IR Spectra and Molecular Structure of Melatonin: A Computational Study

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ABSTRACT

The molecular structure and Infrared spectra of one of the most stable conformers of melatonin (N-acetyl-5-methoxytryptamine) have been systematically investigated by ab initio (MP2) and density functional theory (B3LYP and M06-2X density functional) calculations. Vibrational assignments have been made and many previous assignments in IR spectra are amended. The calculated DFT frequencies and intensities at B3LYP/6-311++G (2d, 2p) level, particularly in the hydride stretching region, were found to be in better agreement with the experimental gas phase IR frequencies. The indole N-H and amide N-H stretching modes of melatonin (B) are predicted at 3524 and 3490 cm^{-1} respectively where former has greater intensity in comparison to later. The calculated TD-DFT vertical excitation electronic energies of the valence excited states of melatonin are found to be in consonance to the experimental absorption peaks and the second lowest excited singlet state ^1L_a ($^1\pi\pi^*$) state, was found about 2750 cm^{-1} above the ^1L_b state for the gas phase MEL B.

Keywords: Melatonin (N-acetyl-5-methoxytryptamine), Infrared spectra and molecular structure, DFT calculation, Electronic excitation energies

1. INTRODUCTION

Melatonin, N-acetyl-5-methoxytryptamine (NA-5-MT), is a naturally occurring hormone that has been found in all life forms [1, 2]. It is also a well-known antioxidant that protects DNA, lipids and proteins from free radical damage [3-6]. Melatonin was first isolated from bovine pineal tissue by Aaron Learner and colleagues [1]. In human it is primarily produced in the pineal gland, in small quantities in the retina, and in other tissues, with highest levels produced during the night [1, 2]. Melatonin acts by specific binding to membrane receptors located in various regions of the brain and plays an important role as a transmitter of photoperiodic information, regulation of circadian rhythms and seasonal reproductive cycles, and mediation of other neuroendocrine and physiological processes [2]. Melatonin (NA-5-MT) is involved in the sleep-wake cycle, functions of the immune and cardiovascular systems, and cell regulation [2]. Age related reduction of

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melatonin has been correlated with disturbance of sleep, deterioration of health and chronic diseases related to oxidative damage, including cancer [3-7].

Melatonin (NA-5-MT) (See Fig. 1) contains a single methyl caped amide group. It possesses two flexible side chain: the N-acetyl ethylamine side -chain at the 3-position on indole and the methoxy group at the 5-postion.This change in structure reduces the complexity of the pathways to isomerisation on potential energy surface. The conformational flexibility of the N-acetyl-ethylamine side chain in NA-5-MT plays an important role in its binding to receptor sites, therefore melatonin is expected to be high relevant for the drug-receptor interaction and molecular recognition. As stated above Melatonin possesses many flexible degrees of freedom, which produce a highly corrugated potential energy surface with several conformational minima. A molecular level understanding under physiological conditions is often hampered by the coexistence of several conformational isomers, the difficulty in assessing solvent effects, and the potential for rapid interconversion between conformational minima. The study of such molecules in the gas phase removes solvent effects, thereby enabling the effects of intra-molecular interactions to be assessed. Florio et al [2] reported the conformational preferences of the isolated melatonin in a molecular beam using a combination of two-color resonant two photon ionisation (2C-R2PI), laser induced fluorescence (LIF), fluorescence-dip infrared spectroscopy (FDIRS) and UV-UV hole burning spectroscopy. Dian et al [8] studied the infrared-induced conformational isomerization and vibrational dynamics in melatonin using IR-UV hole filling spectroscopy and IR-induced population transfer spectroscopy. The above studies in the gas phase, by group of Zwier [2, 8], have sought to probe the conformational preferences of isolated melatonin free from solvent effects and to obtain the spectroscopic signatures of the individual conformations. Five experimentally observed conformational isomers for melatonin divide into two families: trans-amide (three dominant conformers A, B & C) and cis-amide (two minor conformers D & E) [2]. There is a strong energetic preference in NA-5-MT for trans amide over cis-amide conformation, with the former about 3 kcal/mole more stable than latter [2]. Several groups [9-15] reported the IR, electronic spectroscopy and/or quantum chemical calculations for melatonin however result of their work seems to be incomplete and needs further modification. Crystal and molecular structure of melatonin were also reported [16, 17]. Since conformational preferences and single conformational spectroscopy of melatonin are reasonably well understood, we focus our attention on the IR and electronic spectra and molecular structure of the most stable conformer B. The nomenclature for the conformers of melatonin follows the suggestion of Florio et al [2]. The purpose of the present study is to characterize the vibrational fundamentals of the reported IR spectra of NA-5-MT by comparing the vibrational modes of the most stable conformer B obtained from density functional

