-(phenyldiazenyl)naphthalen-1-ol (publ. 2), with the help of

theoretical and experimental methods, the possibility of proton transfer and complex formation was considered as the reason for a change in the direction of the tautomeric equilibrium. According to theoretical calculations, the stabilization of the enol form can be achieved by a strong intramolecular hydrogen bond formed between the donor hydroxyl group and the acceptor carbonyl group. However, intermolecular bonding plays a role in some solvents, as experimental results show. Calculations predict that complexation with alkaline earth metal ions can result in a complete shift of the tautomeric equilibrium to the keto tautomer, which was observed in soln. The 1:1 complexes formed show large bathochromic and hyperchromic shifts in the visible spectra. Similar studies were carried out with other derivatives of 4-(phenyldiazenyl)naphthalen-1-ol (publ. 3), where the symmetrical ionophore substituents varied and different alkali base metal cations were used - Na^+ , K^+ , Mg^{2+} , Ca^{2+} and Zn^{2+} to trace the possibility of a change in the direction of the tautomeric equil. Calculations predict that complexation with alkali metal ions can result in a complete shift of the tautomeric equilibrium to the keto tautomer.

Two series of azo dyes derived from 3-methyl-1-phenyl-4-(phenyldiazenyl)-1H-pyrazol-5-amine and 5-methyl-2-phenyl-4-(2-phenylhydrazono)-2,4-dihydro-3H-pyrazol-3-one (publ. 4). The results clearly show that 3-methyl-1-phenyl-4-(phenyldiazenyl)-1H-pyrazol-5-amines are present in pure azo tautomeric form, while 5-methyl-2-phenyl-4-(2-phenylhydrazono)-2,4-dihydro-3H-pyrazol-3-ones exist as hydrazone tautomers. The tautomeric equilibrium is not significantly affected by the presence of a nitro group in the benzene ring. As a result, the first set of compounds can be used as NMR references for the azo tautomer, while the others represent the pure hydrazone form. According to the crystallographic data (described in the article or from the literature), the conclusions about the tautomerism of the investigated dyes in solution are also valid in the solid state.

Using NMR, UV-VIS, ultrafast spectroscopy and theoretical methods, the mechanism of *E/Z* rotation in ethyl-2-(2-(quinolin-8-yl)-hydrazono)-2-(pyridin-2-yl) -acetate (publ. 5). Three possible mechanisms were theoretically considered: out-of-plane rotation, in-plane inversion, and proton transfer. Considering the presence of water in the solvents used, which affects the measured rate constants, a model of the supermolecule was constructed in which three water molecules forming a bridge between the possible interaction sites (the nitrogen atoms in the pyridine and quinoline rings and the oxygen atoms in the ethoxycarbonyl group). According to this simplified model, water molecules can transfer the proton from the *Z* to *E* form of the switch. This leads to a significant lowering of the energy barrier and corresponds to the experimentally observed rate constants. These results are an attempt to elucidate the mechanism of isomerization in rotary switches, and hence the mechanism of tautomeric reactions in hydrazone compounds.

In publ. 5 of the Candidate's Habilitation report, the synthesis of two new rotary switches, derivatives of 4-hydroxyquinoline containing fixed carbonyl groups in the rotor, is presented, and their properties are investigated by a combination of DFT calculations and molecular spectroscopy (NMR, UV-VIS and fluorescence spectroscopy). The structure of the stator (naphthyl or quinol) and the polarity of the solvents were found not to affect the azo-hydrazone tautomerism. Both compounds exist as keto (hydrazone) tautomers. NMR data show a mixture of isomers of *E* (major) and *Z* (minor) keto forms in solution. The results are in very good agreement with ground state DFT calculations. Keto tautomers exhibit different emission behavior

depending on the structure of the stators. Compared to the naphthyl ring dye, more intense emission and longer lifetime is observed for the quinoline ring compound, where the formation of an intramolecular hydrogen bond between the hydrogen atom of the NH-group of the hydrazone and the N-atom of the quinoline restricts the rotation of the stator. According to spectral data and theoretical calculations at the TDDFT level, the observed emission originates from the excitation of the keto tautomers and does not involve excited-state proton transfer. Protonation is shown to effect an *E/Z* switch in the naphthyl deriv., and a possible mechanism is proposed. In the case of the quinoline switch, addition of acid results in protonation of the quinoline nitrogen atom, which weakly affects the *E/Z* isomerization.

