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Quantum Chemical Study of the Structure and Properties of a Quinolysine Alkaloid Derivative Molecule

Derivatives of quinolisidine alkaloids obtained from plants of the genus *Lupinus* and *Anabasis* is one of such important compounds from the point of view of searching for new biologically active substances. The presence of the primary alcoholic group allows obtaining various modifications of lupinin derivatives. The task of complex study of the spatial structure of quinolisidine derivatives molecules, pathways and obstacles of their conformational transitions, conformational states, and reactivity data remains relevant. Therefore, in continuation of the study of the conformational states of these derivatives, quantum-chemical calculations of the molecule 1-((4-(4-(*m*-tolyl)-1H-1,2,3-triazol-1-yl)methyl)octahydro-1H-quinolysine were performed. Geometrical properties of this molecule, obtained as a result of quantum chemical calculations, were analyzed and compared with experimental data of X-ray diffraction analysis. According to the results of the conformational analysis, conducted by rotating along the labile C12-C13 and C10-N2 bonds, the most favorable conformational states of the molecule were determined. It was shown that the localization of the boundary molecular orbitals falls on the 1-ethyl-4-(*m*-tolyl)-1H-1,2,3-triazole substituent at C12 and C10 atoms, which suggests its participation in the subsequent modification reactions carried out in the search for new biologically active substances.

Keywords: quantum chemical calculations, alkaloids, computer modeling, quinolysine derivative, conformational analysis, thermodynamic stability, lupinine derivatives, X-ray structure analysis

Introduction

Among various lupinine derivatives, compounds with biological activities that are not specific for compounds of this class (antispasmodic, antiarrhythmic, hepatoprotective, analgesic, cholinergic, insecticidal, antioxidant, etc.) are regularly encountered. This has attracted the attention of many researchers to study comprehensively and also to design more complex structures of these derivatives to study the structure-activity relationship.

One of the most effective methods for studying complex systems is computer modeling. Computer modeling methods are aimed at solving various problems and consist in performing a series of computational experiments on a computer. The purpose of these experiments is to analyze, interpret, and compare the results of the modeling with the specific behavior of the object under study. If necessary, the model is refined on the basis of the data obtained.

Molecular modeling is the process of creating a computer model of an object by transferring its spatial coordinates. Information about the initial geometry can be obtained in several ways: by extracting data from the X-ray diffraction database, by searching libraries for standard geometries, or by building structural models using various software tools.

The activity of a molecule in chemical reactions depends mainly on its composition, structure and energy properties. The prediction of reaction centers of organic molecules is an important and urgent task. Using modern quantum chemical methods, chemists can design experimental studies and carry out targeted synthesis of important chemical products.

Research Methods

The object of work is the molecule of lupinine alkaloid derivative 1-((4-(m-tolyl)-1H-1,2,3-triazol-1-yl)methyl)octahydro-1H-quinolysine (*molecule 1*) (Fig. 1) synthesized earlier by the authors [1].

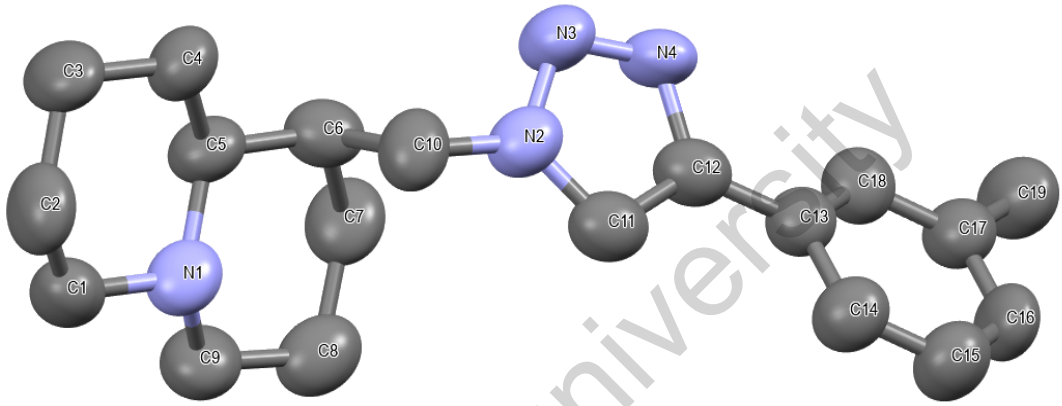

Figure 1. 3D structure of ((4-(m-tolyl)-1H-1,2,3-triazol-1-yl)methyl)octahydro-1H-quinolysine (1)

Nowadays, there is a sufficient number of free and commercial quantum chemistry programs, such as GAMESS, NWChem, HyperChem, VASP, Quantum Espresso, CRYSTAL, etc., for calculating organic molecules [2–3].