theory calculations [17, 18] invoking higher basis sets. Present calculations have aided the interpretation of IR spectra more systematically and many previous incomplete and ambiguous assignments have been analyzed and amended. The optimized geometry of the NA-5-MT was characterized theoretically for the first time using M06-2X calculation [19] employing the higher basis sets 6-311++G(d, p). The electronic absorption spectra was analyzed and assigned by using the Time Dependent Density Functional Theory (TD-DFT) calculations [20] for the vertical electronic excitation energies of NA-5-MT.

2. COMPUTATIONAL METHODS

Electronic structure calculations have been performed using the Gaussian 09 software package [18]. The ground state molecular structure of NA-5-MT has been optimized using the second order Moller-Plesset (MP2) perturbation theory [21] and the density functional theory employing the B3LYP [17, 22], exchange-correlation functional. DFT calculations using Becke's three parameter hybrid exchange functional (B3) [17, 22] with correlation functions such as one proposed by Lee, Yang and Parr (LYP) [23] and with newly developed M06-2X exchange-correlation functional [23] Theoretical methods described above were applied to a molecular geometry without symmetry restrictions. All optimized structures have been verified as minima by performing frequency calculations, in order to ensure that no imaginary frequency were present. The 6-31+G(d), 6-311++G(d, p) and 6-311++G(2d, 2p), basis sets were employed in the geometry optimization and vibrational modes calculation of NA-5-MT. MP2 optimized geometry could be obtained employing the basis set 6-31+G(d) level. All harmonic frequencies were obtained at B3LYP/6-311++G(2d, 2p) level using the B3LYP/6-311++G(d, p) optimized geometry. The computed DFT harmonic frequencies were scaled by 0.965 factor to compare with experimental results. On the basis of DFT optimized structures for the ground state, TD-DFT method [20] with 6-311++G(d, p) basis set were used to predict vertical excitation energies and to assign the electronic absorption peaks.

3. RESULTS AND DISCUSSION

3.1 Optimized geometries of NA-5-MT

The ground state geometry of NA-5-MT (MEL) B, which has been optimized using DFT theory at B3LYP/6-311++G (d, p) level is presented in Fig.1. The structural parameters (bond lengths and selected bond angles) of MEL B as calculated at B3LYP/6-311++G (d, p) and M06-2X/6-311++G (d, p) levels are listed in Table 1. Previously reported crystal structure data are also included in Table 1, to assess the accuracy of the geometry optimizations. The calculated bond distances and bond angles (particularly at B3LYP/6-311++G (d, p) level) are found very close to the reported

experimental molecular structure data in most cases. Molecular structure data of NA-5-MT (B) calculated at MP2/6-31+G(d), is available with authors.

3.2 Comparison between calculated and experimental Vibrational spectra

NA-5-MT (MEL) molecule contains 33 atoms and its all 93 fundamental modes are Infrared active. IR spectra can provide a more direct and sensitive probe of the conformations of flexible bio-molecules. Experimental wave numbers obtained from gas phase IR spectra and conventional IR spectra of Melatonin (NA-5-MT) have been compared with computed ab initio and DFT IR frequencies of the lowest energy conformer B. Ab initio harmonic vibrational wave numbers are typically larger than the fundamentals. The disagreement in this region is partly due to a large anharmonicity of NH & CH-stretching vibrations. The DFT values at basis set 6-311++G(2d, 2p) are found to be in better agreement with the experimental values. The B3LYP wavenumbers are more near in comparison to M06-2X wavenumbers with experimental values. A scaling factor (0.965) for the vibrational wavenumbers in NH-stretching region was found necessary to obtain a good agreement with the experimental values. The predicted relative intensities were also found to be in good agreement with the experimental values for most of the vibrational modes. The unscaled computed harmonic wave numbers and relative intensities at DFT-B3LYP/6-311++G(2d, 2p) level is shown in Fig. 2.

