Spectral and Structural Perspectives of 1,3,3-Trimethyl-2,6-diphenylpiperidin-4-one

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Abstract: In this work, we report spectral, structural and computational studies on 1,3,3-trimethyl-2,6-diphenylpiperidin-4-one (TMP). The molecular structure of the title compound in the ground state has been investigated by DFT-B3LYP method with 6-311G (d,p) basis set. The optimized structural parameters of the title compound acquired from DFT method has been found in accord with the single crystal XRD values. Vibrational and Mulliken analysis, frontier molecular orbitals and molecular electrostatic potential of the title compound have also been calculated and discussed. The small energy gap (E_{HOMO}-E_{LUMO}) show that the charge transfer occurs within the molecule.

Keywords: 2,6-diphenylpiperidin-4-one, DFT, ^1H and ^{13}C NMR spectra, stereochemistry.

I. INTRODUCTION

Piperidine structural motif is found incorporated in a large number of alkaloids available naturally. Besides, it is also functionally important unit in medications and used as a building block in the synthesis of pharmaceuticals which are used as SSRIs (selective serotonin reuptake inhibitors) [1], neuroleptics (antipsychotics) [2], opioids [3] and anticancer compounds [4]. Similarly, piperidin-4-one derivatives are considered as a ubiquitous structural unit as it possesses both nucleophilic (NH) and electrophilic (-CO-) centres which could be modified and aid in building or expanding the structures conveniently. This is evidenced by the availability of literature reports [5-10] about the biologically active compounds of the piperidin-4-one.

There has been a constant interest for exploring the structure and reactivity of the molecules either existing or newly synthesized. In this regard, significant number of such studies revealing the properties experimentally as well as theoretically for piperidin-4-one analogues [11-14]. These studies explored the probable properties of interest related to biological applications [15-17], NLO properties and others [18-23]. Our research group is also interested in that and reported [24] the theoretical studies in addition to the experimental data obtained for a piperidin-4-one derivative.

In continuation of our works related to piperidin-4-one compounds, herein we report the combined structural investigation of 1,3,3-trimethyl-2,6-diphenylpiperidin-4-one (TMP), a six membered heterocyclic ring motif derived from 3-methylbutan-2-one, benzaldehyde and ammonium acetate by Mannich condensation and further methylation with methyl iodide. After crystallization, a single crystal of suitable size was analyzed to get the XRD data [25]. This experimental data was chosen as the basis and theoretical studies using DFT method has been carried out and the results were interpreted in this article.

II. METHODOLOGY

A. General

The solvents used for recrystallization was of analytical grade and used without further purification. Precoated silica gel on aluminum sheets (Type 60 GF254, Merck) were used for monitoring the reaction by thin layer chromatography. The Fourier Transform infra red spectrum was recorded on an AVATAR–330 FT–IR spectrometer (Thermo Nicolet) using KBr in pellet form. The ^1H and ^{13}C NMR spectra were recorded at operating frequencies of 400 MHz and 100 MHz, in a Bruker ULTRASHIELD 400 PLUS instrument, using deuterated chloroform as the solvent. About 10 mg and 50 mg of the compound (TMP) was taken respectively for recording ^1H NMR and ^{13}C NMR spectra. As an internal reference, tetramethylsilane (TMS) was used for both ^1H and ^{13}C NMR spectra, with chemical shifts reported in δ units (parts per million) relative to the standard. The signals in the ^1H NMR spectrum are designated as singlet (s), broad singlet (bs), doublet (d), doublet of doublet (dd), triplet (t) and multiplet (m) and the coupling constants are expressed in Hertz (Hz).

B. Synthesis of 1,3,3-trimethyl-2,6-diphenylpiperidin-4-one

Good quality plagiarism software/ tool (Turnitin / The title compound (TMP) was synthesized [25] by following the procedure reported in the literature.

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C. Computational Details

Theoretical calculation for the title compound (TMP) has been performed with the Gaussian 09W packages [26]. Geometry optimization of TMP in ground state has performed using hybrid functional B3LYP with a 6-311G (d,p) basis set for all the atoms in gaseous state. The vibrational and Mulliken analysis, frontier molecular orbitals (FMOs) and molecular electrostatic potential (MEP) are calculated in order to understand the molecular interaction with another species around the space.