For the quantum-chemical study of molecule **1** we used the non-empirical DFT B3LYP density functional method using the valence-splitting basis set 3-21. To take into account the possibility of displacement of the electron density distribution center from the nucleus (polarization of atomic orbitals), we included a *d*-type polarization function in the basis set. The use of polarization basis functions allows us to correctly describe the energy and geometrical characteristics of organic compounds, including those with heteroatoms, which are present in the molecule under study.

The optimization of the geometry of molecule 1 was performed using the keywords Opt+freg. Opt — means that it is necessary to optimize the configuration of the molecule, i.e. during the optimization process, according to the applied method of extremum search, the program will change the bond lengths and valence angles of the studied structure until a stationary point — the most stable state of the molecule — is found. The keyword Freg was used by us to calculate the thermodynamic properties of molecules, as well as to determine the type of the stationary point (minimum or saddle point).

To find the most favorable conformational states, we used the keyword Scan, with opt=(modredundant, maxcycles=1000) selected in the problem section, and the corresponding dihedral angle after the coordinates by a blank line labeled with the letter D and the four atom numbers of that angle. We used modredundant for incomplete optimization.

Results and discussions

The first step of study was to optimize the geometry of *Molecule 1* — to find the minimum of total energy in all geometrical parameters.

In the course of studying the spatial structure of *Molecule 1*, we compared its geometric properties with X-ray diffraction (XRD) data, as well as with the data of the molecule 1-((4-(4-(3-methoxyphenyl)-1H-1,2,3-

triazol-1-yl)methyl)octahydro-1H-quinolysine (*Molecule 2*) [4], which has a similar structure and has been studied by us previously [5].

The geometric properties of *Molecules 1* and *2* obtained from quantum chemical calculations are close to the corresponding XRD data, which indicates the correctness of the calculated data. The values of the torsion angles are given in Table 1.

Table 1

Values of torsional angles in *Molecules 1* and *2*

Torsional angles	*Molecule 1*		*Molecule* 2	
	XRD	B3LyP 3/21	XRD	B3LyP 3/21
C1-N1-C5-C4	59.2(1)	53.4	–58.0(9)	59.2
C9-N1-C5-C4	176.8(1)	175.2	–176.6(9)	–175.4
C11-N2-C10-C6	–120.8(1)	–129.9	124(1)	–138.5
C10-N2-C11-C12	177.1(1)	–179.5	–176.2(8)	–178.1
N3-N4-C12-C11	0.0(1)	0.2	0(1)	0.2
C2-C3-C4-C5	57.0(2)	57.3	–57(1)	55.0
C3-C4-C5-N1	–58.2(1)	–54.8	59(1)	–56.3
C3-C4-C5-C6	177.5(1)	–176.8	–175.0(9)	–178.0
C4-C5-C6-C7	179.4(1)	–177.0	179.3(8)	112.0
C4-C5-C6-C10	55.2(1)	60.0	–54(1)	–124.1
C5-C6-C7-C8	–54.0(1)	–56.9	54(1)	58.4
C5-C6-C10-N2	175.9(1)	168.4	179.2(7)	61.1
N2-C11-C12-N4	0.7(1)	–0.1	–0(1|)	0.0
N2-C11-C12-C13	–179.8(1)	–179.9	178.1(9)	–179.7
C11-C12-C13-C18	151.6(1)	179.9	160(1)	179.7

The difference in the values of the torsion angles C4-C5-C6-C7, C4-C5-C6-C10 and C5-C6-C10-N2 can be explained by the fact that all the quantum chemical calculations are carried out in the liquid phase of the molecules, whereas the XRD data are obtained in the solid state. Therefore, molecule 2 adopts an energetically more favourable conformation upon crystallization.

To determine the most favorable conformational states of *Molecule 1*, conformational analysis was performed by rotating around the labile C12-C13 (Fig. 2) and C10-N2 (Fig. 3) bonds.

