REVIEW

by Dr. Nikola Tomov Burdzhiev – Associate Professor at the Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski"

of a PhD thesis for the award of the educational and scientific degree of "Doctor"
in: the field of higher education 4. Natural Sciences, Mathematics, and Informatics
professional field 4.2 Chemical Sciences.
Doctoral program "Analytical Chemistry"

Автор: Dimitar Genchev Stoitsov

Topic: NMR and vibrational spectra assignment for verification and elucidation of the structures of aromatic organic and metal-organic coordination compounds

Scientific supervisor:
Prof. DSc. Plamen Nikolov Penchev – Paisii Hilendarski University of Plovdiv
Assoc. Prof. Dr. Marin Neykov Marinov – The Agricultural University - Plovdiv

1. General description of the materials presented

By Order No.РД-22-1706 of 21 July 2025 of the Rector of Paisii Hilendarski University of Plovdiv, I have been appointed as a member of the scientific jury to ensure the procedure for the defense of a dissertation on the topic "NMR and vibrational spectra assignment for verification and elucidation of the structures of aromatic organic and metal-organic coordination compounds" for the acquisition of the educational and scientific degree of "Doctor" in the field of higher education 4. Natural Sciences, Mathematics and Informatics, professional field 4.2 Chemical Sciences, doctoral program "Analytical Chemistry". The author of the dissertation is Dimitar Genchev Stoitsov – doctoral student (full-time) at the Department of Analytical Chemistry and Computer Chemistry, supervised by Prof. DSc Plamen Nikolov Penchev, from Paisii Hilendarski University of Plovdiv, and Assoc. Prof. Dr. Marin Neykov Marinov, from the Agricultural University – Plovdiv.

The set of materials on paper and electronic media presented by Dimitar Stoitsov is in accordance with Article 36 (1) of the Regulations for the Development of Academic Staff at PU and includes the following documents:

– application to the Rector of PU for the initiation of the procedure for the defense of a dissertation;

– curriculum vitae in European format;

– record of the departmental council meeting related to reporting the readiness to open the procedure and preliminary discussion of the dissertation;

– dissertation;

– abstract in Bulgarian and English;

– list of scientific publications on the topic of the dissertation;

– copies of four scientific publications;

– certificate of compliance with the minimum national requirements;

– declaration of originality and authenticity of the attached documents;

– official note certifying the PhD student's participation in a scientific research project.

2. Brief biographical information about the PhD student

PhD student Dimitar Genchev Stoitsov completed his bachelor's degree in Analysis and Control at Plovdiv University "Paisii Hilendarski" in 2019. In 2020, he also completed a master's program in Spectrochemical Analysis at the Faculty of Chemistry of Plovdiv University. In March 2021, he was enrolled in a full-time doctoral program at the Department of Analytical Chemistry, and in November of the same year, he was appointed as an assistant at the Faculty of Chemistry at Plovdiv University.

3. Relevance of the topic and appropriateness of the objectives and tasks set

Determining the structure of newly synthesized compounds is an essential part of chemical synthesis and the development of synthetic chemistry. While the molecular formula of a sample can be determined using techniques such as elemental analysis or high-resolution mass spectrometry, establishing the way atoms are bonded in a molecule can be more difficult, especially for organic compounds with complex structure and a large number of hydrogen and carbon atoms. One possible approach is to use X-ray structural analysis, but this is only applicable in cases where the compounds tend to form single crystals. In all other cases, there is no better alternative than nuclear magnetic resonance. In recent years, the use of NMR to elucidate the structure of various molecules has become increasingly accessible with the introduction of routine use of two-dimensional techniques and, in the case of poorly soluble samples, the use of solid-phase NMR. When interpreting NMR spectra, information from various online databases is often used, so it seems reasonable for the aim of the dissertation to be to interpret in detail the NMR spectra of organic compounds and their complexes that are diverse in type and complex in structure, and to supplement the existing databases.