III. RESULTS AND DISCUSSION

A. Molecular Geometry

The molecular crystal of TMP has grown by slow evaporation technique using ethanol at room temperature. TMP has crystallized in the triclinic system with P-1 space group and four molecules are available per unit cell. An ORTEP view and the numbering scheme of TMP are shown in **Figure 1**. The structural features acquired by X-ray crystallographic analysis of the molecule TMP has been compared with the theoretically deduced one are tabulated in **Table 1.**
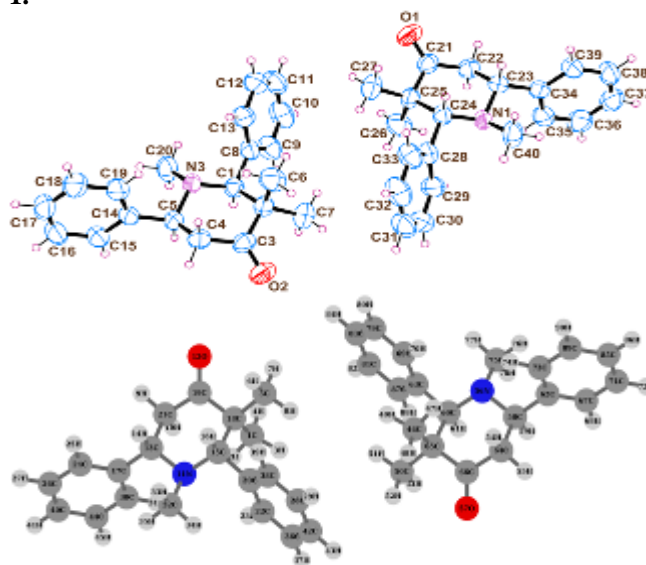

Figure 1 ORTEP view and numbering scheme of TMP

Table 1 Experimental and theoretical data pertaining to optimized molecular geometry of TMP

