

Computational Aspects of (E)-O-Carbomethoxy Methyl Oxime Ether of 1,3-Dimethyl-2,6-Diphenylpiperidin-4-One

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Abstract: Density Functional Theoretical (DFT) studies on the biologically active oxime ether derived from 1,3-dimethyl-2,6-diphenylpiperidin-4-one has been carried out. Various quantum chemical parameters of the molecule viz. molecular geometry, Highest Occupied Molecular Orbital – Lowest Unoccupied Molecular Orbital (HOMO–LUMO) energies, Non-Linear Optical (NLO) properties, Mulliken atomic charge distribution were obtained theoretically and compared with the single crystal data. An insight into the structure and property correlation revealed the probable behavior of the molecule studied.

Keywords: About four key words or phrases in alphabetical order, separated by commas.

I. INTRODUCTION

Heterocyclic compounds containing nitrogen atom constitute the backbone of bioactive molecules belonging both aromatic and aliphatic systems such as aziridine, azetidine, pyrrolidine, pyridine, pyrimidine, and piperidine. Of a number of saturated heterocycles available, piperidine functional group forms a large number of biologically active derivatives which are having many applications in the field of agricultural chemistry, medicinal chemistry, material chemistry and others. Piperidine nucleus is present in many alkaloids widely accepted as drugs in nature itself. Mannich condensation of aldehydes, ketone and primary amines/ammonium acetate leads to the birth of many substituted piperidine derivatives. Biological significance of

these synthesized molecules has also been evaluated through *in vivo* as well as *in vitro* assay procedures.

4–Piperidone is an important drug derivative as well as an intermediate in the synthetic route of certain chemicals and pharmaceutical drugs [1-2] such as fentanyl, and its analogues carfentanyl and ramifentanyl. Further, molecules possessing 4–piperidone nucleus show desirable biological properties viz. antiviral [3], antitumor [4], central nervous system stimulant [5], analgesic [6], anticancer [7] and antimicrobial activity [8].

Oximes and oxime ethers have significance in medicinal chemistry due to their applications such as medicines and pesticides [9]. These functional groups are prevalent in many medicinally important molecules used as antibiotics (e.g. gemifloxacin mesylate), drugs used in the treatment of organophosphate poisoning viz. pralidoxime chloride, obidoxime chloride *etc.* caused by insecticides such as malathion and diazinon. An antidepressant drug, fluvoxamine, used as the selective serotonin reuptake inhibitors (SSRIs) also possesses oxime ether functionality in its structure. Both *O*-alkyl and *O*-aryl oximes have been proved to be stable at physiological pH and *O*-alkyl oxime core is found to be present in a number of approved drugs [10-11]. Besides, oxime–ether derivatives are also widely used in agriculture as fungicides [12], herbicides [13], insecticides [14], and in the senescence of cut carnation flowers [15].

Because of the significance of oxime ethers as cited above, there is a continuous interest amongst the researchers to study the theoretical properties of the former [16-22]. All the above studies explored the features of the compounds associated with their reactivity, structure and advanced applications. Therefore in the present work, computational studies (based on Density Functional Theory) have been done for the methyl oxime ether derivative of piperidin-4-one. The various parameters, and properties such as optimized geometry, HOMO-LUMO visualization and their energy gap, ionization potential, electron affinity, global hardness, chemical potential, global electrophilicity index, Mulliken atomic charges have been calculated. The structural parameters such as bond lengths, bond angles and dihedral angles have been compared with the experimental values obtained from the earlier literature report by us [23].

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II. RESULTS AND DISCUSSION

A. Molecular geometry

Computational study has been carried out using B3LYP/6-31G (d,p) in Gaussian 03 program. The full geometry optimization was carried out using 6-31G (d,p) basis set. The optimized geometry for the molecule predicted in the gas phase is shown in **Fig. 1** and the optimization parameters such as bond lengths, bond angles and dihedral angles along with the experimental data obtained from X-ray diffraction are given in **Table 1, 2 & 3** for comparative purpose.

