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

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CHAPTER - 7

Summary and future scope

7.1 Summary

The confirmation and structural stability of psychedelic compounds like psilocybin, psilocin, mescaline, as well as sulfur-containing molecules such as dithiothreitol and thioglycolic acid and its with their clusters, using quantum chemical calculations were dealt with in this thesis. Furthermore, the interactions between molecules and metal clusters were also studied in order to corroborate the experimentally observed SERS results and identify the most stable binding modes. The present thesis has addressed three primary goals outlined in the first chapter, which have been elaborated upon in five separate chapters. To recap, our objectives were as follows:

1. Identifying all potential conformers, including the most stable conformer, for psychedelic molecules such as psilocybin, psilocin, and mescaline. Additionally, the study aims to determine the structural parameters that contribute to their stability.

2. Conformational analysis of molecules that contain both OH and SH groups in their structure, specifically dithiothreitol and thioglycolic acid and exploring the sulfur-centered hydrogen bonding present in the intramolecular and intermolecular systems of these molecules.

3. Investigating molecule-metal interactions using DFT calculations applying molecule-metal modeling approach. It aims to validate the experimental findings regarding the cleavage of cystine on copper and the adsorption behavior of PATP on different metal surfaces.

Summary of Objective 1

1. Explored conformational analysis of three psychedelic molecules: psilocybin, psilocin, and mescaline, each with unique conformations, including the global minimum conformer.
2. These conformers displayed diverse intramolecular H-bonding and NC-interactions, enhancing the stability of the global minimum. We analyzed these

interactions using AIM, NCI, and NBO calculations, and conducted relaxed dihedral scans with the B3LYP/cc-pVTZ level of theory.

3. Psilocybin had two stable conformers with a 2.08 kcal/mol energy difference, and a 14.6 kcal/mol rotational barrier separated the global minimum from the second most stable conformer.
4. Psilocin has two stable conformers with a 5.4 kcal/mol energy difference. Conformer-A has a strong intramolecular H-bond, while Conformer-B lacks it. In dimer studies, Conformer-A exhibits stronger intramolecular H-bonding, whereas Conformer-B shows stronger intermolecular H-bonding.
5. Another psychedelic molecule, mescaline, was explored. Which revealed two low-energy conformers differing by approximately 0.5 kcal/mol (B3LYP/cc-pVTZ) and 1.5 kcal/mol (CCSD/cc-PVDZ). The difference stemmed from the orientation of the alkylamine group relative to the benzene ring, influenced by NH...π interaction.explored.
6. The geometric characteristics of these conformers closely resembled those observed in a previously conducted X-ray crystallography study. Additionally, our thorough spectroscopic examination, which included techniques such as 1H-NMR and UV spectroscopy, as well as precise vibrational mode calculations, consistently corroborated the data reported in scientific literature for all three molecules: psilocybin, psilocin, and mescaline.

Summary of Objective 2

1. The conformational landscape of dithiothreitol (DTT) was extensively explored and found seven minimum energy geometries.
2. Dihedral angles in the molecule were varied through a relaxed scan at the B3LYP/cc-pVTZ level, followed by geometry optimization at the CCSD/cc-pVDZ level. Single-point energies for all conformers were then calculated at the CCSD(T)/CBS limit using the cc-pVNZ (N=T,Q) level, consistently showing similar energy patterns.

3. Two iso-energic structures, G'TG'1 and G'TT, were found among the conformers, despite their significant structural differences. These two conformers had the lowest energy, while the cyclic and other configurational counterparts of the global minimum had considerably higher energy.
4. The global minimum structure of DTT stabilized via an intramolecular sulfur-centered hydrogen bond, supported by various analyses. Computed data closely matched experimental results.
5. The conformational landscape of thioglycolic acid (TGA), another sulfur-containing molecule, was studied at the CCSD/cc-pVDZ theoretical level. The GGC conformer was identified as the global minimum, closely followed by the GAC conformer. The calculated rotational constant for the GGC conformer matched well with previous experimental results.
6. The study further delved into sulfur-centered hydrogen bonding in TGA's dimer and trimer clusters, using the CCSD/cc-pVDZ theoretical level. It revealed that both oxygen and sulfur atoms equally participated in non-covalent H-bonding, enhancing stability and contributed to their cooperativity. These interactions were confirmed through AIM, RDG, and NBO analysis. ESP charge and vibrational mode analysis provided additional support for these findings.
7. LED analysis employing the DLPNO-CCSD(T)/cc-pVTZ method unveiled that electrostatic correlation energy ranks as the foremost contributor to the interaction energy in all TGA clusters, with exchange and dispersion correlation energy following closely.

Summary of Objective 3

1. The stability of the disulfide bond in cystine when interacting with a copper cluster (Cu9). This investigation employed the B3LYP/LAN-L2DZ/6-311++G(d,p) theoretical approach.
2. The findings suggest that cystine primarily binds to Cu9 through its disulfide and carboxyl functional groups. Simulating the Raman spectrum revealed the

disulfide linkage disruption, as evidenced by the absence of the -S-S- stretching mode, consistent with previous experimental observations.

3. Additionally, NBO analysis showed that lone pairs of electrons from oxygen and sulfur atoms contribute to copper in the Cu9-cystine system. Furthermore, results from MK ESP charge, FMO, and AIM calculations corroborated these findings.
4. The chemical transformation of PATP into its dimer DMAB (p,p-dimercaptoazobenzene) on copper nanoclusters and its stability on bismuth-based clusters, specifically the BOC (bismuthoxycarbonate) cluster were discussed.
5. In this study, the PW91PW91 generalized gradient approximation for exchange-correlation functionals were utilized. Copper and bismuth atoms were treated with relativistic effective core potentials (RECP) using LANL2DZ, while carbon, hydrogen, nitrogen, sulfur, and oxygen atoms were analyzed using the 6-311+G(d,p) basis set.
6. The simulated SERS spectrum of DMAB on copper clusters closely resembled the experimental SERS spectrum of PATP on copper. Conversely, when simulating the SERS spectrum of PATP-BOC, it exhibited a remarkable match with the experimental counterpart, indicating the absence of dimerization.
7. Dimerization of PATP on copper clusters involved metal-to-molecule charge transfer, while the genuine SERS spectrum of PATP emerged from molecule-to-metal charge transfer when the BOC cluster served as the SERS substrate.

7.2 Future Scope:

Going forward, the research endeavors initiated herein may encompass further exploration centered on the following objectives:

- ❖ To conduct molecular dynamics simulations on the psychedelic molecules explored in this study, with the aim of enhancing our understanding of their binding mechanisms to their respective targets and estimating the kinetics and free energy associated with these interactions.

- To investigate the varying solvent effects on these psychedelic molecules, along with the aforementioned sulfur-containing TGA and DTT molecules, in order to gain a deeper understanding of their interactions with solvent molecules.
- To investigate DTT clusters in order to delve deeper into intermolecular sulfur-centered hydrogen bonding.
- To investigate intramolecular versus intermolecular sulfur-centered hydrogen bonding within clusters of biologically and chemically significant molecules.
- To conduct experimental SERS measurements on the molecules studied herein, including novel compounds, using various metal SERS substrates to explore and comprehend the interactions between molecules and metal nanoparticles.