4. Knowledge of the problem

The literature review is divided into three parts and covers some of the most commonly used 1D and 2D NMR techniques, as well as the characteristic vibration intervals of frequently occurring fragments in organic compounds. The main focus is on NMR spectral techniques, and their advantages and disadvantages are discussed in detail. The possibilities for errors when using information from one-dimensional and two-dimensional NMR spectra are also included in the review, which has inevitably enriched the author's knowledge in the field of NMR spectroscopy. The third part is devoted to a review of the information known in the literature about the compounds that are of interest to this dissertation. For certain groups of compounds, the author has focused on the spectral data known in the literature, which I find appropriate, while for others he has been guided by their diverse biological activity and thus there is no information about their structural characterization. In any case, I believe that this review has enriched the PhD student's knowledge and fulfilled its educational role.

5. Research methodology

The main objective of this thesis is the complete assignment of signals from the obtained NMR spectral data of new or known organic compounds from different classes, for which only partially or incorrectly assigned NMR data exist. Of the analytical techniques selected in the dissertation, as well as those available in the country, there is no other method more suitable than NMR spectroscopy.

6. Characteristics and evaluation of the dissertation

The dissertation is 126 pages long, of which 5 pages are devoted to the introduction, 31 pages to the literature review, 3 pages to the methods and equipment used, 75 pages to the description of the results of the structural elucidation of the individual compounds, 1 page for the conclusion, and 11 pages for the bibliography, which includes 157 references, a significant portion of which are from the last 10 years.

After a thorough reading of the dissertation, I have no reason to doubt the reliability of the material on which the contributions of the dissertation are based.

7. Contributions and significance of the development for science and practice

The main scientific contributions of the dissertation are related to the use of new NMR spectral techniques to supplement or correct the spectral data available in the literature for different classes of organic compounds. Of the twenty-three compounds described in the dissertation, seven are completely new and described for the first time, while for the remaining sixteen substances, the spectral data available in the literature have been supplemented and even corrected. To confirm the obtained chemical shifts for the ^{13}C atoms of some compounds, chemical shift prediction based on Hierarchically Ordered Spherical Environment (HOSE) was used.

Some of the referenced NMR spectral data, as well as the raw one-dimensional and two-dimensional NMR spectra together with the structures of the compounds, have been deposited in the NMRShiftDB database, thus enriching the available information and facilitating access to it.

8. Assessment of the publications related to the dissertation

Dimitar Stoitsov participates in the procedure for acquiring the educational and scientific degree of "doctor" with four publications. Three of the publications are in journals with IF; crystals (IF - 2.4, Q2) and Molbank (IF – 0.4, Q4), where the PhD student is the first author, and applied sciences (IF- 2.5, Q2), where he is the second author. There is also one publication in Bulgarian Chemical Communications (SJR-0.15, Q4). All four publications are closely related to the topic of the dissertation, and the results of the dissertation are included in each of them. A comparison of the style of expression in the publications and the dissertation leaves no doubt as to the doctoral student's personal contribution to their development. The publications have no citations at the time of writing the review.

9. Abstract

The abstracts in Bulgarian and English fully reflect the results listed in Section 3: results from the spectral references of the dissertation and are of a length that satisfies the requirements of the regulations for the development of the academic staff of Plovdiv University "Paisii Hilendarski."

10. Critical comments, recommendations, and questions

As we all know, when writing such large scientific work, mistakes are inevitable, but in this dissertation, they are more than normal and are not only technical. For a dissertation whose title begins with "*Treatment of NMR and vibration spectra*...", the lack of a figure expressing any spectrum, even a vibration spectrum, creates a bad impression on the reader. In fact, the author has attached spectra of two of the compounds to his documents, but they will not be available to future readers of the dissertation or the abstract. Overall, there are few figures, and as a result, they are often far from the text in which the structures depicted in them are discussed. This forces the reader