Bond Length	Calc.	Expt.	Bond Length	Calc.	Expt.
C1-C18	1.552	1.524(4)	C18-C19	1.529	1.515(4)
C5-C18	1.539	1.529(4)	C19-C21	1.504	1.492(4)
N11-C13	1.491	1.472(3)	C20-C22	1.405	1.380(4)
N11-C15	1.497	1.478(3)	C20-C38	1.402	1.380(4)
N11-C32	1.484	1.462(3)	C22-C36	1.396	1.379(4)
O12-C19	1.242	1.209(3)	C24-C26	1.398	1.387(4)
C13-C17	1.524	1.511(4)	C26-C40	1.396	1.356(4)
C13-C21	1.548	1.524(4)	C28-C38	1.398	1.384(4)
C15-C18	1.586	1.562(4)	C28-C42	1.397	1.356(5)
C15-C20	1.525	1.513(4)	C30-C44	1.396	1.374(4)
C17-C24	1.4	1.377(4)	C36-C42	1.399	1.362(4)
C17-C30	1.404	1.385(4)	C40-C44	1.399	1.373(4)
Bond Angle	**Calc.**	**Expt.**	**Bond Angle**	**Calc.**	**Expt.**
C13-N11-C15	113.5	112.0(2)	O12-C19-C18	122.7	123.1(3)
C13-N11-C32	109.6	108.2(2)	O12-C19-C21	121.7	121.4(3)
C15-N11-C32	111.1	108.5(2)	C18-C19-C21	115.6	115.4(3)
N11-C13-C17	112.2	110.7(2)	C15-C20-C22	121.7	121.6(3)
N11-C13-C21	111.3	110.5(2)	C15-C20-C38	119.9	120.9(3)
C17-C13-C21	109.2	109.7(2)	C22-C20-C38	118.4	117.5(3)
N11-C15-C18	112.9	112.9(2)	C13-C21-C19	111.6	111.4(3)
N11-C15-C20	111.2	109.8(2)	C20-C22-C36	120.7	121.2(3)
C18-C15-C20	111.7	111.9(2)	C17-C24-C26	120.7	121.0(3)
C13-C17-C24	120.4	120.7(3)	C24-C26-C40	120.1	120.4(3)
C13-C17-C30	120.8	121.4(3)	C38-C28-C42	120.1	120.7(3)
C24-C17-C30	118.8	117.9(3)	C17-C30-C44	120.6	120.6(3)
C1-C18-C5	109.4	109.3(3)	C22-C36-C42	120.3	120.5(4)
C1-C18-C15	112.6	112.9(3)	C20-C38-C28	121	120.8(3)
C1-C18-C19	107.7	106.2(2)	C26-C40-C44	119.6	119.3(3)
C5-C18-C15	110.2	109.4(2)	C28-C42-C36	119.5	119.4(4)
C5-C18-C19	109.7	109.7(2)	C30-C44-C40	120.2	120.7(4)
C15-C18-C19	107.2	109.3(2)			
Dihedral Angle	**Calc.**	**Expt.**	**Dihedral Angle**	**Calc.**	**Expt.**
C15-N11-C13-C17	176.1	-179.5(2)	C13-C17-C24-C26	176.9	179.4(3)
C15-N11-C13-C21	53.5	58.8(3)	C30-C17-C24-C26	-0.2	-0.4(5)
C32-N11-C13-C17	-59	-59.8(3)	C13-C17-C30-C44	-177.1	-179.8(3)
C32-N11-C13-C21	178.4	178.4(2)	C24-C17-C30-C44	-0.1	0(5)
C13-N11-C15-C18	-55.7	-56.9(3)	C1-C18-C19-O12	-111.7	-103.7(3)
C13-N11-C15-C20	177.9	177.5(2)	C1-C18-C19-C21	68.7	74.6(3)
C32-N11-C15-C18	-179.8	-176.4(2)	C5-C18-C19-O12	7.4	14.3(4)
C32-N11-C15-C20	53.8	58.0(3)	C5-C18-C19-C21	-172.2	-167.4(3)
N11-C13-C17-C24	133.9	125.2(3)	C15-C18-C19-O12	127	134.2(3)
N11-C13-C17-C30	-49.1	-55.0(4)	C15-C18-C19-C21	-52.7	-47.5(3)

C21-C13-C17-C24	-102.2	-112.5(3)	O12-C19-C21-C13	-126	-130.3(3)
C21-C13-C17-C30	74.8	67.3(4)	C18-C19-C21-C13	53.6	51.4(4)
N11-C13-C21-C19	-51.2	-55.1(3)	C15-C20-C22-C36	178.9	-177.1(3)
C17-C13-C21-C19	-175.5	-177.5(2)	C38-C20-C22-C36	-0.8	1.3(5)
N11-C15-C18-C1	-65.8	-68.7(3)	C15-C20-C38-C28	-178.7	177.3(3)
N11-C15-C18-C5	171.7	169.5(2)	C22-C20-C38-C28	0.9	-1.2(5)
N11-C15-C18-C19	52.4	49.3(3)	C20-C22-C36-C42	0.1	-0.5(6)
C20-C15-C18-C1	60.4	55.8(3)	C17-C24-C26-C40	0.2	0.6(5)
C20-C15-C18-C5	-62.1	-66.1(3)	C24-C26-C40-C44	0	-0.5(5)
C20-C15-C18-C19	178.6	173.8(2)	C42-C28-C38-C20	-0.4	0.3(6)
N11-C15-C20-C22	46.2	43.5(4)	C38-C28-C42-C36	-0.4	0.5(6)
N11-C15-C20-C38	-134.2	-135.0(3)	C17-C30-C44-C40	0.3	0.2(6)
C18-C15-C20-C22	-81	-82.7(3)	C22-C36-C42-C28	0.5	-0.4(6)
C18-C15-C20-C38	98.6	98.9(3)	C26-C40-C44-C30	-0.3	0.1(6)

