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QUANTUM-CHEMICAL STUDY OF THE STRUCTURE AND PROPERTIES OF MOLECULE OF THE LUPININE ALKALOID DERIVATIVE

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The paper presents the results of a quantum-chemical study of the molecule 1-((4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl) methyl) octahydro-1H-quinolizine. The geometrical characteristics of this molecule obtained from quantum-chemical calculations have been analysed and compared with experimental data of X-ray diffraction analysis. According to the results of the conformational analysis carried out by rotation along the labile bonds C11-N12 and C7-C11, the most favourable conformational states of the molecule have been established. It is shown that the localisation of the boundary molecular orbitals falls on the 1-ethyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole substituent at the C11 atom, which suggests its participation in the subsequent modification reactions carried out to find new biologically active substances.

Keywords: quantum-chemical calculations, quinolizine derivatives, conformational analysis, lupinin derivatives, X-ray diffraction analysis.

1. Introduction

It is well known that alkaloids are among the most promising compounds in terms of possible modification and creation of new biologically active substances based on them. Quinolizidine derivatives are the most interesting among them in terms of their structure. For example, the authors of work [1] obtained compounds with octahydroquinolizine nucleus and found that they are ligands of serotonin receptors 5-HT3and 5-HT4.Analysis of literature data showed that similar compounds also exhibit antimalarial [2,3], antitubercular [4] and anticholinesterase activities [5-8].

A wide range of biological properties of quinolizidine derivatives allows to accumulate specific material for the bank of data on their structural derivatives and use them in the search for new drugs. Therefore, the problem of a comprehensive study of the spatial structure of quinolizidine derivative molecules, their conformational states, pathways and barriers of conformational transitions, as well as their reactivity data remains relevant.

2. Research Methods

Quantum chemical calculations, which are now an integral part of modern chemistry, have been widely used not only as a tool for explaining chemical laws, but also for solving complex, in some cases impossible, problems, one of which is the determination of energy characteristics.

Currently, there are many methods and basis set available to obtain results close to the experiment, but the success of the calculation depends on the proper choice of method and basis set for each specific case. The object of this work is the molecule of the lupinine alkaloid derivative 1-((4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl) methyl) octahydro-1H-quinolizine (Molecule 1) (Fig.1), previously synthesized by the authors of work [9]. Selection of the optimal method and basis for further study of this molecule was made by us on the basis of comparison of experimental (data of X-ray structure analysis) and calculated data of geometrical characteristics.

The X-ray diffraction study of compound (1) was performed on an Xcalibur, Ruby diffractometer with CCD detector (CuKα-radiation, graphite monochromator, λ=1.54184 Å, ω-scanning). Processing of the initial array of measured intensities and absorption accounting was performed using the CrysAlisPro (multi-scan) program [10]. The structure was deciphered by the direct method. The positions of non-hydrogen atoms were refined in the anisotropic approximation by full-matrix least squares. Hydrogen atoms were placed in geometrically calculated positions and their positions were refined in the isotropic approximation with fixed positional and thermal parameters (“rider” model). The structures were decoded by the direct method and refined using the SHELXS-2014 and SHELXL-2014 software packages [11].

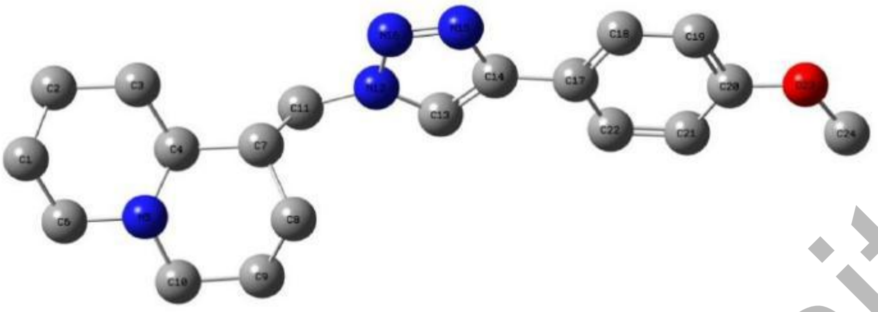

Fig.1. 1-1 - ((4 - (4 - (3 -methoxyphenyl) - 1H - 1, 2, 3 - triazol -1 - il) methyl) octahydro - 1H- quinolizine

The semi-empirical PM6 method and non-empirical quantum chemical methods with basis sets 3-21, 6-31, 6-311**, B3LYP/3-21, B3LYP6-311** were used for the quantum chemical study of molecule 1. The calculations were performed using the MOPAC 9.0 [12] and GAUSSIAN 16 [13] programs.