Synthesis and characterization of two 4-substituted phthalimide 2-hydroxy Schiff bases, (E)-2-ethyl-5-((2-hydroxybenzylidene)amino)isoindoline-1,3-dione (4) and (E)-2-Ethyl-5-(((2-Hydroxynaphthalen-1-yl)methylene)amino)isoindolin-1,3-dione (5) (publ. 7). Using UV-VIS spectroscopy, the influence of 2-hydroxyaryl substituents on the keto-enol tautomerism of the compounds was investigated depending on the solvent. In compound 5 the tautomeric equilibrium is affected by the type of solvent, while in 4 no tautomeric conversion is observed. Theoretical calculations in methanol at the ground state IEFPCM/M06-2X/TZVP level show that the energy barrier of the tautomeric conversion reaction between the enol and keto tautomers is 5.6 kcal mol⁻¹ for 4 and 0.63 kcal mol⁻¹ for 5, which confirms the experimentally observed impossibility of tautomeric equilibrium in 4. The experimentally observed specific effect of the solvent (methanol) is modeled by explicit solvation. Excited-state intramolecular proton transfer (ESIPT) was studied by steady-state fluorescence spectroscopy. Both compounds show high rates of photoconversion into keto tautomers, hence emissions with large Stokes shifts in five alcohols (methanol, ethanol, 1-propanol, 1-butanol, and 1-pentanol) and various aprotic solvents (toluene, dichloromethane, acetone, acetyl cyanide). According to calculations in methanol at the excited state TDDFT level, the enol tautomers of 4 and 5 were found to be higher in energy than the keto tautomers, which explains the origin of the experimentally observed emission of the keto tautomeric form.

The keto-enol tautomeric equilibrium in two newly synthesized Schiff bases derived from 7-hydroxyquinoline was investigated (publ. 8). Their spectral properties were characterized by NMR, UV-VIS and fluorescence spectroscopy, as well as using theoretical methods. The results show that 8-((phenylimino)methyl)quinolin-7-ol exists as a mixture of enol and two keto tautomers in solution, while 8-(((pentafluorophenyl)imino)methyl)quinolin-7-ol is represented only in enol form. Upon irradiation, both compounds, through an intramolecular proton transfer mechanism, undergo excited-state rotation around the C_{quin}-CH bond, making them suitable for switches.

In publ. 9 examines ground and excited state tautomeric conversion by intramolecular proton transfer in two new molecular switches, N-(benzo[d]thiazol-2-yl)picolinamide and N-(benzo[d]thiazol-2-yl)isonicotinamide. For this purpose, a combination of experimental (steady-state fluorescence spectroscopy and time-dependent spectroscopy) and theoretical methods were used. Although theoretical calculations suggest two potential switching pathways in N-(benzo[d]thiazol-2-yl)picolinamide, either through the pyridine or through the benzothiazole moiety, experimental results show the same photodynamics as N-(benzo[d]thiazol-2-yl)isonicotinamide. This indicates that excited-state proton transfer from the NH-group to the nitrogen atom of the benzothiazole moiety is favored in both compounds.

Similar studies have been done in publ. 10 of the Habilitation Reference for 10-Hydroxybenzo[h]quinoline (HBQ) and its nitro derivatives, 7-nitrobenzo[h]quinolin-10-ol (2) and 7,9-dinitrobenzo[h]quinolin-10-ol (3), in acetonitrile. According to the experimental and theoretical studies, in the ground state HBQ exists only as the enol tautomer, while in the excited state only the keto form is presented. In the ground state of compounds 2 and 3, the enol form is also more stable, while in the excited state of 3 it is the keto tautomer.

Publications 11-14 investigated the possibility of proton transfer in solution of several nitrogen-containing aromatic organic compounds such as arylhydrazones, pinene-bipyridine, pinene-phenanthroline and 1,3,5-triazine derivatives, as well as favipiravir. The elucidation of tautomeric processes in these compounds is relevant to their applications as molecular switches, coordination compounds of d and f metals, organic light-emitting diodes (OLEDs), and drugs.

In the materials presented to me for review in the first scientific direction, the contributions of Dr. Deneva are related to the application of absorption UV-VIS and fluorescence spectroscopy, as well as quantum-chemical methods for the study of the various tautomeric systems.

