International Journal of Bioorganic Chemistry
2024; 9(1): 8-13
http://www.sciencepublishinggroup.com/j/ijbc
doi: 10.11648/j.ijbc.20240901.12
ISSN: 2578-9384 (Print); ISSN: 2578-9392 (Online)

Review Article

Short Review on Quantum Chemical Calculation, Chemical Reactivity, Biological Activity Comparison of 1,10-Phenanthroline and Adenine Ligands

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To cite this article:

Tadesse Bizuayehu Mersha, Abebaw Agegne. (2024). Short Review on Quantum Chemical Calculation, Chemical Reactivity, Biological Activity Comparison of 1,10-Phenanthroline and Adenine Ligands. *International Journal of Bioorganic Chemistry*, *9*(1), 8-13. https://doi.org/10.11648/j.ijbc.20240901.12

Received: December 8, 2023; **Accepted**: December 25, 2023; **Published**: January 18, 2024

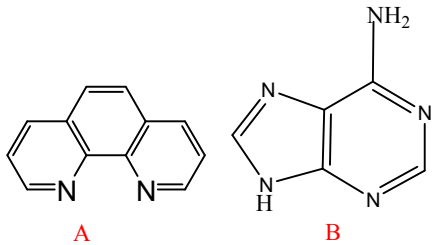
Abstract: In many scholars' investigation, inhibition of bacterial infectious diseases is one feature of organic ligands. However, identifying the right properties of the ligand have a significant role in medicinal applications. Therefore, 1, 10-phenanthroline and adenine are a rigid planar bidentate chelating agent ligand; which have a high stack interaction with the DNA base and have high biological activities. Furtherly, the quantum chemical distributors are also the key condition to get the therapeutic property. Hence in this review, we conduct the calculated quantum chemical distributors and in relating to this, the chemical reactivity and biological activity of ligands also carried out. The calculated energy gap for 1, 10-phenantheroline and adenine is 4.755 eV and 5.350 eV, respectively suggests that 1, 10-phenantheroline has good chemical reactivity and biological activity than adenine. Other calculated quantum chemical parameters namely, electronegativity, electronic chemical potential, global hardness, global softness, global electrophilicity index, and nucleophilicity index values, their chemical properties, and biological properties of the ligands summarized. The result of these parameters is agreed with the experimental values. The in *vitro* antibacterial activities of the ligands were tested on two G+ *Streptococcus pyogenes, Staphylococcus aureus* and two G-; *Escherichia coli*, *Klebsiella pneumoniae* bacteria and the results showed that, the in vitro antibacterial activity of 1, 10-phenanthroline significantly greater than adenine.

Keywords: Quantum Chemical Parameters, Chemical Reactivity, Biological Activity and Ligands

1. Introduction

1,10-phenanthroline is a rigid planar bidentate chelating agent [1-4] and it's a tricyclic aromatic organic compound of the three fused benzene rings [5]. Due to its planer structure, it found high affinity stack interactions between the DNA base pairs and due to also have a tendency to coordinate with many metals within the lone pairs of electrons through N-atoms in 1 and 10 position shown in (scheme 1**A**) [6].

Adenine is a purine nucleotide that exists in either the amino or imino tautomer forms. However, the amino tautomer is more stable and indeed predominantly under cellular conditions [7]. The exocyclic amino group is less expected to coordinate and the lone pair of electrons is mostly delocalized inside the ring through resonance. Therefore, N-atom of the imidazole ring is the best coordination site for adenine presented in (scheme 1B) [8].