3. Results and discussions

To study the spatial structure of Molecule 1, the geometrical characteristics obtained from quantum-chemical calculations and data of X-ray structure analysis were compared. The values of bond lengths, valence angles, and torsion angles are given in Tables 1-3.

Table 1. Values of interatomic distances in Molecule 1.

Bond	X-ray structure analysis	PM6	3-21	6-31	6-311**	B3LYP/3-21	B3LYP6-311**
C2-C1	1.526(2)	1.532	1.535	1.528	1.527	1.543	1.538
C3-C2	1.519(2)	1.531	1.533	1.527	1.526	1.541	1.537
C4-C3	1.516(1)	1.546	1.540	1.537	1.535	1.543	1.539
N5-C4	1.471(1)	1.505	1.473	1.467	1.469	1.491	1.484
C6-N5	1.479(1)	1.504	1.474	1.464	1.465	1.484	1.475
C7-C4	1.549(1)	1.560	1.560	1.558	1.556	1.566	1.565
C8-C7	1.539(1)	1.538	1.537	1.536	1.535	1.543	1.539
C9-C8	1.506(1)	1.529	1.531	1.525	1.525	1.547	1.543
C10-N5	1.472(1)	1.504	1.478	1.468	1.468	1.482	1.472
C11-C7	1.526(1)	1.549	1.539	1.537	1.536	1.542	1.545
N12-C11	1.461(1)	1.476	1.464	1.456	1.455	1.478	1.464
C13-N12	1.320(1)	1.400	1.351	1.353	1.352	1.362	1.365
C14-C13	1.373(1)	1.407	1.366	1.370	1.367	1.388	1.389
N15-C14	1.354(1)	1.414	1.370	1.369	1.370	1.385	1.387
N16-N15	1.355(1)	1.299	1.300	1.286	1.289	1.344	1.331
C17-C14	1.485(1)	1.454	1.463	1.464	1.465	1.461	1.464
C18-C17	1.379(1)	1.415	1.395	1.399	1.399	1.409	1.410
C19-C18	1.408(2)	1.386	1.373	1.378	1.377	1.384	1.388
C20-C19	1.353(1)	1.412	1.389	1.391	1.390	1.404	1.401
C21-C20	1.360(1)	1.399	1.381	1.385	1.383	1.398	1.398
C22-C17	1.373(1)	1.398	1.383	1.388	1.387	1.395	1.398
O23-C20	1.376(1)	1.376	1.371	1.373	1.374	1.385	1.394
C24-O23	1.388(2)	1.448	1.435	1.427	1.425	1.459	1.452

Table 2. Valence angles in Molecule 1.

