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Vibrational and electronic spectroscopic studies of melatonin

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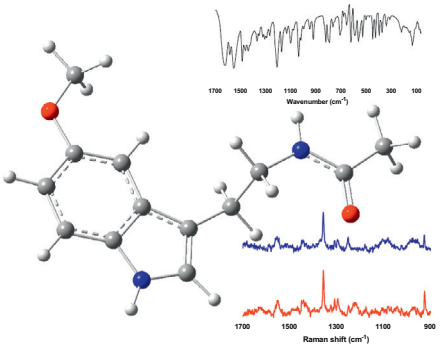
HIGHLIGHTS

- IR spectra of melatonin in 3600–2700 and 1700–70 cm^{-1} regions are reported.
- Raman spectra recorded with 488 and 632.8 nm excitations are also included.
- Structure optimized with DFT. Vibrational frequencies and PED calculated.
- IR and Raman bands assigned. N—H stretch frequency mismatch is due to H-bonding.
- UV–Vis spectrum recorded and compared with spectra calculated from TD-DFT method.

GRAPHICAL ABSTRACT



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ABSTRACT

We report the infrared absorption and Raman spectra of melatonin recorded with 488 and 632.8 nm excitations in 3600–2700 and 1700–70 cm^{-1} regions. Further, we optimized molecular structure of the three conformers of melatonin within density functional theory calculations. Vibrational frequencies of all three conformers have also been calculated. Observed vibrational bands have been assigned to different vibrational motions of the molecules on the basis of potential energy distribution calculations and calculated vibrational frequencies. Observed band positions match well with the calculated values after scaling except N—H stretching mode frequencies. It is found that the observed and calculated frequencies mismatch of N—H stretching is due to intermolecular interactions between melatonin molecules.

Introduction

The indole hormone N-acetyl-5-methoxytryptamine, also known as melatonin, is an important biological compound. It is found in various living species including mammals, in which it is primarily produced by the pineal gland during night [1,2]. Melatonin is responsible for regulation of seasonal reproductive cycles and transmission of photoperiodic information [3]. It also takes part in variety of neuroendocrine, cellular and physiological processes [4]. Melatonin is a potent antioxidant [5–8] as it reduces oxidative cellular and molecular damage, effectively [5]. Hence, study of melatonin is important due to its antioxidant properties, since oxidative stress is considered to be responsible for several diseases such as cancer, cardiovascular disorders, atherosclerosis and several neurological disorders including Parkinson's and Alzheimer's diseases. Some studies also suggest that melatonin is a efficient endogenous free radical scavenger [9]. It is further established in literature that melatonin acts as cytoprotective agent against many highly toxic materials like paraquat and carbon tetrachloride [10].

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Vasilescu and Broch [11] reported four minimal energy conformations of melatonin from *ab initio* and semi-empirical quantum computations. Conformational studies of the molecule using PM3, AM1 and wave-function based methods have also been reported [12–14]. Bayari and Ide [12] also reported its infrared spectrum. A comprehensive study of the conformational space of melatonin by Fogueri et al. [15] has recently appeared in literature. These authors have determined conformational energies for the 52 unique conformers of melatonin by correlated *ab initio* and correlation consistent composite approach methods. It is further reported that many DFT functionals are able to reproduce the accurate conformational energies when these functionals are combined with the suitable empirical dispersion correction [15].

Gunasekaran et al. [16] simulated the infrared absorption spectrum and calculated electronic excitations along with oscillator strength of electronic transitions of melatonin using density functional theory (DFT) and time-dependent-DFT (TDDFT) techniques. By comparing the theoretically calculated frequencies with the observed infrared absorption band frequencies, these authors assigned the observed bands. However, band assignments lack potential energy distribution/total energy distribution. We have also reported the infrared absorption and Raman spectra of the molecule elsewhere without assignments of observed bands except four bands [17]. Infrared absorption spectroscopy has been utilized by Andrisano et al. [18] for the study of photo-degradation of melatonin apart from other techniques. Recently, Tu et al. [19] reported surface-enhanced Raman spectra of serotonin, melatonin and other indolic molecules. Surface-enhanced Raman spectra have further been used to detect and distinguish serotonin from closely related indolic molecules [19]. However, IR spectrum in lower wavenumber region (below 400 cm^{-1}) is not reported in the literature to the best of our knowledge and assignments of Raman bands also largely remain incomplete. Therefore, in this work we report IR absorption spectrum of melatonin in 3600–2700 and 1700–70 cm^{-1} regions and Raman spectra recorded with excitations at 488.0 and 632.8 nm. All the observed bands have been assigned with the help of scaled frequencies, calculated using DFT.