Scheme 1. *The structure of 1,10-phenanthroline (A) and adenine (B).*

Inhibition of bacterial infectious diseases is one feature of organic ligands [9, 10]. However, identifying the further properties of the ligands have a significant role in medicinal applications. Based on this, it is well known that high Eigen value of HOMO, small HOMO-LUMO energy band gap and the biological activities of a compound are associated to its large dipole moment values [11]. This has initiated the researchers to think about new chemical and biological activities of the compounds [12]. Hence, the aim of this review is to calculate the quantum chemical descriptor values of the compounds and to examine the relative reactivity, the HOMO-LUMO frontier molecular orbitals were used and the wave function distribution of the molecules also described [13]. Moreover, other quantum chemical parameters like energy gap (Eg), electronegativity (χ), electronic chemical potential (μ), global hardness (η), global softness (σ), global electrophilicity index (ω), and nucleophilicity index (Nu) were derived from the energy HOMO – LUMO band gaps and this is important to rationalize or analyze the chemical reactivity of the compounds [13]. Generally, the quantum parameters of many compounds were reported [29, 30, 39]. However, there is no any information on the quantum chemical parameter calculations, chemical reactivity, and biological activity of 1, 10-phenanthroline and adenine. Therefore, in this review, we reported the quantum chemical calculations, chemical reactivity, and biological activity of 1, 10-phenanthroline and adenine ligands.

2. Materials and Methods

2.1. Computational Details

All computations were done with the Gaussian 16 program package. [14]. Geometry optimizations, absorption and frequency calculations of the ligands were performed at DFT/B3LYP [15] level together with 6-311++ G(d, p) basis set for the chelating agents [16] and the Los Alamos National Laboratory 2-Double-zeta (LanL2DZ) pseudopotential for cobalt atom [17]. Grimme's dispersion correction [18] was used to treat non-bonding interactions during the calculations. Such combination of functional and basis sets has been used in our previous studies [19, 20]. The results were visualized using Gauss View 06 software [21] and Chemcraft (Version 1.8) [22] software. The optimized geometries were confirmed to be real minima without any imaginary vibrational frequency by performing vibrational frequency calculations at the same level of the theory. The LUMO-HOMO and quantum chemical descriptors were also analyzed at the same level of theory [23, 24]. Such quantum chemical descriptors are used to relate the association between the antibacterial activity, stability and reactivity of compounds [24]. 1, 10-Phenanthroline (Chemical company BDH Ltd., Poole, England>99%), adenine (~ 99%, ACROS), and methanol (100%) were obtained from Hi Media Laboratories Limited., India. For physio-chemical characterization, UV-Vis spectrophotometer (Sanyo SP65) was used to record the electronic spectra in the absorbance range from 200 - 800 nm. FT-IR spectra in KBr pellets were recorded with the help of Perkin Elmer spectrum BX spectrophotometer in the range of 400 - 4000 cm^{-1}.

2.2. Assessment of Antibacterial Activities

Using disc diffusion methods, the in vitro antibacterial activities of 1, 10-phenanthroline and adenine ligands were tested on two Gram negative *E. coli* and *K. pneumonia bacteria* [25]. The isolated bacterial were cultured on Muller Hinton agar and nutritional Blood agar [26]. At 4°C, these bacterial strains were kept in an adequate blood agar. Antibiotic disc (gentamicin) used as a standard.

3. Results and Discussion

3.1. FT-IR Spectroscopy

The FT-IR vibrational bands (experimental/calculated) at 1621/1630 cm^{-1} (s), 1588/1536 cm 1 (s), assigned for νC=C, νC=N vibrational stretching respectively, for 1, 10-phenanthroline ligand [26]. The experimental/calculated vibrational bands of free adenine imidazole νN-H vibrational band appeared at 3295/3542 cm^{-1} (m) and primary amine of the pyrimidine ring at 3121/3508 cm^{-1} (s) ν(H-NH). The higher vibrational band appeared at 3295/3542 cm^{-1} (m) indicates that, in chemical reaction the coordination site of adenine through N-atom (νC=N) of the imidazole ring [26]. The exocyclic amine group is not the coordinate site and lone pair of electrons mostly delocalized into the ring via resonance [24, 27].