Valence angles	X-ray structure analysis	PM6	3-21	6-31	6-311**	B3LYP/3-21	B3LYP6-311**
C3-C2-C1	109.6(1)	109.4	108.1	108.8	109.0	109.6	110.6
C4-C3-C2	110.3(9)	111.7	112.5	113.1	113.2	111.4	111.9
N5-C4-C3	111.7(7)	109.2	110.5	110.6	110.7	109.7	109.8
C6-N5-C4	107.2(7)	111.5	114.9	115.9	115.3	111.5	112.6
C7-C4-C3	112.2(7)	108.9	108.6	109.1	109.3	110.5	111.6
C8-C7-C4	110.3(8)	112.1	111.8	112.2	112.2	110.4	111.1
C9-C8-C7	109.7(9)	111.1	109.8	110.4	110.6	111.6	112.4
C10-N5-C4	112.0(7)	112.5	113.8	115.8	115.1	110.6	112.2
C11-C7-C4	113.4(7)	111.2	108.8	108.9	108.9	111.8	110.2
N12-C11-C7	111.4(7)	112.1	111.8	113.0	113.2	111.0	113.0
C13-N12-C11	130.2(8)	127.6	130.6	129.7	129.6	129.8	129.8
C14-C13-N12	105.0(8)	104.9	105.9	105.3	105.3	106.2	105.7
N15-C14-C13	111.1(8)	106.7	107.3	106.9	106.9	108.3	107.6
N16-N15-C14	106.9(7)	109.6	110.0	109.8	109.7	109.7	109.6
C17-C14-C13	130.7(8)	130.2	130.7	131.3	131.4	130.1	130.8
C18-C17-C14	121.3(8)	120.0	119.5	120.1	120.1	119.2	120.1
C19-C18-C17	122.0(9)	120.6	120.8	120.9	120.9	120.9	121.0
C20-C19-C18	119.2(1)	118.8	120.5	120.2	120.2	120.5	120.1
C21-C20-C19	121.4(1)	121.7	119.3	119.9	119.8	119.1	120.0
C22-C17-C14	120.6(8)	118.5	122.3	121.8	121.8	120.1	119.4
O23-C20-C19	114.5(9)	112.6	116.2	116.0	116.0	115.9	115.7
C24-O23-C20	117.1(1)	117.9	120.8	121.6	121.3	118.0	119.2

Table 3. Values of torsion angles in Molecule 1.

Torsionangle	X-ray structure analysis	PM6	3-21	6-31	6-311**	B3LYP/3-21	B3LYP6-311**
C4-C3-C2-C1	-56.6(1)	56.8	58.0	56.5	55.8	55.0	53.0
N5-C4-C3-C2	58.9(1)	-57.2	-53.2	-51.5	-51.7	-56.3	-55.0
C6-N5-C4-C3	-58.0(9)	57.5	50.4	48.7	49.5	59.2	58.2
C7-C4-C3-C2	-175.0(9)	-178.0	-173.9	-173.9	-174.3	-178.0	-178.7
C8-C7-C4-C3	179.3(8)	134.4	138.4	139.5	139.0	112.0	110.5
C9-C8-C7-C4	54.1(1)	43.9	42.8	40.4	40.9	58.4	56.4
C10-N5-C4-C3	-58.0(9)	179.4	177.4	-180.0	179.2	-175.4	-172.4
C11-C7-C4-C3	-54.3(1)	-102.9	-97.1	-95.0	-95.3	-124.1	-123.3
N12-C11-C7-C4	179.2(7)	69.0	169.1	167.2	167.5	61.1	171.7
C13-N12-C11-C7	123.9(1)	-94.3	111.5	109.0	110.6	-138.5	105.8
C14-C13-N12-C11	-176.2(8)	178.1	-179.6	179.9	179.7	-178.1	-179.3
N15-C14-C13-N12	-0.53(1|)	-0.2	-0.1	-0.1	-0.1	0.0	0.0
N16-N15-C14-C13	0.72(1)	-0.1	0.0	0.0	0.0	0.2	-0.1
C17-C-14-C13-N12	179.9(9)	179.6	-180.0	-180.0	-179.9	-179.7	-179.8
C18-C17-C14-C13	-155.6(1)	-177.9	179.9	179.6	179.3	179.7	-179.7
C19-C18-C17-C14	176.6(9)	180.0	-180.0	-180.0	-180.0	180.0	179.8
C20-C19-C18-C17	-178.8(9)	0.0	0.0	0.0	0.0	0.0	0.0
C21-C20-C19-C18	-1.2(2)	0.0	0.0	0.0	0.0	0.0	0.0
C22-C17-C14-C13	21.6(1)	0.0	-0.1	-0.4	-0.7	0.0	0.0
O23-C20-C19-C18	-178.7(9)	-180.0	180.0	180.0	180.0	180.0	180.0
C24-O23-C20-C19	175.0(2)	56.8	58.0	56.5	55.8	55.0	53.0

The configurations of the chiral centers C4 and C7 are correlated with the absolute in the crystal structure of lupinin chloride [14]. From the obtained data it follows that the bond lengths and valence angles in compound (1) are close to the usual ones [15].