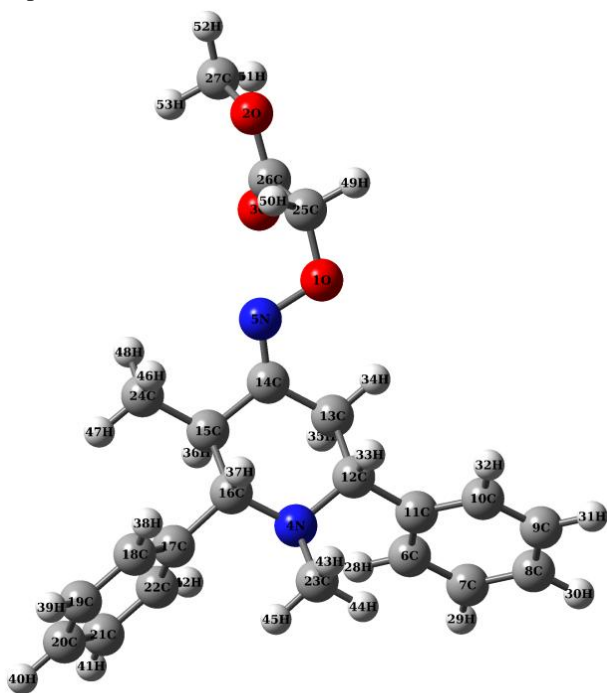


Fig. 1 Optimized geometry of the Oxime Ether

Table 1 Optimization parameters of Oxime Ether (Bond Lengths (°))

Bond length	Comp.	Expt.	Bond length	Comp.	Expt.
O1-C25	1.4128	1.413(2)	C11-C12	1.5084	1.508(2)
O2-C26	1.3388	1.339(3)	C12-C13	1.527	1.527(3)
O2-C27	1.4339	1.434(3)	C13-C14	1.4858	1.486(3)
O3-C26	1.1844	1.184(3)	C14-C15	1.49	1.490(3)
N4-C12	1.4706	1.471(2)	C15-C16	1.5422	1.542(3)
N4-C16	1.4688	1.469(2)	C15-C24	1.511	1.511(3)
N4-C23	1.4672	1.467(3)	C16-C17	1.514	1.514(3)
N5-C14	1.2719	1.272(2)	C17-C18	1.3709	1.371(3)
C6-C7	1.3694	1.369(3)	C17-C22	1.388	1.388(3)
C6-C11	1.383	1.383(3)	C18-C19	1.3884	1.388(4)
C7-C8	1.3659	1.366(4)	C19-C20	1.3615	1.362(4)
C8-C9	1.3554	1.355(4)	C20-C21	1.3764	1.376(5)
C9-C10	1.3837	1.384(3)	C21-C22	1.3832	1.383(4)
C10-C11	1.3808	1.381(3)	C25-C26	1.4952	1.495(3)

From the above said table, it is noticeable that there is considerable agreement between Computational and experimental values of most of C-C, C-N and C-O bond lengths and as for as the C-H bonds considered in most cases the bond lengths are diminished by about 0.14 Å. There are

several agreements/anomalies between the bond angles and dihedral angles of the optimized structure obtained by Computational study and that one proposed based on NMR spectra and by single crystal X-ray diffraction.

Despite some deviations in bond angles and dihedral angles, the stereochemical orientations of the substituents are not changed much. The variations observed between computational and experimental parameters could be understandable from the fact that in the solid state, intra as well as intermolecular interactions (such as hydrogen bonding and van der Waal's forces of attraction) play an important role in the molecular packing and stability of the molecule. Moreover, in the Computational study an isolated molecule in the gaseous state is considered for calculations.