3.2. Electronic Absorption Spectra

Two absorption bands at 229 nm and 263 nm are the electronic transitions of π→π* (C=C) and π→π* (C=N), respectively, for 1, 10-phenantheroline (L1) [29], and other absorption bands appeared at 205nm and 257nm assigned to be the electronic transitions of *π→π*(C=C) and n →π*(C=N) respectively.*

3.3. Quantum Chemical Calculations and Analysis

It is well known that high Eigen value of HOMO, small HOMO-LUMO energy band gap and the biological activities of a compound are associated to its large dipole moment values [29, 30]. Hence, we investigated the quantum mechanical descriptors of the studied ligands. To examine the relative reactivity, the HOMO and LUMO frontier molecular orbitals were used and the wave function distribution of the molecules also described [30]. Quantum chemical parameters: energy gap were calculated from the energy of LUMO and HOMO orbitals and these molecular orbitals were used to analyze the reactivity and the wave function distribution of the molecules. The energy of HOMO and LUMO were directly calculated form the Gaussian software; which are -6.690 and -1.935 respectively in 1, 10-phenantheroline ligand [31]. In adenine, the HOMO and LUMO values are -6.444 and -1.096 respectively [30].

The energy gap (ΔE) the compound calculated as ΔE = Energy of lowest unoccupied molecular orbital E_{LUMO}- Energy of highest occupied molecular orbital (E_{HOMO}) [29]. Hence, the energy gap for 1, 10-phenantheroline was 4.755 eV and the energy gap for adenine was 5.350 eV. Therefore, the energy band gap of 1, 10-phenantheroline less than the energy band gap of adenine. The minimum HOMO-LUMO energy band gap of 1, 10-phenantheroline confirms that high chemical reactivity and sizable intramolecular charge transfer than adenine.

According to Mersha, T. B. et al. and Bitew M, Desalegn et al. [29, 30], the electronegativity (χ) of the compound can be calculated as;

$$\text{Electronegativity } (\chi) = ½(\text{ELUMO} + \text{EHOMO})$$

Where ELUMO is Energy of Lowest Unoccupied Molecular Orbital

EHOMO is Energy of Highest Occupied Molecular Orbital

The electronegativity result of 1, 10-phenantheroline and adenine was -0.158 and -0.138 respectively, the higher electronegativity value of 1, 10-phenantheroline has the higher reactivity and also confirms has the higher biological activity while the less electronegativity value of adenine shows the less reactivity and biological activity; this was agreed with the reported experimental facts.

According to Bitew M, Desalegn et al.[30], the electronic chemical potential (μ) value obtained from the mathematical equation;

$$(\mu) = -½(\text{ELUMO} + \text{EHOMO}) \; or - \chi$$

Where ELUMO is Energy of Lowest Unoccupied Molecular Orbital

EHOMO is Energy of Highest Occupied Molecular Orbital

χ is electronegativity

Using the above mathematical equation, the electronic chemical potential (μ) value of adenine and 1, 10-phenantheroline was 0.138 and 0.158 electron volt respectively. This indicates, the higher electronic chemical potential (μ) value of the compound has a higher tendency of chemical reactivity and biological activity than the adenine ligand. According to [31], the global hardness (η) of the compound also calculated as;

$$\text{global hardness } (\eta) = ½(\text{ELUMO} - \text{EHOMO})$$

Where, ELUMO is Energy of Lowest Unoccupied Molecular Orbital

EHOMO is Energy of Highest Occupied Molecular Orbital

The calculated results of 1, 10-phenantheroline and adenine was 0.025 and 0.019 electron volt, respectively. The higher global hardness (η) value of 1, 10-phenantheroline confirms that has the good chemical and biological activity than the adenine ligand and here was agreed with the experimental values; presented in the supportive information.

According to Mersha, T. B. et al. [29], global chemical softness (σ) of the molecules calculated as,

$$(\sigma) = ½ \text{ (global hardness } (\eta)) = ½ (\eta)$$

The global chemical softness (σ) result of adenine and 1, 10-phenantheroline are 0.098 and 0.087, respectively. In this report, we confirm that the global softness (σ) was inversely related with chemical reactivity and the biological activity. Based on the calculated result, 1, 10-phenantheroline has higher chemical reactivity and biological activity than adenine.