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The conformations of the six-membered cycles N5, C1 ... C6 (A) and N5, C4 ... C10 (B) in the quinolizidine framework in molecule (1) are close to the corresponding ones in the crystal structure of lupinin [16,17] and are in a conformation close to a slightly distorted armchair. In molecule (1), the orientation of the 1,2,3-triazole cycle is equatorial: torsion angle C7-C11-N12-N16 = 123.9°. The 1,2,3-triazole and phenyl cycles are planar to within ±0.013Å. The angles between the planes of the triazole and aryl substituents in crystal (1) are 23 and 21°, respectively. The geometrical characteristics of molecule 1 obtained from quantum-chemical calculations are close to the corresponding data of X-ray structural analysis, which indicates the correctness of the calculated data.

To determine the most favorable conformational states of Molecule 1, a conformational analysis was performed by rotation along the C11-N12 and C7-C11 labile bonds. The conformational states along these bonds are shown in Figures 2 and 3, respectively.

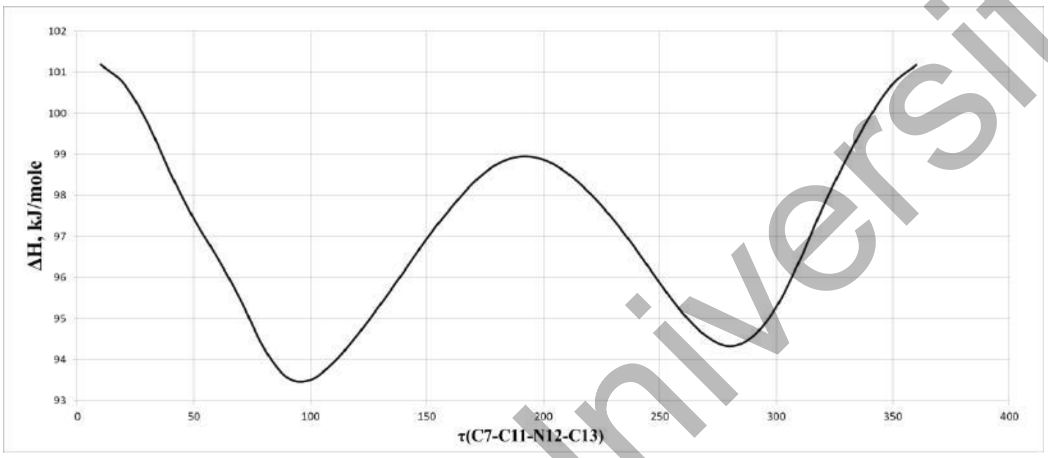

Fig.2. Dependence of the heat of formation on the confomation along the C11-N12 bond.

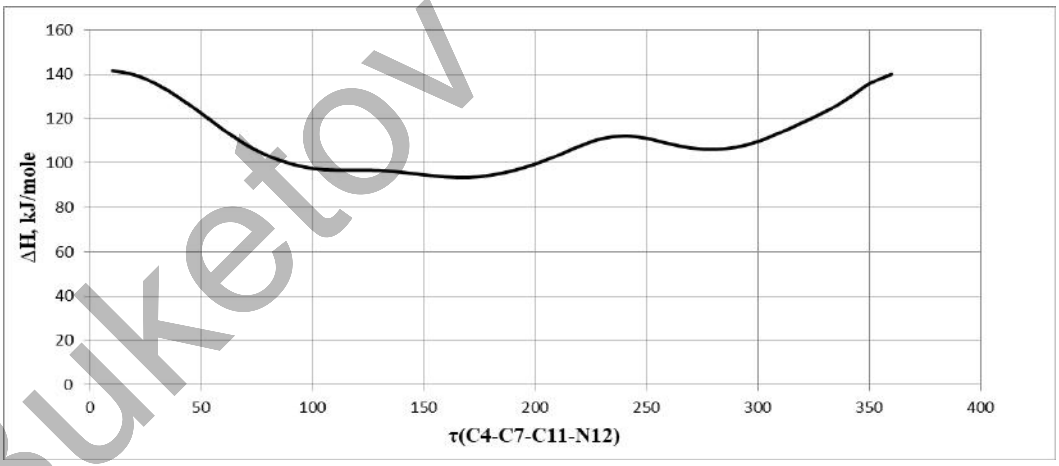

Fig.3. Dependence of the heat of formation on the confomation along the C7-C11 bond.