3.2.1Region 4000-2000 cm^{-1}

Briefly to simplify the interpretation of complex vibrational spectra of MEL B, in this region the vibrations can be divided into three groups: the heterocyclic system of indole, the acetyl ethylamine side chain (or group) and a methoxy group OCH_3. The infrared spectra of the MEL conformers exhibit two NH stretch fundamentals (the indole NH & amide NH) in the 3400-3600 cm^{-1} region, and a collection of aromatic, alkyl, and methyl CH stretch fundamentals spread over the region from 2800 to 3100 cm^{-1}. In all five conformers, the indole NH stretch vibration mode appears between 3522 cm^{-1} and 3526 cm^{-1} in gas phase experimental IR (RDIR and FDIR) spectra [2], very close to its frequency in the indole monomer (3525 cm^{-1}). Our calculations predicted the indole NH stretch vibration mode of MEL B at 3524 cm^{-1}, exactly similar to gas phase IR value. Not surprisingly, this fundamental is not sensitive to the conformations of the side chains of MEL. Surprisingly Bayari and Ide [12] reported that they did not observed indole NH stretch in conventional IR spectra, which seems to be ambiguous. The amide NH stretch fundamentals of conformer B appear at 3495 cm^{-1} in the experimental RIDIR and FDIR (gas phase) spectra [2]. Our calculations predicted the amide NH stretch vibration mode at 3490 cm^{-1}, very close to the corresponding experimental IR frequency [2]. Intensity of indole NH stretch band is predicted greater in comparison to amide NH stretch band (See Fig. 2) is found in consonance to the

experiment [2]. Singh et al [13] assigned the bands observed at 3302 cm^{-1} and 3280 cm^{-1} in the conventional IR spectra, as NH stretching modes. Infact, these two bands represent the indole NH and amide NH stretching modes and are significantly red shifted due to intermolecular interactions in condense phase.

The CH stretch region of each conformer of MEL is unique and can potentially serve as a confirming diagnostic of the molecular conformation. In fact, the assignment of the vibrations of -CH_2 is very difficult because of the presence of the -CH_3 group. For the methoxy group, the methyl asymmetric stretch can fall between 2970 and 2920 cm^{-1}. The symmetric stretch of a methoxy group falls between 2830 and 2842 cm^{-1}. The most intense band observed in the CH stretch region is observed at 2837 cm^{-1} and predicted by our DFT calculations at 2888 cm^{-1}, was attributed to symmetric CH_3-stretching vibration in methoxy group. The Zwier's group [2] reported that the methoxy methyl group produces three CH stretch fundamentals spread over the 2800-3000 cm^{-1} region. The symmetric methyl stretch occurs at 2837 cm^{-1}, while the two “antisymmetric” methyl CH stretch bands appear at 2902 and at 2952 cm^{-1}. Our calculated symmetric and asymmetric methoxy methyl stretch frequencies for MEL B are obtained at 2888 cm^{-1} (symmetric), 2940 cm^{-1} (antisymmetric) and 3000 cm^{-1} (antisymmetric) respectively. The experimental gas phase spectrum contains only two other CH stretch bands (3010 and 3042 cm^{-1}), ascribable to the aromatic CH stretch fundamentals of the indole moiety which are predicted to occur at 3039 cm^{-1} and 3068 cm^{-1} respectively by our DFT calculations. CH-stretching mode of pyrrole ring of indole predicted at 3106 cm^{-1}. Computed CH stretching modes overestimate the experimental value due to high anharmonicity of CH-stretching mode.