Experimental and computational details

Melatonin purchased from Sigma–Aldrich Chemicals was used without further purification. IR spectra of the sample in KBr pellet were recorded with the help of Perkin Elmer Spectro 400 FTIR/FTFIR Spectrophotometer. Raman spectra were recorded on either a JY HORIBA iHR550 spectrograph, equipped with gratings of 2400 lines/mm and peltier cooled CCD or a LabRam JY HORIBA HR 800 spectrograph equipped with the Olympus Bx41 microscope and ANDOR Model DU 420-0E-323 CCD detector. Measurements were carried out either in 90° geometry with former spectrograph or back scattering geometry with the latter spectrograph. In both cases, incident light was linearly polarized and scattered light was detected unpolarized. The excitation lines at 488.0 and 632.8 nm were provided by air cooled Ar^+ and He—Ne lasers, respectively. Ultraviolet–Visible spectrum of melatonin in water was recorded with a Perkin Elmer Lambda 750 spectrophotometer.

Due to fluorescent nature of melatonin, we have removed the fluorescence background by fitting it with a non-linear curve and subtracting the fitted background from the recorded Raman spectra, as described by the authors elsewhere [20].

Computational details

DFT calculations of melatonin have been performed with the Becke hybrid exchange and the Lee–Yang–Parr [21,22] correlation functionals (B3LYP) and the 6–31 + G(d,p) and 6–311++G basis sets [23,24] using Gaussian 09 Revision C.01 program package [25]. Vibrational frequencies have been calculated for the optimized structures. Nonobservation of any imaginary frequency has confirmed that the optimized structures correspond to the true minima on the potential energy surfaces. Calculated frequencies of low energy conformer have been scaled using linear fitting ($y = mx + c$). The values of $m = 0.96369$, and 0.95272 and of $c = 12.69841$ and 6.79382 give the best fitting for 6–31 + G(d,p) and 6–311++G basis sets, respectively. Scaling of vibrational frequencies is needed due to the incompleteness of basis sets and neglect of anharmonicity in the frequency calculations. For assignments of the experimentally observed IR absorption and Raman bands, we have calculated potential energy distribution (PED) using the VEDA program [26]. The equation

$$PED = F_{ij}L_{ij}^2/\lambda_j$$

relates potential energy contribution of the jth vibrational mode to force constant F_{ij}, normalized amplitude L_{ij}, and the eigen value, λ_j. Energy contribution of less than 10% has not been considered for assignments. It is observed that deviations of calculated frequencies from the experimentally observed frequencies is minimum for 6–311++G basis set. Hence reported PED is calculated for B3LYP/6–311++G calculations.

Ultraviolet–Visible absorption spectrum of the molecule has also been simulated with time dependent-DFT technique.

Results

Optimized geometry

The geometrical structure of melatonin has been optimized for the singlet ground state with both the basis sets. We have considered three different conformers of the molecule. Conformers *tm* and *cm* are *trans*- and *cis*-melatonin based on the orientation of N12—H27 group. We have further explored two conformers, *cm*1 and *cm*2, of *cis*-melatonin, which differ in the orientation of methyl group attached to O16 atom. The optimized structure of all the conformers of melatonin, represented as *tm*1, *cm*1 and *cm*2, are shown in Fig. 1. Figure also shows the atomic numbering scheme of the molecule. Absence of any negative frequency in the calculated harmonic vibrational frequencies confirms the attainment of true minima on the potential energy surface for all the conformers. Calculated bond lengths of optimized structures of *tm*1, *cm*1 and *cm*2 conformers have been listed in Table 1. Other molecular parameters (bond angles and dihedral angles) are given separately in supplementary Table S1. Calculated values of bond lengths, bond angles and dihedral angles have also been compared with the experimental values taken from the X-ray structure data available in the literature [27,28]. The energy of *tm*1 conformer is lower than conformer *cm*1 by 2.36 and 3.29 kcal/mol with basis sets 6–31 + G(d,p) and 6–311++G, respectively, whereas the energy of *cm*2 is higher than *cm*1 by 0.83 kcal/mol and 0.68 kcal/mol for basis sets 6–31 + G(d,p) and 6–311++G, respectively. Since the difference in energy of three conformers is very small, possibility of their coexistence in vapour phase cannot be ruled out. However, conformer *tm*1 is similar to the observed crystal structure of the molecule, therefore, further discussion is based on this conformer, except stated otherwise.

From Table 1, it is clear that there are differences between calculated bond lengths and experimental bond lengths [27] irrespective of the conformer and basis set. The standard deviations in the calculated values of bond lengths are 0.016 and 0.019 for the basis sets 6–31 + G(d,p) and 6–311++G, respectively for *trans* (*tm*1) and *cis*-conformers (*cm*1 and *cm*2). For 6–31 + G(d,p) basis set calculated lengths of C10—C11, N12—C13 and C13—C15 bonds are larger