Table 2 Optimization parameters of Oxime Ether (Bond Angles (Å))

Bond angle	Comp.	Expt.	Bond angle	Comp.	Expt.
N5-O1-C25	108.332	108.3(1)	C13-C14-C15	114.0079	114.0(2)
C26-O2-C27	117.5645	117.6(2)	C14-C15-C16	108.9303	108.9(1)
C12-N4-C16	112.0594	112.1(1)	C14-C15-C24	114.4111	114.4(2)
C12-N4-C23	108.7394	108.7(1)	C16-C15-C24	112.2351	112.2(2)
C16-N4-C23	110.0465	110.0(1)	N4-C16-C15	111.5863	111.6(1)
O1-N5-C14	109.9711	110.0(2)	N4-C16-C17	110.8342	110.8(1)
C7-C6-C11	120.9041	120.9(2)	C15-C16-C17	110.6536	110.6(1)
C6-C7-C8	120.4904	120.5(2)	C16-C17-C18	121.2778	121.3(2)
C7-C8-C9	119.4491	119.5(2)	C16-C17-C22	120.4668	120.5(2)
C8-C9-C10	120.9087	120.9(2)	C18-C17-C22	118.1871	118.2(2)
C9-C10-C11	120.1062	120.1(2)	C17-C18-C19	121.2235	121.2(2)
C6-C11-C10	118.1322	118.1(2)	C18-C19-C20	119.8743	119.9(2)
C6-C11-C12	121.1467	121.1(2)	C19-C20-C21	120.1519	120.1(3)
C10-C11-C12	120.654	120.6(2)	C20-C21-C22	119.7317	119.7(3)
N4-C12-C11	112.0805	112.1(1)	C17-C22-C21	120.8292	120.8(2)
N4-C12-C13	110.6753	110.7(1)	O1-C25-C26	113.0769	113.1(2)
C11-C12-C13	108.9585	109.0(1)	O2-C26-O3	123.3392	123.3(2)
C12-C13-C14	109.8857	109.9(1)	O2-C26-C25	109.4313	109.4(2)
N5-C14-C13	126.7342	126.7(2)	O3-C26-C25	127.2192	127.2(2)
N5-C14-C15	119.2255	119.2(2)			

B. HOMO-LUMO energies

The HOMO and LUMO energies calculated are -5.9897 eV and 0.3284 eV respectively. The LUMO and HOMO are being measures of electron affinity (A) and ionization energy (I) as $-E_{\text{LUMO}} = A$ and $-E_{\text{HOMO}} = I$ respectively. The energy gap between the LUMO and HOMO is also indicative of the global hardness ($\eta = \frac{1}{2}[E_{\text{LUMO}} - E_{\text{HOMO}}]$) which is associated with the stability of the system while the term chemical potential (μ) is given by $\frac{1}{2}[E_{\text{LUMO}} + E_{\text{HOMO}}]$. Further, the global electrophilicity index (ω) is derived from the relation $\omega = \mu^2/2\eta$. The above molecular properties calculated are depicted in **Table 4**.

The energy gap between the HOMO and the LUMO is 5.6613 eV which suggests that the molecule is soft, more polarizable, associated with appreciable chemical reactivity. Moreover,

the HOMO and LUMO energy gap explains the eventual charge transfer interactions that take place within the molecule which are responsible for the bioactivity of the molecule. It is observed from the HOMO and LUMO orbital diagrams (Fig. 2) that in the HOMO, the electron density is localized mainly in the phenyl rings attached to the C2, C6 carbons and the piperidine ring while in the LUMO; the electron density is distributed mainly over the piperidine ring and also over the oxime ether moiety. This indicates that the HOMO is having contribution from mostly the π -type orbitals of aromatic rings and the LUMO is devoid of the contribution from π -type orbitals. Therefore when electronic transitions occur from HOMO to LUMO in the molecule, electron density significantly decreases in the electron-donating benzene ring systems and result in an increase in the oxime ether moiety which behaves as an electron acceptor in the molecule.

