

KOPBALINA KYMBAT BAGDATKYZY

Quantum-Chemical calculations of the reactivity and energy stability of alkaloid derivatives of the quinolysine series

ABSTRACT

of the dissertation submitted for the degree of
Doctor of Philosophy (PhD) in the educational program
8D05302 – Physics

Relevance of the theme. The study of the conformational flexibility of lupinine azide, lupinine-1,2,3-triazole derivatives, and their complexes with Cd^{2+} ions and the cytisinylcoumarin complex (CC) is of particular interest, since the features of their molecular structures determine their physicochemical properties and potential reactivity.

A combination of experimental methods (X-ray diffraction analysis, IR spectroscopy, UV spectroscopy, and NMR spectroscopy) and theoretical approaches (density functional theory and molecular dynamics) provides the following opportunities:

- to theoretically determine possible conformational states of the molecules and confirm them experimentally;
- to evaluate their stability and probability based on energy parameters;
- to predict their reactivity.

Special attention is paid to the influence of the arrangement of functional groups and hydrogen bonds on the energy barriers of conformational transitions.

Lupinine azide (1-(azidomethyl)octahydro-2H-quinolizine) and triazole derivatives obtained from it through reactions with various phenylacetylenes represent new 1,2,3-triazole compounds, including: 1-azidomethyloctahydro-1H-quinolizine (lupinine azide), 1-((4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)octahydro-1H-quinolizine (1), 1-((4-(m-tolyl)-1H-1,2,3-triazol-1-yl)methyl)octahydro-1H-quinolizine (2), 1-((octahydro-1H-quinolizin-1-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl-3-(tert-butyl)-5-ethyl-2-hydroxybenzoate (M_a), 4-((1-((octahydro-1H-quinolizin-1-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (M_b) and 1-((4-(4-benzyloxy)-3-methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)octahydro-1H-quinolizine (M_c).

Based on compounds M_a , M_b , and M_c , cadmium ion (Cd^{2+}) complexes were synthesized and designated as C_a , C_b , and C_c , as well as a cytisinylcoumarin complex (CC).

These compounds are considered promising objects for studies in the field of organic and medicinal synthesis. Lupinine azide serves as a key reagent for obtaining new derivatives, while the cytisinylcoumarin molecule combines cytisine and coumarin fragments, making it a convenient platform for further chemical modifications.

The molecular structure and conformational flexibility determine the reactivity and stability of these compounds. The spatial arrangement of the azidomethyl group in the lupinine azide molecule, as well as in its triazole derivatives, indicates the presence of multiple low-energy conformational states.

In the CC molecule, low-energy rotational conformers are observed, caused by the mutual orientation of the cytosine and coumarin fragments. These features are reflected in their spectroscopic properties.

In this work, the structural properties of the mentioned molecules were comprehensively studied, energy levels of the conformers were calculated, and their spectroscopic characteristics were simulated — including chemical shifts in NMR spectra, vibrational properties in IR spectra, and electronic properties in UV spectroscopy and emission spectra.

The structural analysis of the cytosinylcoumarin complex was carried out both in the crystalline state and in solution (molecule in a solvent medium). The crystal structure of CC was determined by X-ray diffraction analysis. Overall, the obtained data made it possible for the first time to determine the most probable conformational states of the studied molecules.

Purpose of the study. The purpose of this research is a comprehensive study of the conformational states, energetic characteristics of conformers, and molecular structures of lupinine azide, lupinine-1,2,3-triazole derivatives, their complexes with Cd^{2+} ions, and the cytosinylcoumarin complex (CC). In addition, the study aims to establish correlations with experimental spectroscopic data and to determine the most probable conformational states of the molecules in solution and in the solid state.

Research objectives:

1. Quantum-chemical modeling of lupinine azide, lupinine-1,2,3-triazole derivatives, their Cd^{2+} ion complexes, and the structure of the CC molecule.
2. Determination of possible conformational states and calculation of their energetic characteristics, including potential barriers of rotational transitions.
3. Modeling of spectroscopic properties (NMR, IR, and UV spectroscopy) and comparison with experimental data.
4. Investigation of molecular conformations in solution, their dynamics, and energetic stability.