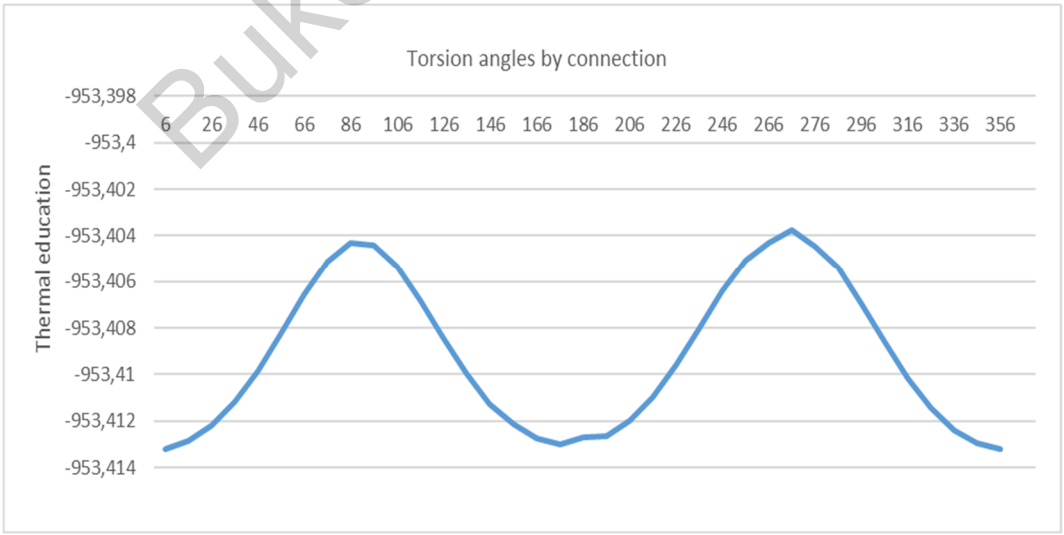

Figure 2. Dependence of the total energy of *Molecule 1* on the rotation along the C12-C13 bond

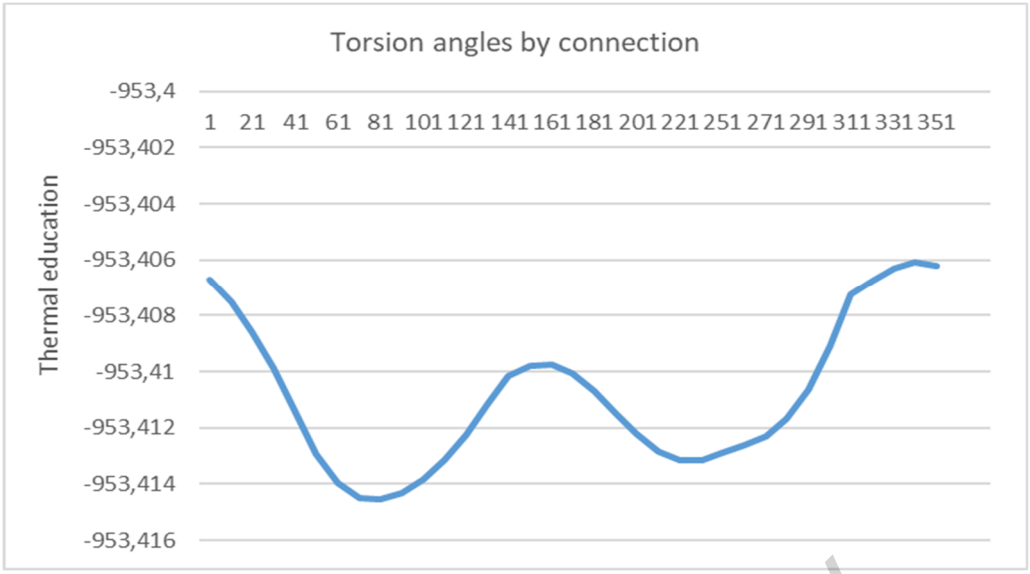

Figure 3. Dependence of the total energy of *Molecule 1* on the rotation along the C10-N2 bond

From the analysis of the obtained data we can conclude that the most thermodynamically favorable (having the minimum electron energy of the molecule) conformational states of the free *Molecule 1* takes at the values of the torsional angle C11-C12-C13-C14 355° and 176° and at values of the torsional angle C6-C10-N2-C11 71° and 221° (–953.41HF) –2502 kJ/mol. The conformation along the C12-C13 and C10-N2 bonds has an energy minimum in the range of -2502 kJ/mol.