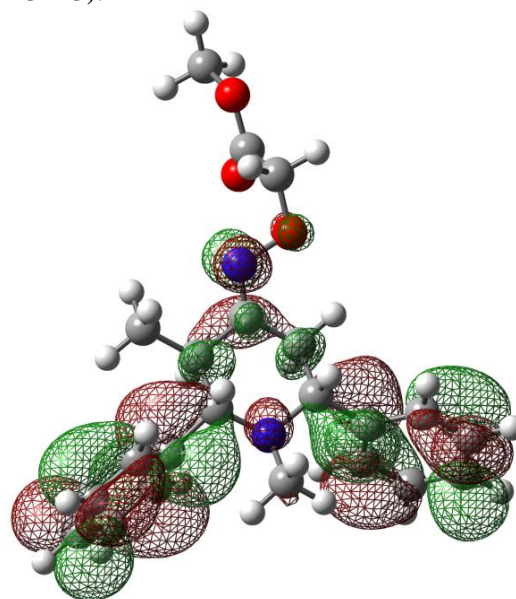
Table 3 Optimization parameters of Oxime Ether (Torsion Angles (°))

Torsion angle	Comp.	Expt.	Torsion angle	Comp.	Expt.
C25-O1-N5-C14	-172.815	-172.8(2)	N4-C12-C13-C14	55.1838	55.2(2)
N5-O1-C25-C26	-71.8869	-71.9(2)	C11-C12-C13-C14	178.8577	178.9(1)
C27-O2-C26-O3	1.6574	1.7(3)	C12-C13-C14-N5	122.6649	122.7(2)
C27-O2-C26-C25	-179.437	-179.4(2)	C12-C13-C14-C15	-55.2319	-55.2(2)
C16-N4-C12-C11	-179.501	-179.5(1)	N5-C14-C15-C16	-124.122	-124.1(2)
C16-N4-C12-C13	-57.6431	-57.6(2)	N5-C14-C15-C24	2.3884	2.4(2)
C23-N4-C12-C11	58.6259	58.6(2)	C13-C14-C15-C16	53.9463	53.9(2)
C23-N4-C12-C13	-179.516	-179.5(2)	C13-C14-C15-C24	-179.543	-179.5(2)
C12-N4-C16-C15	57.3397	57.3(2)	C14-C15-C16-N4	-53.7678	-53.8(2)
C12-N4-C16-C17	-178.852	-178.9(1)	C14-C15-C16-C17	-177.679	-177.7(2)
C23-N4-C16-C15	178.4617	178.5(1)	C24-C15-C16-N4	178.4821	178.5(2)
C23-N4-C16-C17	-57.7295	-57.7(2)	C24-C15-C16-C17	54.5714	54.6(2)
O1-N5-C14-C13	3.254	3.3(3)	N4-C16-C17-C18	125.0251	125.0(2)
O1-N5-C14-C15	-178.948	-178.9(1)	N4-C16-C17-C22	-58.0351	-58.0(2)
C11-C6-C7-C8	0.7656	0.8(4)	C15-C16-C17-C18	-110.634	-110.6(2)
C7-C6-C11-C10	-0.5546	-0.6(3)	C15-C16-C17-C22	66.3063	66.3(2)
C7-C6-C11-C12	176.4848	176.5(2)	C16-C17-C18-C19	177.2413	177.2(2)
C6-C7-C8-C9	-0.0956	-0.1(4)	C22-C17-C18-C19	0.2338	0.2(3)
C7-C8-C9-C10	-0.7682	-0.8(4)	C16-C17-C22-C21	-176.821	-176.8(2)
C8-C9-C10-C11	0.9713	1.0(4)	C18-C17-C22-C21	0.2115	0.2(3)
C9-C10-C11-C6	-0.2997	-0.3(3)	C17-C18-C19-C20	-0.4559	-0.5(4)
C9-C10-C11-C12	-177.354	-177.4(2)	C18-C19-C20-C21	0.2247	0.2(4)
C6-C11-C12-N4	51.3325	51.3(2)	C19-C20-C21-C22	0.2138	0.2(4)
C6-C11-C12-C13	-71.5025	-71.5(2)	C20-C21-C22-C17	-0.4373	-0.4(4)
C10-C11-C12-N4	-131.703	-131.7(2)	O1-C25-C26-O2	175.58	175.6(2)
C10-C11-C12-C13	105.4625	105.5(2)	O1-C25-C26-O3	-5.5676	-5.6(3)

