Conformational landscape and metal-molecule interaction of diverse molecular systems: Insights from *ab initio* electronic structure calculations

THESIS SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE

DOCTOR OF PHILOSOPHY

By

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Dedicated to
My brother (Late W.O. Mahavir Singh Bhadoria) and
My parents (Smt. Pushpa and Shri Vishwanath singh Bhadoria)

CERTIFICATE

It is certified that the work contained in the thesis titled "**Conformational landscape and metal-molecule interaction of diverse molecular systems: Insights from *ab initio* electronic structure calculations**" by **POONAM BHADORIA** has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive Examination, Candidacy and SOTA for the award of Ph.D. Degree.

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DECLARATION BY THE CANDIDATE

I, **POONAM BHADORIA**, certify that the work embodied in this thesis is my own *bona-fide* work and carried out by me under the supervision of **Dr. V. Ramanathan** from **July, 2018** to **September, 2023** at the **Department of Chemistry,** Indian Institute of Technology (BHU) Varanasi. The matter embodied in this thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, etc., reported in journals, books, magazines, reports dissertations, theses, etc., or available at websites and have not included them in this thesis and have not cited as my own work.

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It is certified that the above statement made by the student is correct to the best of my knowledge.

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---- POONAM BHADORIA

CONTENTS

ABBREVIATIONS

IUPAC	International union of pure and applied chemistry
NC	Noncovalent
NCI	Noncovalent interaction
CHB	Conventional hydrogen bond
UHB	Unconventional hydrogen bond
SCHB	Sulfur centered hydrogen bonds
HF	Hartree-Fock
AM1	Austin Model 1
PM6	Parameterization Method 6
M06	Minnesota 06
PW91PW91	Perdew-Wang 1991 (PW91) generalized gra- dient approximation
LANL2DZ	Los Alamos National Laboratory 2 Double-Zeta
DFT	Density Functional Theory
TD-DFT	Time dependent density functional theory
LDA	Local density approximation
GGA	Generalized gradient approximation
BLYP	Becke Lee Yang Parr
B3LYP	Becke 3-parameter Lee Yang Parr
MP2	Møller-Plesset second order perturbation theory
CC	Coupled cluster
CCSD	Coupled cluster single double excitation
CCSD(T)	Coupled cluster single double triple excitation
IE	Interaction Energy
LED	Local energy decomposition
DOS	Density of states
TDOS	Total density of states
PDOS	Projected density of states
BSSE	Basis set super position error
ZPE	Zero-point energy correction
CBS	Complete basis set
QTAIM	Quantum theory of atoms in molecule theory

BCP	Bond Critical point
RDG	Reduced density gradient
NAOs	Natural atomic orbitals
DMOs	Delocalised molecular orbitals
NBO	Natural bond orbital
FMO	Frontier molecular orbital
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
MK	Merz Kollman
ESP	Electrostatic potential
UV	Ultraviolet
NMR	Nuclear magnetic resonance
GIAO	Gauge-independent atomic orbital
IR	Infrared
PES	Potential energy surface
LSD	Lysergic acid diethylamide
5-HT	5-hydroxytryptamine
EC	Effective concentration
DTT	Dithiothreitol
TGA	Thioglycolic acid
BOC	Bismuthoxycarbonate
PATP	para-aminothiophenol
DMAB	Dimercaptoazobenzene
SERS	Surface-enhanced Raman Scattering

List of Symbols

Ψ	Wave function
$\hat{H}$	Hamiltonian operator
ρ(r)	Electron density
ρ_{BCP}	Electron density at BCP
G_{BCP}	Kinetic electron energy density
V_{BCP}	Potential electron density
$\nabla^2 \rho_{BCP}$	Laplacian electron density
H_{BCP}	Total electron density
a.u.	Arbitrary unit
ZPE	Zero point energy
E_{int}	Interaction energy
IE	Interaction energy
μ	Chemical potential
χ	Electronegativity
η	Hardness
ω	Electrophilicity index
D	Debye
kcal/mol	Kilo calorie per mole
eV	Electron volt
μ	Dipole moment
Ɵ	Theta
Å	Angstrom
Φ	Phi
E(2)	Second order perturbation stabilization energy
LP	Lone pair of electron
σ	Bonding molecular orbital
σ*	Antibonding molecular orbital
π	Pi bonding orbital
π*	Pi antibonding orbital
ν	Stretching frequency
ν_s	Symmetric stretching
ν_{as}	Aasymmetric stretching