3.2.2Region 2000-400 cm^{-1}

The carbonyl group exhibits a strong absorption band due to C=O stretching vibration and is observed in the region 1850-1550 cm^{-1}. We ascribed the strong band observed at 1630 cm^{-1} [12] at 1624 cm^{-1} [13] in the conventional IR spectrum of NA-5-MT [12, 13] and predicted by our DFT calculations at 1655 cm^{-1}, to the C=O stretching mode. Conventional IR spectrum [13] exhibits a strong band at 1554 cm^{-1} and medium weak band at 1513 cm^{-1} in the IR spectrum and predicted at 1591 and 1557 cm^{-1} are assigned to the C=C stretching modes. The intense IR band observed at 1488 cm^{-1} and predicted at 1489 cm^{-1} is ascribed mainly to CN stretching and NH bending modes. Conventional IR spectrum [13] exhibits a medium band at 1370 cm^{-1} in the IR spectrum [12, 13] which is assigned to the symmetric CH_3 deformation for the acetyl group. In the IR spectrum of NA-5-MT, the very strong band at

1212 cm^{-1} is assigned to mixing of C-OCH_3 stretching and CH_3 & CH_2 deformation and its shoulder (See Fig. 2) as mixing of N-H bending and C-N stretching mode. We assigned bands at 796 cm^{-1} and 769 cm^{-1} in the IR spectra of NA-5-MT to the CH wagging mode.

3.3 Electronic spectra and Vertical Electronic Excitation Energies

In order to investigate at least the prediction of electronic absorption transition wavelengths, a relatively more accurate time dependent density functional theory (TD-DFT) is available in Gaussian 09. The time dependent formulation of density functional theory [35] proved to yield electronic excitation energies that are closest to experiment in previous work [24]. The strength of this method is expected to be better for low lying excited states transitions well below the ionization threshold of melatonin. Therefore, TD-DFT calculations have been carried out to determine the vertical excitation energies of low-lying excited electronic states of conformer B of NA-5-MT employing 6-311++G(d, p) basis set. The work described by Zwier's group [2] is truly wonderful in its detail for experimental gas phase structures and corresponding lowest energy transitions of melatonin lowest energy conformers, however their TD-DFT calculations overestimates the transition energies. Our calculated TDDFT vertical electronic excitation energies of NA-5-MT are found in consonance to experimentally observed absorption peaks [13]. It is well known that the excited state dynamics of indole derivatives are described in terms of the low lying $\pi\pi^*$ and $n\pi^*$ excited states. Much of what we currently know about the mechanism of the photochemistry of indole derivative is based on the detailed spectroscopic study of its aromatic chromophore indole. It has been established that the ^1L_b state is the lowest excited state in the gas phase, while the ^1L_a state becomes the lowest -energy state in polar solvents . Present calculations predicted the second lowest singlet excited state is the ^1L_a ($^1\pi\pi^*$) state, about 2750 cm^{-1} above the ^1L_b state for MEL B and this energy is found consistent with the absorption spectrum of NA-5-MT.On the basis of TDDFT calculations, the lowest energy singlet excitation can be assigned to S0 - S1 transition from highest occupied molecular orbital (HOMO) to lowest unoccupied molecular orbital (LUMO) and corresponds to observed electronic absorption shoulder peak at 283 nm of MEL [13].The excitation to the second excited singlet state ^1L_a, is mainly HOMO-1→LUMO character and corresponds to observed intense electronic absorption peak at 264 nm of MEL [13]. Zwier's group [2] reported that the $S_0 \rightarrow S_1$ origin transitions of methoxy indole and melatonin are shifted to red of the indole by 2103 cm^{-1} and 2400-2800 cm^{-1} respectively. In a recent publication on 5-methoxyindole [25], it was mentioned that the methoxy substituent introduces an additional node in the molecular orbital, which was formerly the HOMO-1 in indole, and which becomes the HOMO in 5-methoxyindole. This causes a change in energy ordering between indole, 5-methoxyindole and melatonin for the HOMO and HOMO-1, respectively, and is responsible for the

altered excitation scheme of melatonin compared to indole. So it is clear that the excitation schemes for the ^1L_a and ^1L_b states in melatonin are different than those of indole. It is the presence of the methoxy group at the C5 position that is responsible for the dramatic stabilization of the excited electronic state of melatonin with respect to that of indole [2].