Table 4 Molecular properties of Oxime Ether

Molecular property	Value (eV)
E_{HOMO}	-5.9897
E_{LUMO}	-0.3284
Energy Gap (Δ)	5.6613
Ionization Potential (I)	5.9897
Electron Affinity (A)	0.32844
Global Hardness (η)	2.8306
Chemical Potential (μ)	-3.1591
Global Electrophilicity index (ω)	1.7605

Highest Occupied Molecular Orbital (HOMO):



Lowest Occupied Molecular Orbital (LUMO):

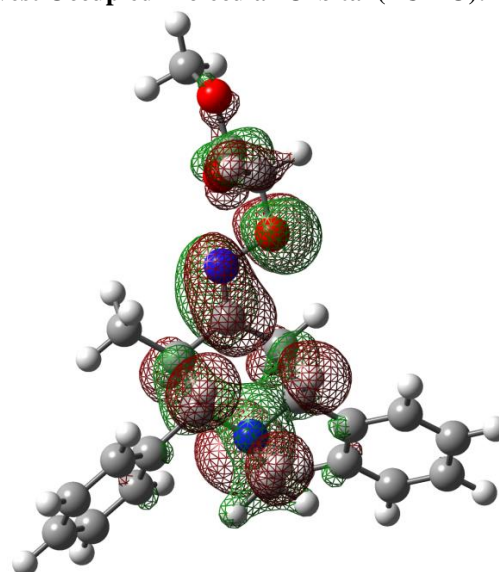


Fig. 2 HOMO and LUMO diagrams of Oxime Ether

C. NLO properties

The NLO properties such as dipole moment, polarizability and hyperpolarizability calculated by computational study are shown in **Table 5**. The dipole moment value equal to 0.9791D indicates the polar nature of the molecule. The highest value of dipole moment is observed for the component μ_x (0.2541) in the molecule. The calculated polarizability is higher for the component α_{xy} (-0.6498) and the hyperpolarizability is higher for the β_{xxx} (247.8589) component. It is interesting to note that the calculated polarizability (α) value for the oxime ether is equal to -0.6498×10^{-18} e.s.u. which is almost four times greater than that of *p*-nitroaniline, a typical NLO material [24-25]. Also the comparison of hyperpolarizability (β , 247.8589×10^{-18} e.s.u.) of the oxime ether (which is twice that of the standard NLO material urea, $\beta = 0.72137 \times 10^{-30}$ e.s.u.) reveals that the former could be used an effective NLO material.

Table 5 NLO properties of the Oxime Ether

Polarizability		Hyperpolarizability	
α_{xx}	-139.5246	β_{xxx}	247.8589
α_{yy}	-149.0363	β_{xxy}	-49.1473
α_{zz}	-153.5783	β_{xyy}	-6.3071
α_{total}	-442.1392	β_{yyy}	23.5407
		β_{xxz}	26.7375
Dipole moment		β_{xyz}	-17.6307
		β_{yyz}	-7.7219
X	0.2541	β_{xzz}	5.0284
Y	-0.2549	β_{yzz}	-0.7467
Z	-0.9105	β_{zzz}	-0.0765
Total	0.9791	β_{Total}	221.5353

D. Atomic charge distribution

The charge distribution on a molecule has a significant influence on dipole moment, molecular polarizability, electronic structure, vibrational spectra and other properties of molecular systems. Mulliken atomic charge distribution is calculated for the oxime ether and the table summarizing the charge distribution is given along with the graph explaining the same pictorially (**Table 6** and **Fig. 3**). It is seen from the graph that the heteroatoms O1, O2, O3, N4, N5 and carbon atoms C13, C23 and C24 are accumulated with negative charges as a result of molecular relaxation and these atoms behave as electron acceptors. There is a large accumulation of positive charge on C14 & C26 and a large negative charge on O2 & O3 atoms. It is also notable that both oxygen and nitrogen atoms are having equal negative charges. The excess is taken from the nearby carbon and hydrogen atoms and as a result of this they are found with positive sign in the graph. Further, most of the carbon atoms are negatively charged indicating that there are charge transfers occurred from hydrogen atoms to carbon atoms in the molecule.

