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STRUCTURE OF MATTER AND QUANTUM CHEMISTRY

Vibrational Spectra and Stable Conformations of *N*-Methylacetamide and (1S,5S,6R)-6-Acetylamino-(5'-Methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene

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Abstract—IR absorption and Raman spectra of *N*-methylacetamide and (1S,5S,6R)-6-acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene are investigated. Optimized structures and harmonic force fields of stable conformers of both compounds are obtained by means of MP2 and DFT (B3LYP) methods using the 6-31+G** basis set. Based on quantum mechanical calculations, a detailed interpretation of spectra is proposed and vibrational frequencies of the most stable conformations are assigned. Correlations between structures and the spectra of *N*-methylacetamide and (1S,5S,6R)-6-acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene were considered and analytical spectral regions were proposed.

Keywords: vibrational spectrum, molecular conformation, vibrational frequency, *N*-methylacetamide, (1S,5S,6R)-6-acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene.

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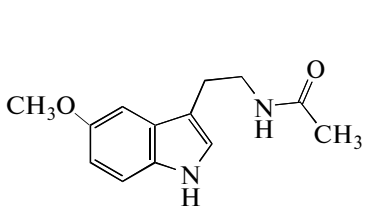
INTRODUCTION

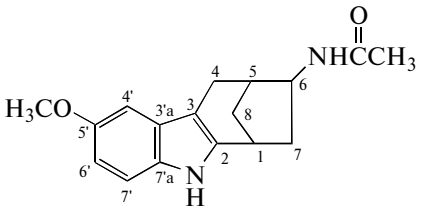
Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous hormone with immune regulatory, oncostatic, and other types of activities [1]. Melatonin receptors are protein molecules incorporated into cytoplasmic membranes and influencing the molecular signal of a hormone. Disturbances in hormonal transmission involving melatonin result in a variety of diseases, making the ligands of melatonin receptors potential therapeutic agents [2].

The properties of melatonin derivatives depend strongly on the nature and position of substituents, e.g., the simultaneous presence of methoxy-group and ethylamide side chains is crucial for the high affinity of a receptor. By restricting the conformational mobility of a molecule via the incorporation of its side chain into a cyclic fragment, different melatonin analogs can be obtained whose activities depend on the location of an acetamide substituent in the resulting cycle. The spatial structure of melatonin derivatives' ligands thus plays a crucial role in their physical and chemical properties, and finding correlations between their structures, molecular spectra, and properties can help in designing structures with specified characteristics.

This work presents the results from investigations of the IR absorption and Raman spectra of *N*-methylacetamide **I** (the simplest model system relevant to the peptides) and the conformationally restricted melatonin analog 6-acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene **II**, in which the mobility of acetamide group is restricted due to the fusion of the indole ring with bicyclooctane fragment. The structures of melatonin **III** and compound **II** are shown below:



(III)



(II)

The quantum mechanical approach using the Becke-3-parameter-Lee-Yang-Parr (B3LYP) hybrid functional [3] with the 6-31+G** basis set, which has been shown earlier as very effective with moderate computational effort for calculations of different organic molecules [4–8], was chosen as

Table 1. Experimental and theoretical structural parameters of *trans*-*N*-methylacetamide and corresponding optimized parameters of 6-acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene

N-Methylacetamide			6-Acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene	
parameter	experimental [17]	B3LYP/6-31+G**	**II**-A	**II**-B
C1–C2	1.520 ± 0.005	1.520	1.521	1.521
C2–N3	1.386 ± 0.004	1.369	1.365	1.365
N3–C4	1.469 ± 0.006	1.454	1.452	1.452
C2–O8	1.224 ± 0.003	1.228	1.231	1.231
C–H	1.106 ± 0.005	1.094	1.094	1.094
C1–C2–N3	114.1 ± 1.5	115.6	115.7	115.7
O8=C2–N3	121.8 ± 0.4	122.8	122.8	122.9
C1–C2=O8	124.1 ± 1.5	121.6	121.4	121.4
C2–N3–C4	119.6 ± 0.8	123.0	123.2	123.3
C2–N3–H9	110.0 ± 2.0	118.4	119.3	119.3
H–C–H (average)	110.4 ± 5.0	109.0	109.0	109.0

Note: For H–C–H parameter the average values are given. Bond lengths, Å; angle values, deg.

basic level of theory to interpret the investigated in this work experimental spectra.

EXPERIMENTAL

Materials and Methods

(1S,5S,6R)-6-acetylamino-(5'-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene **II** was synthesized at the Laboratory of Biologically Active Organic Compounds, Chair of Organic Chemistry, Department of Chemistry, Moscow State University. Presumably the substance is a racemic mixture of conformers and at room temperature it is a white crystalline powder with purity about ~95–96%. Vibrational spectra were investigated at the Laboratory of Molecular Spectroscopy, Department of Physical Chemistry, Moscow State University. Fourier-Transform (FT) IR absorption spectra of **I** and **II** were recorded in the region of 200 to 4000 cm^{-1} in pellets with KBr using a Tensor-27 Fourier Transform spectrometer (Bruker, Germany) with 1 cm^{-1} resolution (32 scans). FT Raman spectrum of **II** was recorded with an Equinox 55 Bruker spectrometer incorporating an integrated FRA 106S Raman module (Bruker, Germany) using excitation with 1064 nm line of a Nd-YAG laser of 300–400 mW power (resolution, 2 cm^{-1}; number of scans, 2000).

Method of Calculation

Quantum mechanical calculations were performed using the Gaussian 03 (E. 01 version) [9] and Gaussian 09 (E. 01 version) [10] software packages at the Hartree–Fock level of theory and allowing for the electron correlation within second-order perturbation theory (MP2) [11] and the density functional theory using a three-parameter B3LYP functional [3] with the 6-31G* and 6-31+G** basis sets [12]. All values of the energy differences given in this work are corrected to the zero-point vibrational energies. The geometric parameters of possible conformers of **I** and **II** were optimized without symmetry restrictions, and the harmonic force fields, vibrational frequencies, and intensities of bands in the IR absorption spectra in the gas phase were also calculated, as were the activities in Raman spectra. The Chemcraft software [13] was used to visualize the results of quantum mechanical calculations. Theoretical results for the calculated structures, vibrational frequencies, and visualized spectra are summarized in Tables 1–3 and shown in Figs. 1–5. The transformation of the quantum chemical force field to the redundant system of internal coordinates, the normal coordinate analysis, and the calculation of potential energy distribution on the vibrations of the studied conformers of **I** and **II** were carried out using the SPECTRUM software package [14, 15]. The potential energy distribution was calculated by the equation proposed in [16]; a description of the internal coordinates introduced for **I** and **II** is given in the footnotes of Tables 2 and 3.