The optimized structural parameters *i.e.* bond lengths, bond angles and dihedral angles of TMP have been determined using DFT-B3LYP method with 6-311G (d,p) basis set. The theoretical results revealed that the piperidine ring adopts a chair conformation which is indicated by the dihedral angles between the planes C13-C21 and C15-C18 as -51.2 [-55.1(3)] and 52.4 [49.3(3)]. Moreover, the two phenyl rings connected to the piperidine ring equatorially with the terminal bond angles of C13 and C15: 109.2 [109.7(2)] and 111.7 [111.9(2)], respectively. The optimized carbon-carbon (C-C, C=C) bond lengths in piperidine and phenyl rings are falling in the range (1.54 and 1.39Å); which are closer to the experimental values for carbon-carbon bond (1.52 and 1.38Å). Theoretically investigated N11-C32 (1.484Å), N11-C13 (1.491Å) and N11-C15 (1.497Å) are typical single bonds which agree well with the experimental ones. The bond length associated with carbonyl function (C=O/1.242Å) is closer to the experimental deduced C=O bond length (1.209(3) Å). The other bond lengths and angles computed by DFT calculations show good agreement with the corresponding single crystal XRD values.

Vibrational Analysis

The FT-IR spectrum of TMP has been recorded in the frequency range of 400-4000 cm^{-1} and shown in **Figure 2**. The strong and sharp absorption zone arises in the region of 1600-1750 cm^{-1} in the spectrum is assigned to carbonyl group present in the molecule [27]. The TMP showed strong absorption peak at 1713 cm^{-1} which reveals the presence of carbonyl group (C=O). Generally, the stretching frequencies of aromatic and aliphatic C-H bands appeared in the region 2800-3100 cm^{-1} [27]. In the FT-IR spectrum, a collection of bands observed in the region 2776-3083 cm^{-1} are ascribed to the C-H stretching frequencies of aromatic and aliphatic groups.
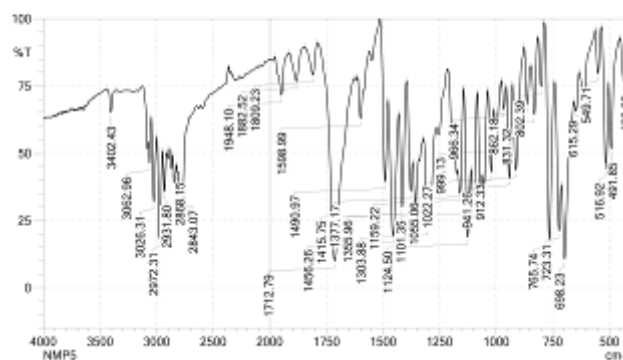

Figure 2 FT-IR spectrum of TMP

B. Mulliken Population Analysis

Mulliken population analysis is a noteworthy quantum chemical parameter to a molecular system due to the fact that the atomic charges influence dipole moment, molecular polarizability, electronic structure and many more properties of molecular systems [28]. Mulliken charge distribution of TMP has been acquired by B3LYP method with 6-311G (d,p) basis set and the data are given in **Table 2**. The results have been represented pictorially in **Figure 3**.

Table 2 Mulliken charge distribution of TMP

Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
C1	-0.5126	C24	-0.1234	C46	-0.5126	C69	-0.0882
H2	0.1943	H25	0.1561	H47	0.1943	H70	0.1714
H3	0.2134	C26	-0.1620	H48	0.1842	C71	-0.1620
H4	0.1842	H27	0.1501	H49	0.2134	H72	0.1501
C5	-0.4809	C28	-0.1611	C50	-0.4809	C73	-0.0837