Research methodology. Modern quantum-chemical methods were applied, including DFT and TD-DFT approaches, semi-empirical calculations, and molecular dynamics adapted for organic compounds. Possible conformations of lupinine azide, lupinine-1,2,3-triazole derivatives, their Cd^{2+} complexes, and the CC were determined. Rotational conformational transitions were simulated, geometries of the molecules in their most stable low-energy states were found, and their concentrations at room temperature were estimated. Spectroscopic properties (NMR, IR, and UV spectra) were calculated. The crystalline structure of the CC was determined by X-ray diffraction analysis. Theoretical results were compared with experimental data.

Scientific novelty of the research:

1. For the first time, a comprehensive quantum-chemical study of the conformational flexibility and stereochemistry of lupinine azide, lupinine-1,2,3-triazole derivatives, their Cd^{2+} complexes, and the cytisinylcoumarin complex has been carried out.

2. Low-energy conformational states of the molecules and their distribution in solution have been determined.

3. Conformational transitions and energy barriers have been calculated.

4. Spectroscopic characteristics have been computed and compared with experimental data.

5. The crystalline structure of the CC has been established.

6. The influence of functional group positioning on the chemical reactivity of the molecules has been demonstrated.

Main findings submitted for defense:

1. In the lupinine azide molecule (1-(azidomethyl)octahydro-2H-quinolizine), the axial conformer of the methylazide fragment forms a series of low-energy configurations whose energies exceed that of the ground state by 0.15–0.60 kcal/mol. These configurations give rise to characteristic vibrational modes in the spectrum at 2100, 1250, and 650 cm^{-1} .

2. Complex formation in lupinine-1,2,3-triazole derivatives and their Cd^{2+} complexes is accompanied by charge redistribution, changes in the molecular orbital energy levels, an enhancement of electron-shell polarization, and a red shift of the absorption bands in the 200–500 nm region.

3. In the cytisinylcoumarin complex, the interaction between donor and acceptor fragments stabilizes the π -electron system and enhances intramolecular charge transfer. The energy difference between the unstable and stable configurations is approximately 6.4 meV. Four stable conformers exist, two of which form strong hydrogen bonds, with energies 0.6 kcal/mol above the ground state.

Compliance with scientific and state research programs.

The dissertation was carried out within the framework of the research projects coordinated by the Ministry of Education and Science of the Republic of Kazakhstan: “Spatial structure and stereochemistry of derivatives of quinolizidine alkaloids and guaiane sesquiterpenoids” (Grant No. IRN AP23487966, 2024–2026).

Approbation and publications. The main results of the research were presented and discussed at the following international conferences:

- International Scientific and Practical Conference “XV Saginov Readings: Integration of Education, Science and Production” (Karaganda, June 16–17, 2023);

- International Scientific Conference “Chemical Physics of Molecules and Multifunctional Materials” (Russia, Orenburg, November 28–30, 2024);

- International Scientific and Practical Conference “XVI Saginov Readings: Integration of Education, Science and Production” (Karaganda, June 13–14, 2024).

Publications. 9 scientific papers have been published based on the results of the dissertation, including: 4 articles in journals indexed in Web of Science and

Scopus databases, among them: 2 articles in *Molecules* (Impact Factor = 4.6, Q1, percentile – 87%), 1 article in *Materials* (Impact Factor = 3.2, Q1, percentile – 79%); 1 article in *Materials Letters* (Impact Factor = 2.7, Q2, percentile – 74%), 2 articles in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan; 3 articles in proceedings of international conferences.

Practical significance of the research. The results of this study make it possible to predict the conformational flexibility and stability of lupinine azide, lupinine-1,2,3-triazole derivatives, their Cd^{2+} complexes, and the CC, which is of great importance for their potential pharmacological applications. The obtained data can be used for the synthesis of new alkaloid derivatives. The identified spectroscopic and crystallographic features of the molecules contribute to the improvement of quality control and purity assessment methods in the production of natural and synthetic alkaloids. The research can serve as a foundation for the targeted search for new physiologically active compounds and the development of promising pharmaceutical agents.

Author's personal contribution. The author performed the quantum-chemical calculations, simulated the spectroscopic characteristics (NMR, IR, and UV spectra), and compared theoretical data with experimental results. The formulation of research objectives, analysis of the obtained results, and conclusions were carried out jointly with the scientific supervisors.

Structure and volume of the dissertation. The structure of the dissertation corresponds to the research objectives and includes: an introduction, five chapters, a conclusion, and references. The dissertation consists of 129 pages of text, contains 52 figures, 20 tables, and a list of 237 references.