δ	In-plane bending
δ_s	In-plane scissoring
ω	Out of plane wagging
τ	Out of plane twisting
β	Out of plane bending
ρ	In-plane rocking
γ	Out of plane bending vibration
ϕ	Scissoring vibration
α	Ring deformation
nm	Nanometer
ppm	Parts per million
amu	atomic mass unit
cm^{-1}	centimeter inverse/wavenumber

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PREFACE

The quantum chemical computations were conducted to explore conformations of few organic molecules and to study the interaction using different methods like DFT, MP2 and CCSD with different basis sets. Gaussian 16 suit of program, Orca 5.0 and Multiwfn were utilized to perform these calculations. The following paragraphs present the summary of each chapter.

Chapter 1 serves as an introduction to conformational analysis and non-covalent interactions, exploring their diverse aspects. The non-covalent interactions were explored, encompassing their nature and strength. An array of spectroscopic details that could be computed gets introduced which are helpful in gaining insight on the conformation and non-covalent interactions. Furthermore, the effectiveness of DFT calculations in understanding the interaction between metal clusters and molecules was discussed. The chapter further provides comprehensive information on quantum chemical methods, basis sets, and computational tools employed to infer diverse molecular properties. Finally, the chapter was concluded by outlining the objectives of the work entailed in this thesis.

Chapter 2 focuses on the conformational analysis of three psychedelic molecules namely psilocybin, psilocin, and mescaline. Each molecule exhibited distinct conformers, including the global minimum conformer. These conformers demonstrated various intramolecular H-bonding interactions and other NC-interactions, contributing to the stability of the global minimum. These interactions were studied through AIM, NCI and NBO calculations. Relaxed dihedral scans were performed utilizing the B3LYP/cc-pVTZ level of theory. Psilocybin exhibited the existence of two stable conformers. The energy difference between global minimum and second most stable conformer was found to be 2.08 kcal/mol with a rotational barrier of 14.6 kcal/mol between them. Similarly, psilocin also exhibited two stable conformers, with an energy difference of 5.4 kcal/mol between the local and global minimum. Notably, these conformers displayed different intramolecular hydrogen bonding patterns. Conformer-A of psilocin exhibited a strong intramolecular H-bond between the indolic hydroxy group and ethyl amine, whereas Conformer-B lacked this interaction. To further understand the strength of intra- versus intermolecular H-bonding, we studied dimers of both conformers of psilocin. The dimers of Conformer-A displayed a stronger intramolecular H-bond compared to the intermolecular H-bond, while the reverse was observed in Conformer-B. Another psychedelic molecule namely mescaline was investigated. Two equally populated low-energy conformers differing by approximately 0.5 kcal/mol and 1.5 kcal/mol at the

B3LYP/cc-pVTZ and CCSD/cc-PVDZ levels of theory, respectively, were identified. These conformers varied in the orientation of the alkylamine group relative to the benzene ring, mediated by the NH....π interaction. The geometrical parameters of these conformers aligned well with a previously reported X-ray crystal structure study. Furthermore, our spectroscopic analysis, including 1H-NMR, UV, and vibrational mode calculations, exhibited agreement with literature data for all three molecules (psilocybin, psilocin, and mescaline).