|							
H6	0.1707	H29	0.1501	H51	0.1982	H74	0.1713
H7	0.1936	C30	-0.0837	H52	0.1936	C75	-0.3868
H8	0.1983	H31	0.1713	H53	0.1706	H76	0.2089
H9	0.2033	C32	-0.3868	H54	0.2214	H77	0.2112
H10	0.2214	H33	0.1533	H55	0.2034	H78	0.1533
N11	-0.4473	H34	0.2112	N56	-0.4472	C79	-0.1596
O12	-0.3477	H35	0.2089	O57	-0.3477	H80	0.1526
C13	-0.1336	C36	-0.1596	C58	-0.1336	C81	-0.1610
H14	0.1635	H37	0.1526	H59	0.1635	H82	0.1501
C15	-0.0783	C38	-0.1344	C60	-0.0784	C83	-0.1290
H16	0.1621	H39	0.1545	H61	0.1621	H84	0.1565
C17	-0.0354	C40	-0.1292	C62	-0.0354	C85	-0.1292
C18	-0.2157	H41	0.1519	C63	-0.0399	H86	0.1519
C19	0.3937	C42	-0.1290	C64	-0.4241	C87	-0.1344
C20	-0.0400	H43	0.1566	C65	-0.2157	H88	0.1545
C21	-0.4241	C44	-0.1633	C66	0.3937	C89	-0.1633
C22	-0.0881	H45	0.1496	C67	-0.1234	H90	0.1496
H23	0.1714			H68	0.1561		
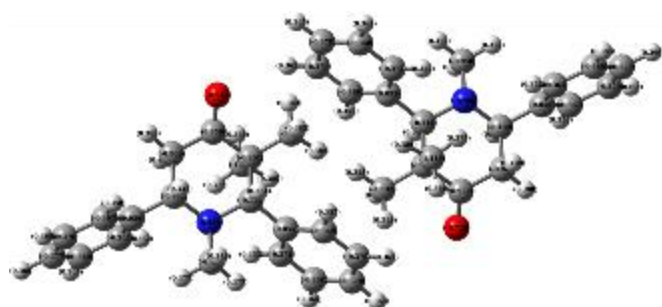
Figure 3 Mulliken charge distribution of TMP

From the DFT-B3LYP calculation, it is observed that the atomic charges of TMP have covered a wide range of numerical values from -0.5126 to +0.3937 which suggests that the intramolecular charge transfer occur inside the molecule. The magnitude of the positive charge on carbon atoms C19 and C66 have been found to be a maximum of 0.3937 while all the other carbon atoms attained negative atomic charges. From this observation we know that, the carbon atoms (C19 and C66) which are directly attached to the electronegative atoms (O12 and O57) results in electropositive character because of the attraction of the electrons from C19 and C66 by O12 and O57 and while the other carbon atoms behaves as electron acceptors. Further, all the hydrogen atoms present in the molecule acquired positive atomic charges.

C. Frontier Molecular Orbitals (FMOs) Analysis

The frontier molecular orbitals (FMOs) are important quantum chemical parameters to determine the optical and electric properties of a molecule. Generally, the highest occupied and lowest unoccupied MOs are represented as electron donor and acceptor, respectively. Besides, the energy gap between FMOs is generally investigated to determine the chemical stability, reactivity, hardness and softness of a molecule [29]. The 3D plot of FMOs of TMP can be visualized in **Figure 4** and their corresponding energy gap values are presented in **Table 3**.

Table 3 FMO parameters of TMP

Parameters	Energies (eV)
HOMO	-8.2877
LUMO	-4.7610
ΔE	3.5267

From the FMOs profile of TMP, the highest occupied MOs are nearly located over the nitrogen atom of the piperidine ring. On the other hand, the lowest unoccupied MOs are almost spread over two phenyl rings and carbonyl carbon of the piperidine ring. Thus, the electronic transition from the ground state to the excited state is clearly indicated by the flow of electron over the entire molecule. Further, the calculated HOMO, LUMO energies and energy gap between HOMO-LUMO of TMP are -8.2877 (HOMO), -4.7610 (LUMO) and 3.5267 (ΔE) eV, respectively.
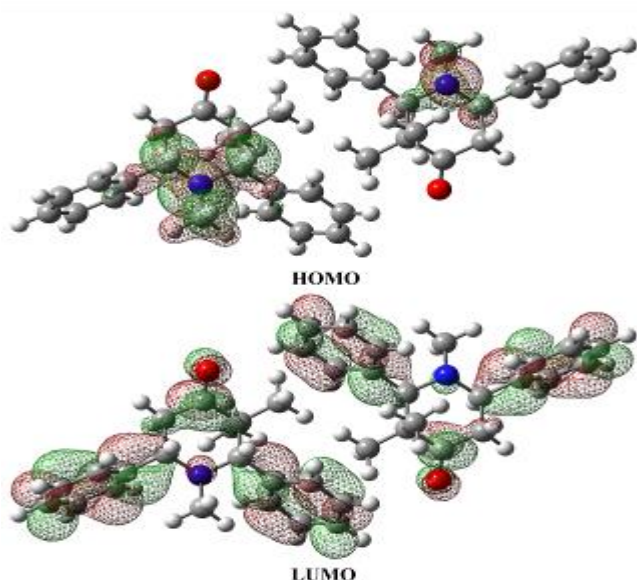
Figure 4 Frontier Molecular Orbitals (FMOs) picture of TMP