In the *second scientific direction*, the candidate's contributions include spectroscopic studies related to clarifying the composition of herbs and different varieties of wine. Publication 15 used near-infrared spectroscopy to rapidly quantify the active components in *Arnicae* flos obtained from the plants *Arnica montana* L. and *Arnica chamissonis* Less. A calibration model using near-infrared (NIR) absorption spectra was developed to quantify the content of these active components in *Arnicae* flos samples, and high-performance liquid chromatography was used as a reference technique. According to the obtained results, NIR spectroscopy is a promising and effective method for non-destructive analysis of *Arnicae* flos. Dr. Deneva's contributions in publ. 16 are related to the application of Raman spectroscopy as a fast, non-destructive analytical technique for classifying Bulgarian wines based on their variety and geographical origin, as well as evaluating their chemical composition. Calibration models have been developed for the measurement of phenolic compounds in both red and white wines. Vibrational spectroscopy has been shown to be a suitable method that can be used to control the authenticity of spirits. Raman spectroscopy has an advantage over infrared spectroscopy due to the ability to analyze water-containing samples such as wine.

4. Critical remarks and recommendations

After carefully examining all the documents submitted to me for the preparation of a review, I can define several critical remarks and recommendations related to both technical and terminological inaccuracies.

1. The electronic set of documents is missing the Application for participation in the competition for "associate professor" professional direction 4.2 Chemical sciences, scientific specialty: "Organic chemistry" for the needs of the lab. OSS, announced in the State Gazette, issue 9 of 30.01.2024. Such a document, with the personal signature of the candidate and a list of the attached documents, must be present in the electronic medium, as it certifies the handwritten submission of the materials for the competition.

2. The materials submitted to me for review lack information about the candidate's contributions to the scientific works. There is no such thing in the Habilitation certificate either.

3. The Habilitation reference was not made in accordance with the requirements of the Law for the development of the academic staff in Republic of Bulgaria and the Rules of the IOCCP-BAS. It should mainly include the scientific contributions of the candidate in the works of the Habilitation thesis, i.e. those under Indicator B, not all articles under the competition.

4. The list of publications included in the Habilitation reference does not correspond in terms of numbering to those from the lists of articles according to indicators B and D. In parallel, the numbering of the articles themselves in the electronic medium are not arranged according to any of the presented lists, which makes it difficult essential reviewer activity.

My critical remarks related to the terminology in my presented materials begin with the title of the Habilitation reference. It is too general and not only incorrect, but does not describe the information contained well enough. The very essence of the reference is presented too briefly and at times unclearly. In it and in the publications it includes, there are numerous systematic terminological errors, such as the use of the terms "tautomeric state", "tautomeric fragment", "tautomeric skeleton", "tautomeric studies", etc. Tautomerism is a type of structural isomerism and as such could not be a state. The terms "tautomeric process", "tautomeric equilibrium", "reactions of tautomeric conversion", etc. may be used instead. I also have critical remarks about the part related to the prospects for research in the next 3 years of the candidate. There are no clearly defined future plans for scientific development and subject matter.

I would encourage future Associate Professor Dr. Vera Deneva for more self-confidence and independent work on a topic of interest to her.

5. Personal impressions

My personal impressions of Dr. Vera Deneva are very good. I've known her since she was a PhD student. She is a very good specialist in the field of absorption and fluorescence spectroscopy and there is no doubt that most of the contributions in these fields from her publications are hers. She is a respected colleague who knows how to work in a team. This, together with the high level of her research activity, proves her competence in an indisputable way and makes her a well-established scientist in the field of Chemical Sciences.

CONCLUSION

In the competition for the occupation of academic position "Associate Professor", Associate Professor Vera Deneva, Ph.D., has presented a sufficient number of scientific works published in refereed international journals with an impact factor and impact rank, which fully correspond to the topic of the competition, to the Law for the development of the academic staff in Republic of Bulgaria and the Rules of the IOCCP-BAS for its application. The presented scientific production proves in an indisputable way the candidate's competence to conduct and lead valuable research in the future. The results achieved in her research activity, as well as her participation in a number of scientific projects and forums, outline the profile of a talented young and thorough scientist, with clearly formed research interests and achievements in the field of organic chemistry. After the analysis of the materials presented in the competition and based on my personal impressions, I find it reasonable to give my positive assessment and to confidently vote "yes" for the election of Assistant Professor Dr. Vera Ventsislavova Deneva of academic position "Associate Professor" in Professional direction 4.2. "Chemical Sciences", scientific specialty "Organic Chemistry".

21.05.2024

Reviewer:

Assoc. Prof. Nadezhda Markova