Chapter 3 encompasses an extensive exploration of the conformational landscape of dithiothreitol (DTT), resulting in the identification of seven minimum energy geometries. This investigation involved varying the prominent dihedral angles in the molecule through a relaxed scan, with a step size of 5°, initially carried out at the B3LYP/cc-pVTZ theoretical level. Further geometry optimization was conducted at the CCSD/cc-pVDZ theoretical level. And at the CCSD(T)/CBS limit with the cc-pVNZ (N=T,Q) level of theory, single point energies were also calculated for all conformers which consistently revealed similar energy patterns. Among the conformers, two iso-energic structures, namely G'TG'1 and G'TT, were identified, despite their significant structural differences. These two conformers exhibited the lowest energy compared to the others. In contrast, the cyclic and other configurational counterparts of the global minimum had a considerable higher energy. An intriguing observation was the stabilization of the global minimum structure of DTT through an intramolecular sulfur-centered hydrogen bond. This was established through various analyses, including AIM, NBO, FMO, and ESP charge analysis. Furthermore, the computed harmonic normal modes and NMR (Nuclear Magnetic Resonance) spectra of DTT matched appreciably with the available and observed experimental data.

In Chapter 4, the conformational landscape of thioglycolic acid (TGA) was examined using the CCSD/cc-pVDZ theoretical level. The GGC conformer was identified as the global minimum with the GAC conformer following closely. The rotational constant calculated for the GGC conformer exhibited good concordance with the earlier reported experimental findings. Furthermore, the study explored sulfur-centered hydrogen bonding in TGA's dimer and trimer clusters, employing the CCSD/cc-pVDZ theoretical level where it was seen that both oxygen and sulfur atoms were equally involved in the non-covalent H-bonding contributing to the stability. The presence of these non-covalent interactions in TGA clusters were further elucidated through AIM, RDG, and NBO analysis. Additionally, ESP charge and vibrational mode analysis provided further support for these findings.

In Chapter 5, an exploration into the stability of the disulfide bond within cystine on a copper cluster (Cu9) was undertaken. This investigation utilized the B3LYP/LAN-L2DZ/6-

311++G(d,p) level of theory. The geometries of unconnected cystine and Cu9 were optimized individually and the resulting geometry was used as an input. The outcomes indicated that cystine adhered to Cu9 primarily through its disulfide and carboxyl functional groups. The simulation of the Raman spectrum revealed the disruption of the disulfide linkage, marked by the absence of the -S-S- stretching mode, aligning with prior experimental observations. Furthermore, the NBO results unveiled the contribution of lone pairs of electrons from oxygen and sulfur atoms to copper in the Cu9-cystine system. Moreover, the outcomes derived from MK ESP charge, FMO, and AIM calculations supported the aforementioned findings.

In Chapter 6, the chemical transformation of PATP to its dimer DMAB (p,p-dimercaptoazobenzene) on copper nanoclusters and its stability on bismuth-based cluster i.e. the BOC (bismuthoxycarbonate) cluster, are discussed. For this study the generalized gradient approximation for exchange-correlation functionals PW91PW91 was employed. For the copper and bismuth atoms, relativistic effective core potentials (RECP) using LANL2DZ were used, whereas the C, H, N, S, and O atoms were studied using the 6-311+G(d,p) basis set. The SERS spectrum of DMAB on copper clusters, as simulated, was significantly similar to the SERS spectrum of PATP on copper observed in experiment. In contrast, the SERS spectrum simulated for PATP-BOC exhibited notable agreement with the corresponding experimental SERS spectrum, showing no dimerization. The dimerization of PATP on copper clusters was associated with metal-to-molecule charge transfer, while the authentic SERS spectrum of PATP was derived from molecule-to-metal charge transfer when the BOC cluster was employed as the SERS substrate.

Appendix: It includes the calculation of vibrational frequencies for Ba(CO)n and Ca(CO)n systems, where n=1, and 2. The main objective is to support experimental vibrational results by employing various combinations of basis sets in ab initio and DFT methods. A noteworthy investigation conducted by Xuan et al., revealed the existence of a novel covalent bond between CO and alkaline earth metals such as Ba, Ca, and Sr. However, there was a considerable disparity between their experimentally determined vibrational frequencies and the frequencies calculated theoretically. Our aim was to identify an appropriate method for accurately calculating the vibrational frequencies of alkaline earth metal complexes. To achieve this, we employed several ab initio and DFT methods, along with varying combinations of basis sets.