D. Molecular Electrostatic Potential (MEP) Analysis

A topographical MEP map has been extensively used to enlighten the features of chemical reactivity (electrophilic and nucleophilic sites), pharmacological activity and hydrogen bonding interactions of a molecule [30]. For knowing that, we have determined the molecular electrostatic potential and explained their spatial distribution over the molecule. The colour code of MEP map represents the electron rich zone as red in colour which is having partial negative charge; electron deficient regions represented by blue colour which holds partially positive charge; and neutral areas are designated as green in colour.

To predict the reactive sites of the analyzed molecule, the MEP has been calculated using optimized geometry at the B3LYP/6-311G (d,p) method in the gas phase. The MEP map of TMP, computed at 0.002 a.u isosurface is shown in **Figure 5**.
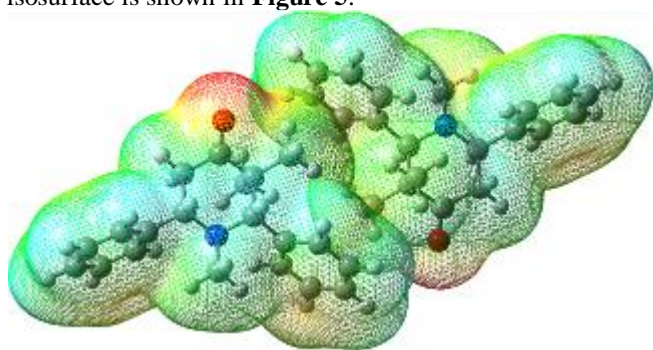

Figure 5 Molecular Electrostatic Potential (MEP) map of TMP

As can be seen in the figure, the negative potentials are mainly localized over the carbonyl oxygen while the positive regions spreaded over the nitrogen atom of the piperidine ring. These colour codes reflect that the region of electrophilic and nucleophilic reactivities and intermolecular interactions in the molecule. The calculated values of MEP global maxima and minima of the TMP are +58.73 and -58.73 kcal mol^{-1}. These values imply that the carbonyl region is favoring electrophilic attack. The predominance of

the light-green region in the MEP surfaces corresponds to a potential halfway between the two extremes of red and blue colour.

E. NMR analysis

In the ^{1}H NMR spectrum of TMP (**Figure 6**), the three upfield signals corresponding to three protons each respectively at 0.85, 1.28 and 1.78 ppm are assignable to the methyl group protons of C3-Me(eq), C3-Me(ax) and N-Me groups. The singlet at 3.14 ppm with one proton integral is attributed to the H2 proton oriented axially in the piperidine ring. Of the two doublet of doublets found around 3.4 and 2.4 ppm, the downfield signal at 3.35 ppm is ascribable to the H6a proton and the upfield one is due to the resonance of H5e proton. The triplet at 3.06 ppm is due to the H5a proton. The resonances of aromatic protons are observed between 7.24 and 7.46 ppm as a multiplet.
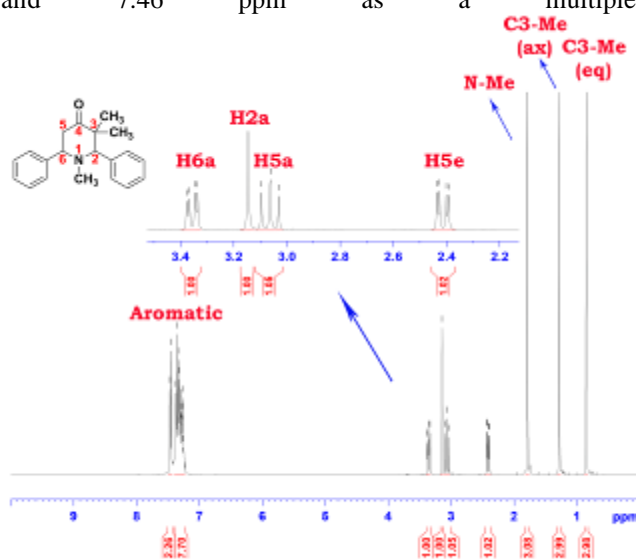