It is believed that the reactivity of a molecule depends on its boundary molecular orbitals (MOs): the highest occupied and the lowest free orbitals (HBMOs and LFMOs) [6]. One of the most important properties of the MOs is the boundary electron density, i.e. the electron density on the individual atoms of the molecule involved in the reaction. According to this theory, a reaction between molecules is most likely to occur when there is a maximum overlap of boundary MOs. This process results in a charge transfer from the highest occupied orbital of the donor (gives) to the lowest free orbital of the acceptor (receives).

It is known that the reactivity of a molecule is characterized by the values and localization of HBMOs (highest occupied molecular orbital) and LFMOs (lowest free molecular orbital) [7]. The energy characteristics and localization of MBOs (molecular boundary orbitals) have therefore been calculated.

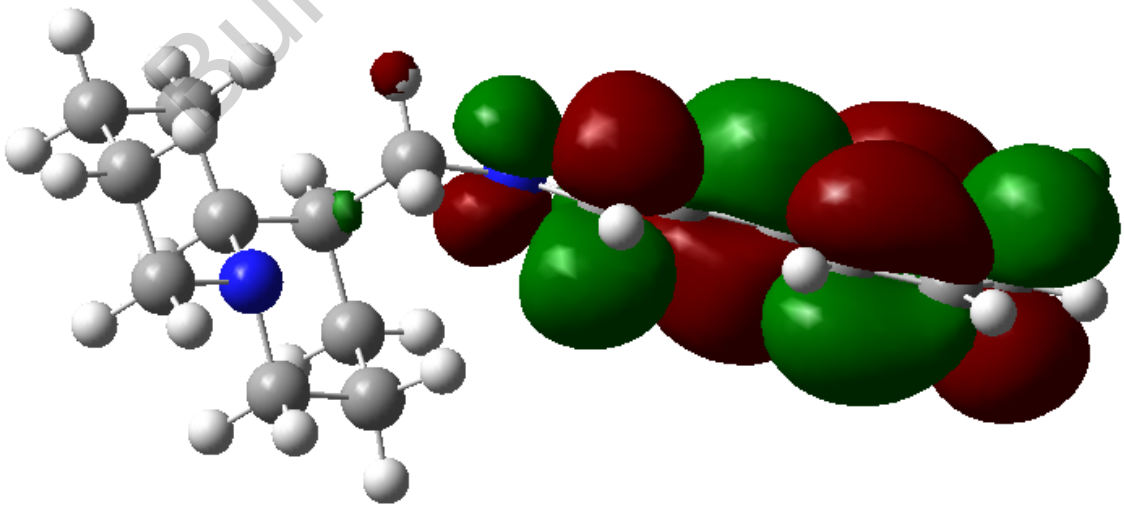

Figure 4. Localization of MBOs in molecule 1

Figure 4 shows that the localization of MBOs in molecule 1 falls on the substituent — 1-((4-(*m*-tolyl)-1H-1,2,3-triazol-1-yl)methyl. Therefore, it can be assumed that further reactions of synthesis of new derivatives of molecule 1 will take place with participation of this substituent.

The "hardness" or "softness" of the studied molecules can be estimated from the values of HBMO and LFMO energies (Table 2). The "hardness η/softness" of molecules according to the Pearson criterion can be calculated on the basis of the formula η = (LFMO – HBMO)/2, and then S =1/(2η) = 1/(LFMO – HBMO). The application of these formulas implies that the studied molecular systems are "rigid" reactants, since they have an energy gap of more than 1 eV between LFMO and HBMO [8]. The calculated rigidity (Ƞ) indicates that this molecule is quite rigid, which in turn indicates its low reactivity and high electronic stability. Sufficient thermodynamic stability is indicated by the value of heat of formation also presented in Table 2.