4. CONCLUSION

The optimized geometry, harmonic vibrational wave numbers and intensity of MEL B were calculated by MP2 and DFT (using B3LYP and M06-2X functional) calculations employing higher basis sets 6-31+G(d), 6-311++G(d, p) and 6-311++G(2d, 2p). In most cases the calculated bond lengths and bond angles are found very close to the reported crystal structure data. Vibrational assignments have been approximated for each experimental IR fundamentals of NA-5-MT and our calculated values were found very close to corresponding experimental wave numbers in comparison to previous reported values. The electronic spectra of NA-5-MT are analyzed and assigned well by TD-DFT vertical electronic excitation energies and the second lowest singlet excited state ^1L_a ($^1\pi\pi^*$) state, was found about 2750 cm^{-1} above the ^1L_b state for the gas phase MEL B.

5. ACKNOWLEDGEMENT

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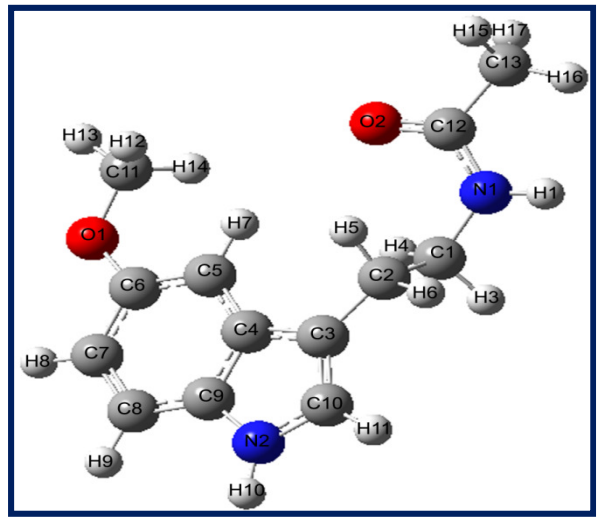

Fig. 1 Optimized geometry of the most stable conformer (B) of melatonin (N-acetyl-5-methoxytryptamine) at B3LYP/6-311++G(d, p) level.