to constantly go back and forth through the text, which makes reading and understanding the information difficult. To illustrate this point, one of the figures is 17 pages and two sections away from the place in the text where it is mentioned. The numbering used in the compounds also does not facilitate easy comprehension of the information. In some cases, within a single compound (XII, XIII, and XIV), there are both Roman and Arabic numerals with and without prims, as well as letters. This situation becomes even more confusing when, to describe the magnetically inequivalent protons in compound XIV, they are also numbered with letters, even though there are already carbon atoms with this numbering. While we are on the subject of magnetic inequivalence, I should point out that instead of this term, throughout the dissertation the protons are referred to as chemically inequivalent. There is no possibility for the protons from a single CH_2 group to be chemically inequivalent, but in different cases they can be magnetically inequivalent, which can lead to the appearance of more than one signal in the spectrum.

On page 65 is written: "*Furthermore, the signal of the carbon atom nucleus, C-3, is split, appearing almost as a doublet, most likely under the influence of F. Consequently, the chemical shifts of the signals of the carbon atom nuclei, C-3, C-2', C-3'/7', C-4'/6', and C-5', are presented as the arithmetic mean of two values in Table 5.*" It is not clear what is meant by "almost like a doublet" since it is known that the fluorine nucleus is magnetically active and causes splitting of the signals of nearby ^{13}C atoms. In this case, the arithmetic mean value referred to is actually the chemical shift, and it would have been better if the signals in Table 5 had been described as doublets with the corresponding spin-spin coupling constant $^{n}J_{CF}$.

Other errors have also been noted, which only spoil the good impression made by the otherwise substantial work carried out by the PhD student.
I have the following questions for the PhD student:

1. On page 30 of the literature review, you write, "*As the s-character increases from sp^3 to sp^2 and sp orbitals, the bonding electrons move closer to carbon, thereby moving away from the proton nuclei and de-shielding them. This is why the signals of methane and ethane protons have a chemical shift of 0.23 ppm and 0.86 ppm, respectively, while the signal of ethene protons is recorded at 5.28 ppm.*" How would you explain the chemical shift of the acetylene proton, which is only 1.91 ppm?

2. When interpreting the COSY spectrum of compound XIII, you write: "*For each of the doublets at 7.88 ppm and 7.54 ppm, three COSY correlations were found.*" How is it possible for a proton to have three correlations, but only one of them to manifest itself in the spectrum?

3. When synthesizing compound XIV, you assume the formation of two tautomers. Evidence for this is the signal in the ^{1}H NMR spectrum located at 2.72 ppm. The same signal exhibits two correlations in the HSQC spectrum with the signals at 28.90 and 32.09 or 29.17 and 32.14 (both sets of numbers are present) from the ^{13}C NMR spectrum. For one of the correlations, you claim that it is due to the CH group of one tautomer of the benzodiazepine ring, and the other to the CH_2 group of the other tautomer. I find this coincidence of chemical shifts for protons attached to carbon atoms in different hybrid states very strange. Moreover, none of the listed values for the chemical shift of carbon atoms corresponds to an atom participating in a double bond. Do you have any scientific information to support your claim?

CONCLUSION

The dissertation contains scientific and applied scientific results that represent an original contribution to science and meet all the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria (ZRASRB), the Regulations for the Implementation of the ZRASRB, and the relevant Regulations of Plovdiv University "Paisii Hilendarski."

The dissertation shows that the doctoral student has in-depth theoretical knowledge in the field of Nuclear Magnetic Resonance spectroscopy, as well as practical skills in interpreting complex one-dimensional and two-dimensional NMR spectra.

For the reasons stated above, I give my **positive assessment** of the research presented in the dissertation reviewed above, abstract, achieved results and contributions, and **I propose that the honourable scientific jury award the educational and scientific degree of "Doctor"** to Dimitar Genchev Stoitsov in the field of higher education: 4. Natural Sciences, Mathematics, and Informatics, professional field 4.2 Chemical Sciences, doctoral program "Analytical Chemistry."

30.09.2025 г. Reviewer: .....

(Assoc. Prof. Dr. Nikola Burdzhiev)