Table 2

The energy properties of *Molecule 1*

Basis	B3LYP/3-21
ΔH, hartree, eV	–953.413251
HBMO, eV	–9.2326
LFMO, eV	–8.6188
Ƞ, eV	–3.6951

Conclusion

Thus, as a result of quantum chemical calculations performed by density functional theory methods B3LYP/6-21G*:

– geometrical parameters of conformational states of molecule 1 with values of torsional angles C11-C12-C13-C14 355° and 176°, and C6-C10-N2-C11 90° and 230° were determined;

– a satisfactory agreement between the computational-theoretical and experimental structural data is shown;

– the studied molecule was found to exhibit low reactivity and high electronic stability.

These calculations will allow further modelling of the chemical properties of molecules for the subsequent synthesis and search for new drugs based on quinolizidine derivatives.

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Хинолизин алкалоидты туынды молекуласының құрылымы мен қасиеттерін кванттық химиялық зерттеу

Lupinus және *Anabasis* тұқымдас өсімдіктерден алынған хинолизидин алкалоидтарының туындылары жаңа биологиялық белсенді заттарды іздеу тұрғысынан маңызды қосылыстардың бірі. Бастапқы спирттік тобының болуы лупинин туындыларының әртүрлі модификацияларын алуға мүмкіндік береді. Хинолизидин туындыларының молекулаларының кеңістіктік құрылымын, олардың конформациялық ауысуларының жолдары мен кедергілерін, конформациялық күйлер мен реакциялық қабілеттілігін кешенді зерттеу міндеті маңызды. Сондықтан, бұл туындылардың конформациялық күйін зерттеуді жалғастыра отырып, 1-((4-(*м*-толил)–1Н-1,2,3-триазол-1-ил)метил)октагидро–1Н-хинолизин молекуласына кванттық-химиялық есептеулер жүргізілді. Кванттық-химиялық есептеулер нәтижесінде алынған бұл молекуланың геометриялық сипаттамалары талданып, рентгендік құрылымдық талдаудың эксперименттік мәліметтерімен салыстырылған. C12-C13 және C10-N2 лабильді байланыстары бойымен айналу арқылы жүргізілген конформациялық талдау нәтижелері бойынша молекуланың ең тиімді конформациялық күйлері анықталды. Шекаралық молекулалық орбитальдардың локализациясы C12 және C10 атомдарындағы 1-этил-4-(*м*-толил)-1Н-1,2,3-триазол алмастырғышында болатындығы көрсетілген, бұл оның жаңа биологиялық белсенді заттарды іздеу үшін жүргізілетін кейінгі модификация реакцияларына қатысуын болжайды.

Кілт сөздер: кванттық химиялық есептеулер, алкалоидтар, компьютерлік модельдеу, хинолизин туындысы, конформациялық талдау, термодинамикалық тұрақтылық, лупинин туындылары, рентгендік құрылымдық талдау

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Квантово-химическое исследование структуры и свойств молекулы производного хинолизинового алкалоида

Производные хинолизидиновых алкалоидов, полученные из растений рода *Lupinus* и *Anabasis*, с точки зрения поиска новых биологически активных веществ, являются важными соединениями. Наличие первичной спиртовой группы позволяет получать различные модификации производных лупинина. Актуальной остается задача комплексного изучения пространственной структуры молекул производных хинолизидина, а также путей и препятствий их конформационных переходов и состояний, определяемых реакционной способностью. В продолжение изучения конформационных состояний этих производных были проведены квантово-химические расчеты молекулы 1-((4-(*m*-толил)–1Н-1,2,3-триазол-1-ил)метил)октагидро–1Н-хинолизина. Геометрические характеристики данной молекулы, полученные в результате квантово-химических расчетов, проанализированы и сопоставлены с экспериментальными данными рентгеноструктурного анализа. По результатам конформационного анализа, осуществленного путем вращения вдоль лабильных связей C12-C13 и C10-N2, были установлены наиболее стабильные конформационные состояния молекулы. Показано, что локализация граничных молекулярных орбиталей приходится на 1-этил-4-(*m*-толил)-1Н-1,2,3-триазоловый заместитель при атомах C12 и C10, что предполагает его участие в последующих реакциях модификации, проводимых для поиска новых биологически активных веществ.

Ключевые слова: квантово-химические расчеты, алкалоиды, компьютерное моделирование, производное квинолизина, конформационный анализ, термодинамическая стабильность, производные лупинина, рентгеновский структурный анализ

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