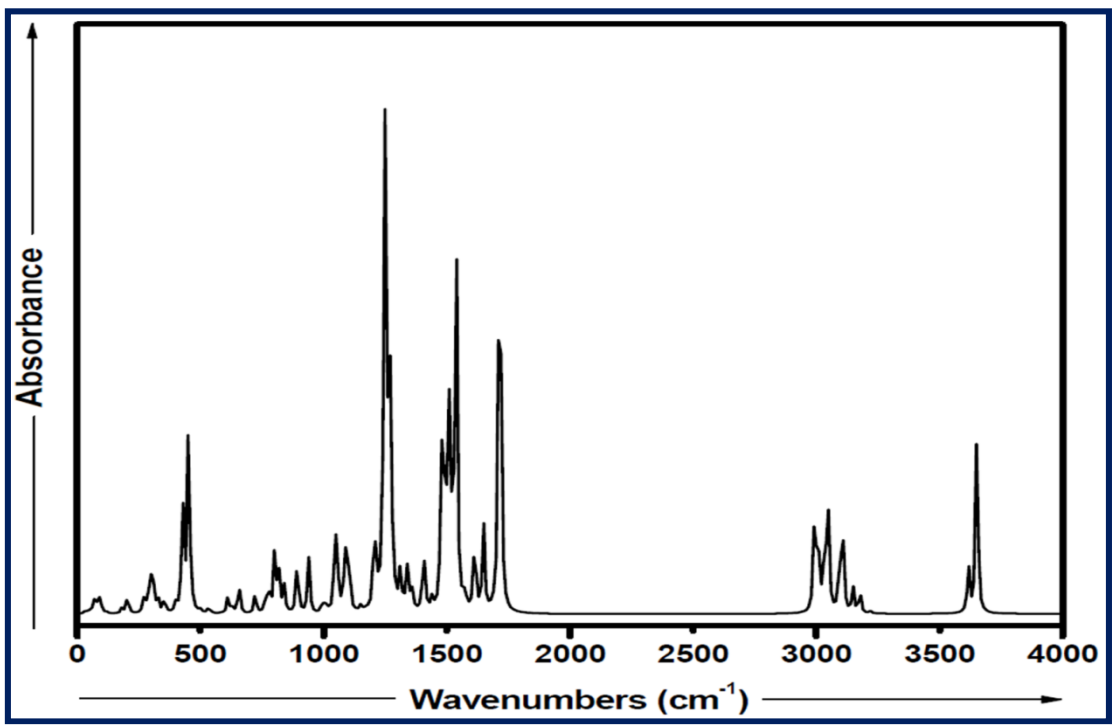

Fig. 2 Theoretical IR spectra of the most stable conformer (B) of melatonin (N-acetyl-5-methoxytryptamine) at B3LYP/6-311++G(2d, 2p) level.

Table 1: Selected calculated structural parameters of the most stable conformer (B) of melatonin (N-acetyl-5-methoxytryptamine)

Parameters [a]	Exptl. [b]	Exptl. [c]	6-311++G(d, p)	
			B3LYP	M06-2X
Bond lengths [Å]				
C1-C2	1.501	1.505	1.544	1.538
C2-C3	1.491	1.500	1.499	1.495
C3-C4	1.425	1.443	1.441	1.437
C4-C5	1.406	1.408	1.409	1.407
C4-C9	1.400	1.413	1.413	1.405
C5-C6	1.368	1.376	1.388	1.383
C6-C7	1.398	1.407	1.414	1.414
C7-C8	1.369	1.372	1.383	1.379
C8-C9	1.391	1.389	1.398	1.399
C9-N2	1.368	1.383	1.383	1.380
N2-C10	1.370	1.367	1.381	1.379
C10-C3	1.354	1.369	1.373	1.368
C6-O1	1.379	1.382	1.371	1.363
O1-C11	1.409	1.416	1.421	1.414
C1-N1	1.449	1.445	1.459	1.455
N1-C12	1.326	1.329	1.364	1.359
C12-O2	1.236	1.239	1.224	1.219
N1-H1	0.970	0.850	1.007	1.006
C1-H3	1.090	0.970	1.092	1.091
C1-H4	1.090	0.980	1.092	1.091
C2-H5	1.070	1.010	1.094	1.095
C2-H6	1.050	0.970	1.095	1.093
C5-H7	1.060	0.960	1.082	1.084
C7-H8	1.050	0.960	1083	1.083
C8-H9	1.080	0.910	1.084	1.084
N2-H10	0.900	0.900	1.005	1.005

Parameters [a]	Exptl. [b]	Exptl. [c]	6-311++G(d, p)	
			B3LYP	M06-2X
C11-H12	1.110	1.030	1.095	1.095
C11-H14	1.120	0.960	1.095	1.094
C13-H15	1.090	0.930	1.091	1.090
C13-H16	1.070	0.940	1.091	1.091
Bond angles [°]				
C2-C3-C4	125.4	125.2	125.8	123.8
C2-C3-C10	128.6	129.3	127.7	129.8
C4-C3-C10	106.0	105.5	106.4	106.4
C3-C4-C5	132.7	132.6	132.7	131.7
C3-C4-C9	107.8	107.5	107.3	107.5
C5-C4-C9	119.4	119.8	119.9	120.8
C4-C5-C6	118.4	118.2	118.2	117.7
C5-C6-C7	121.0	121.2	121.0	121.1
C5-C6-O1	124.4	124.1	124.3	123.9
C7-C6-O1	114.7	114.7	114.6	114.9
C6-C7-C8	122.1	121.3	121.2	121.5
C7-C8-C9	117.1	118.1	117.9	117.7
C4-C9-C8	122.0	121.3	121.5	121.2
C4-C9-N2	106.9	107.2	107.3	107.3
C8-C9-N2	131.1	131.5	131.1	131.5
C3-C10-N2	110.3	111.2	109.9	109.8
C13-C12-O2	121.8	121.5	121.7	121.6
N1-C12-O2	121.1	121.3	122.3	122.1
C9-N2-C10	108.9	108.6	108.9	109.0
C6-O1-C11	117.0	117.3	117.9	116.7

[a] See Fig. 1 for the atom numbering.

[b] Ref. [17]; [c] Ref. [15].