COMPARATIVE COMPUTATIONAL ANALYSIS OF ALCOHOLS (C1–C4): IMPLICATIONS IN PHARMACEUTICAL AND DRUG DESIGN APPLICATIONS

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ABSTRACT

In this study, we perform a comparative quantum chemical analysis of methyl, ethyl, propyl, and butyl alcohols using ORCA 4.2.1 software. The primary focus includes zero-point energy (ZPE), infrared spectra, dipole moments, and rotational constants. Geometry optimization was done using the MMFF94 force field with steepest descent in Avogadro. The optimized structures were used to compute vibrational and spectroscopic data through RHF/def2-SVP methods. The data reveals a correlation between molecular weight and properties such as ZPE, IR peak intensities, and dipole moment magnitude. These physicochemical parameters provide insight into potential pharmacokinetic and pharmacodynamic behavior, highlighting the importance of small-molecule alcohol analogs in drug formulation, delivery, and interaction profiles.

Keywords: Zero-point energy, IR spectroscopy, Dipole moment, Alcohols, ORCA, Molecular modeling, Drug design, Quantum chemistry.

1. INTRODUCTION

Small alcohols like methanol, ethanol, propanol, and butanol are among the most common organic compounds used in pharmaceutical formulations, both as excipients and as active intermediates. Their physicochemical properties, such as dipole moment, hydrogen bonding capabilities, and solubility parameters, make them critical in drug solubilization and bioavailability enhancement. Furthermore, alcohol-based scaffolds are often used in medicinal chemistry to modify drug molecules to improve membrane permeability or alter binding interactions with biological targets [1,2].

Quantum chemical modeling has emerged as an essential tool in understanding molecular properties, reactivity, and interaction potential [3,4]. Computational chemistry approaches such as Hartree-Fock (HF) and density functional theory (DFT) provide accurate insights into molecular structure, energy profiles, and vibrational characteristics [5]. These properties play pivotal roles in predicting drug-likeness and pharmacological behavior.

Recent studies have explored the quantum properties of alcohols using computational techniques for understanding intermolecular interactions, solvent effects, and protein-ligand binding mechanisms [6]. Spectroscopic fingerprints such as IR and vibrational frequencies are critical for identifying functional groups and elucidating molecular environments, often correlating with biological activity [7].

In this study, we extend the quantum chemical analysis of alcohols from methyl to butyl alcohol, comparing their zero-point energies, IR vibrational frequencies, dipole moments, and rotational constants. This comparative study aims to provide a deeper understanding of how molecular weight and structure influence these properties and their relevance to the pharmaceutical and drug design fields.

2. METHODOLOGY

All geometry optimizations were performed using the MMFF94 force field with a steepest descent algorithm in Avogadro software. The optimized structures were then used to generate input files for ORCA 4.2.1. The following parameters were applied: ! RHF OPT FREQ def2-SVP. This method includes:

- Hartree–Fock theory (RHF)

- Geometry optimization (OPT)
- Frequency analysis (FREQ)
- Basis set: def2-SVP

The IR spectra, zero-point energies (ZPEs), and dipole moments were computed from frequency calculations. Each alcohol (C1–C4) was modeled separately with consistent convergence criteria.

3. RESULTS AND DISCUSSION

Table 1 summarizes the computational results for each alcohol, showing trends with increasing molecular weight.

Table 1: Computationally derived quantum chemical properties of C1–C4 alcohols (methanol to butanol), illustrating their molecular weight, zero-point energy (ZPE), infrared (IR) peak frequencies, dipole moments, and rotational constants.

Property	Methanol	Ethanol	Propanol	Butanol
Molecular Weight (g/mol)	32.04	46.07	60.10	74.12
Zero-point Energy (ZPE, Eh)	0.09811	0.13123	0.15353	0.17656
ZPE (kcal/mol)	61.56	82.36	96.38	110.79
Highest IR Frequency (cm^{-1})	3987.15	4190.12	4186.61	4194.75
Dipole Moment (Debye)	1.79	1.95	1.68	1.63
Rotational Constant A (MHz)	13782.7	10183.0	8574.8	7721.3

As expected, ZPE increases with molecular weight due to the increase in vibrational modes. However, the highest IR frequency remains consistently in the region associated with O–H stretching (~3900–4200 cm^{-1}), which is essential for H-bonding in biological systems. Dipole moments show minor variations, reflecting subtle structural changes that may influence solvation behavior and protein binding.

Rotational constants show a decreasing trend with increasing chain length, indicating increased moment of inertia. These constants can affect microwave spectra and molecular recognition.

Pharmaceutical Relevance:

The physicochemical parameters derived here have direct applications in pharmaceutical sciences:

- **Solubility & Permeability**: Molecules with higher dipole moments and optimal ZPEs are generally more soluble and can cross membranes efficiently [8].
- **Drug Delivery**: Short-chain alcohols are often used as co-solvents in injectable formulations to enhance the solubility of poorly soluble drugs [9].
- **Binding Affinity**: IR spectra and dipole behavior are vital in understanding drug-receptor interactions, particularly for H-bond-dependent targets such as enzymes or transporters [10].

Quantum chemistry, especially when applied to small bio-relevant molecules like alcohols, enables rational drug design by allowing prediction of molecular behavior without extensive empirical testing. Such approaches complement experimental pharmacology and contribute to cost-effective lead identification.

4. CONCLUSION

This research provides a computational insight into the comparative quantum properties of C_1–C_4 alcohols, highlighting how molecular weight and structure influence spectroscopic and electronic behavior. The trends observed in ZPE, IR spectra, dipole moments, and rotational constants align well with theoretical expectations and bear pharmaceutical significance. These alcohols not only serve as chemical scaffolds but also play critical roles as excipients and bioactive agents in drug formulation and design. The application of quantum chemical modeling, as demonstrated here, supports the rational development of small molecules in medicinal chemistry.

5. REFERENCES

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