From the analysis of the obtained data we can conclude that the free molecule 1 adopts the most thermodynamically favourable conformational states (with the minimum electron energy of the molecule) at values of the torsion angle C7-C11-N12-C13 equal to 100° and 280° with a barrier of 5 kJ/mol between them. The conformation along the C7-C11 bond does not have a pronounced energy minimum in the 50-330° range.The conformational mismatch along the N12-C13 bond in quantum chemical calculations and data of X-ray structure analysis is probably due to the influence of intermolecular interactions of Molecule 1 in the crystal. To determine the thermodynamic stability of Molecule 1, the heats of formation were calculated and the results are presented in Table 4. The obtained negative values of the heats of formation indicate that molecule 1 is thermodynamically stable.

The reactivity of a molecule is characterized by the values and localization of the HOMO (highest occupied molecular orbital) and LUMO (the lowest unoccupied molecular orbital) [18-20]. Reactivity analysis based on boundary molecular orbitals showed that the localization of the HOMO and LUMO falls on the 1-ethyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole substituent at the C11 atom (Figure 4), thus subsequent reactions of modification are expected to occur with the participation of the substituent. The reactivity is also affected by the hardness/softness of the molecules [21].

Table 4. Energy characteristics of Molecule 1.

Basis	3-21	6-31	6-311**	B3LYP/3-21	B3LYP6-311**
ΔH, Hartrey	-1021.018	-1026.292	-1026.499	-1027.739	-1033.358
HOMO, eV	-7.713	-7.740	-7.832	-5.409	-5.841
LUMO, eV	3.563	3.411	3.169	-0.326	-0.919
Ƞ, eV	5.638	5.575	5.501	2.541	2.461

Knowing of the values of the HOMO and LUMO energies makes it possible to determine the "hardness" or "softness" of the studied molecules. The Pearson indices of "hardness η /softness S" of the molecules can be calculated on the basis of the following calculation formulae:

$$\eta = (E_{LUMO} - E_{HOMO})/2,$$

$$S = 1/(2\eta) = 1/(E_{LUMO} - E_{HOMO}).$$

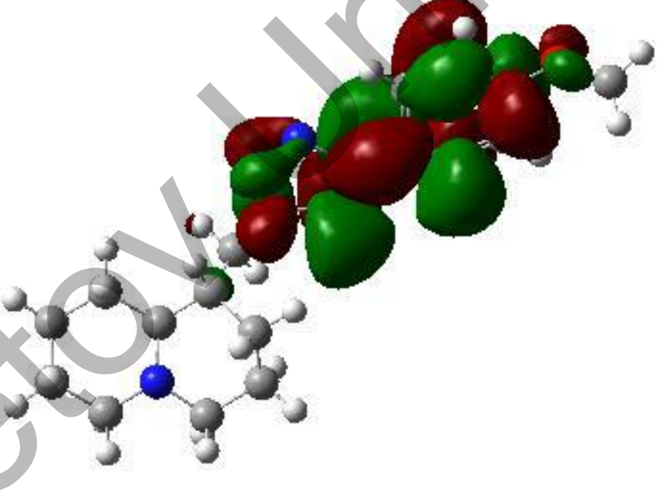

Fig.4. Localization of HOMO and LUMOinMolecule 1.

The application of the above formulae allowed us to show that all the studied molecular systems are "hard" reagents, since they have an energy gap between HOMO and LUMO greater than 1 eV. The calculated stiffness (η) shows that this molecule is quite rigid, indicating its low reactivity and high electronic stability

4. Conclusion

The results of the conducted studies showed that the geometrical parameters are close to the standard parameters. For the free molecule 1, two conformers with torsion angle values C7-C11-N12-C13 equal to 100° and 280° can be realized. The energy barrier between them is negligible and is equal to 5 kJ/mole. The conformation along the C7-C11 bond does not have a pronounced energy minimum in the 50-330° range.

The orbital control data show that both HOMO and LUMO are almost completely centered on the 1-ethyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole substituent at the C11 atom, indicating that this substituent can act as both an electron donor and acceptor in the following reactions. Thus, the established quantum-chemical properties can be the basis for further synthesis and the search for new drugs based on quinolizidine derivatives.

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