Table 6 Mulliken Atomic Charge distribution

Atom	Charges	Atom	Charges
O1	-0.39132	H28	0.094216
O2	-0.46297	H29	0.085461
O3	-0.4611	H30	0.084195
N4	-0.45141	H31	0.084983
N5	-0.23752	H32	0.081632

C6	-0.10324	H33	0.073021
C7	-0.08796	H34	0.139102
C8	-0.08444	H35	0.12327
C9	-0.08695	H36	0.110693
C10	-0.12087	H37	0.068183
C11	0.087118	H38	0.082344
C12	0.035418	H39	0.085553
C13	-0.20582	H40	0.084864
C14	0.295929	H41	0.085939
C15	-0.10334	H42	0.093639
C16	0.047585	H43	0.078587
C17	0.086688	H44	0.121308
C18	-0.11979	H45	0.122716
C19	-0.08682	H46	0.107819
C20	-0.0851	H47	0.109931
C21	-0.08836	H48	0.120201
C22	-0.10159	H49	0.137385
C23	-0.17097	H50	0.135482
C24	-0.31251	H51	0.130419
C25	0.006564	H52	0.120811
C26	0.591771	H53	0.132769
C27	-0.08354		

III. EXPERIMENTAL

Computational calculations were done by considering the crystal structure of oxime ether as the initial structure using B3LYP/DFT methods using 6-31G (d, p) as the basis set in Gaussian 03 package [26] to optimize the structure. The lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) energy differences for the molecule were calculated with these methods. The other properties like bond lengths, bond angles, dihedral angles, dipole moment, polarizability, hyperpolarizability and Mulliken charge distribution pattern and some other important molecular properties are also calculated using the same package. Gauss View program is used to visualize the results obtained from calculations, which were made by Gaussian 03 program.

IV. CONCLUSION

Computational studies using Density Functional Theory (DFT) has been done to get optimized structure, HOMO-LUMO energies, dipole moment values etc. Anomalies between the experimental and computational values of optimized structure could be accounted by the difference in their physical state.

HOMO-LUMO energy gap of the oxime ether corresponds to about 5.6613 eV and this energy gap provides stability of the molecule. The dipole moment value suggests that the probable use of the compound as a NLO material. The Mulliken population analysis revealed the electrophilic and nucleophilic centres present in the molecule.

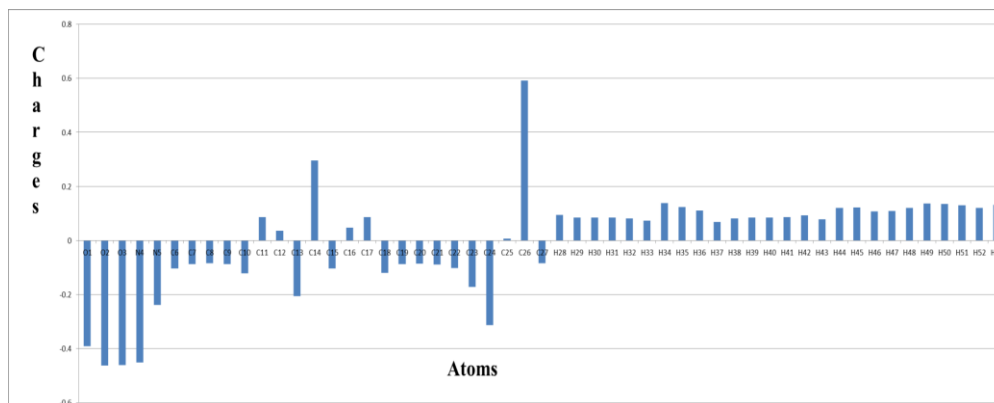


Fig 3 Mulliken Atomic Charge distribution

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