Figure 6 ^{1}H NMR spectrum of TMP

In the ^{13}C NMR spectrum of TMP (**Figure 7**), the axial and equatorial methyl carbons attached to the C3 carbon are found to resonate isochronously around 21 ppm. The N-Me carbon atom showed its signal at 42.4 ppm. The resonance of C3 and C5 carbons are observed with a difference of about 2 ppm respectively at 49.3 and 47.2 ppm. The C2 carbon experiences a downfield shift at 78.7 ppm and the C6 carbon experiences an upfield shift with respect to the former at 70.9 ppm. The far downfield signal at 212.1 ppm is accountable due to the carbonyl carbon (C4). The unsymmetrical environment of the ipso carbons are exemplified by their varying chemical shifts at 138.7 and 143.9 ppm. Aromatic carbons of the phenyl rings collectively resonate between 127 and 129.8 ppm.
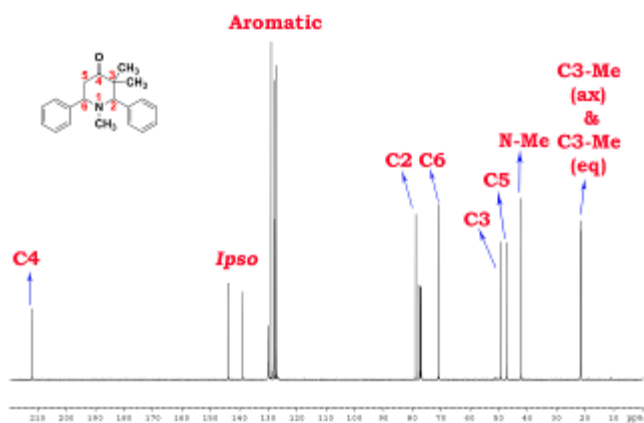
Figure 7 ¹³C NMR spectrum of TMP

F. Stereochemistry

The magnitudes of vicinal coupling constants observed in a six membered cyclic system tell about the conformational preference of the ring. In the case of TMP, the diastereotopic methylene protons at C5 carbon namely H5a and H5e, couple unequally with the H6a proton and resulted in the formation of a triplet and two doublet of doublets. The magnitude of the coupling constant found in this AMX spin system of protons is greater than 10 Hz which is possible only when the dihedral angle between them is about 180° allowing the substituents to take an equatorial orientation. The equatorial preference of the substituents present in the piperidine ring system facilitates the chair conformation which is favourable in the energy point of view. Hence, the piperidine ring system of TMP adopts a chair conformation with all the substituents in equatorial orientation and at C3 carbon, the second methyl group orients axially.

IV. CONCLUSION

The effort to correlate the experimental and theoretical data to account for the structure and reactivity of the title molecules was achieved through DFT calculations. Optimized geometry, FMO visualization, vibrational and Mulliken population analyses, molecular electrostatic potential map, ¹H and ¹³C NMR spectral interpretation have been carried out. Both the experimental and theoretical data supports a chair conformation for the piperidine ring system of TMP. The electron delocalization is ascertained by the HOMO-LUMO pictures. The electrophilic and nucleophilic nature of the constituent atoms of TMP is also accounted by Mulliken analysis. The spectral data is in accordance with the theoretical data computed.

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