According to Bitew M, Desalegn et al. [30], global electrophilicity index (ω) of the molecules calculated as;

$$(\omega) = \frac{½ \text{ (Electronic chemical potential } (\mu))2}{(\text{global hardness } (\eta))}$$

Or

$$\text{Global electrophilicity index} = \frac{-½(\text{EUMO} + \text{EHOMO})2}{2\eta}$$

Using the above mathematical formula, the global electrophilicity index (ω) of adenine and 1, 10-phenanthiroline was 0.196 and 0.175 respectively. The result of the studied ligands have indirect relationship with the chemical reactivity and biological activities. Therefore, the lower global electrophilicity index of 1, 10-phenantheroline confirms higher chemical reactivity and biological activity than the adenine ligand.

The nucleophilicity index (Nu) is the reciprocal of global electrophilicity index (ω); mean that of nucleophilicity index (Nu) calculated as;

$$\text{nucleophilicity index (Nu)} = \frac{1}{\text{global electrophilicity index } (\omega)}$$

Or

$$\text{Nu} = \frac{2\eta}{\mu 2}$$

The nucleophilicity index result of 1, 10-phenantheroline and adenine are 5.723 and 5.088 respectively. The nucleophilicity index (Nu) value was the invers of the experimental data presented in (Table 1). Therefore, from this finding we confirm that 1, 10-phenantheroline has the higher chemical reactivity and biological activity than the adenine ligand.

Generally, all quantum chemical parameter value was derived from E_{HOMO}-E_{LUMO}, these are used to analyze the chemical reactivity and biological activity of the compounds and their results are presented in (Table 1). The energy gaps (in eV) for 1, 10-phenantheroline and adenine were calculated to be 4.755 and 5.350, respectively inferring that 1, 10-phenantheroline has good chemical reactivity and biological activity than adenine. The small HOMO-LUMO energy gap showed the moderate reactivity of the studied compound [29].

Table 1. *Quantum chemical descriptors of the studied ligands adapted from [29, 30].*

Compounds	HOMO	LUMO	Energy gaps (eV)	Electronic chemical potential	Electronegativity	Global hardness	Global softness	Global Electrophilicity index	nucleophilicity index	dipole moment
L1	-6.690	-1.935	4.755	0.158	-0.158	0.025	0.087	0.175	5.723	5.192
L2	-6.444	-1.096	5.350	0.138	-0.138	0.019	0.098	0.196	5.088	3.398

Where L1 is 1, 10-phenantheroline and L2 is adenine

3.4. In Vitro Antibacterial Assessment

The *in vitro* antibacterial of free 1,10-phenanthroline ligand exhibited the greatest antimicrobial activities with inhibition zones ranging from 19.2±0.7 mm to 31.2±0.3 mm [32-34], for all the four organisms due to its flat geometry and the unbounded conjugation enables to entrapped with the genetic material of microbes and establishing a π-π connections with DNA base pairs [34]. The global softness (σ) of the studied compounds was found to increase from 1, 10-phenanthroline to adenine. This confirmed us the tendency of our compounds to interact with biological molecules (DNA, Proteins, enzymes, etc.) [34]. Furthermore, Comparing the magnitudes of global hardness 10-phenanthroline is higher than the magnitudes of global hardness of adenine, which indicates the, 10-phenanthroline ligand would have promising activity to interact with soft biological molecules [35].

According to Mersha, T. B. et al. and Bitew M, Desalegn et al. [29, 30], the magnitudes of electronic chemical potential (μ), nucleophilicity index (Nu) and dipole moment of 1, 10-phenanthroline also higher than the magnitudes of global hardness, electronic chemical potential (μ), nucleophilicity index (Nu) and dipole moment of adenine, which indicates the 1, 10-phenanthroline ligand would have promising activity to interact with soft biological molecules.

On the experimental studied bacteria strain, adenine showed good activities with inhibition zones ranging from 16±0.5 mm to 22±0.7 mm [29, 36] and its activity lower than 1, 10-phenanthroline [37, 38]. The global chemical softness of adenine grater 1, 10-phenanthroline, indicates the adenine ligand would have promising activity to interact with hard biological molecules [39].

In many scholars finding, the free ligands have high toxicity and they could not be directly used for medicinal applications, this caused by its strong chelating nitrogen atoms binds with metal centers and inhibiting metalloenzymes [39, 40]. However, by identifying their properties its possible know the mechanism to minimize their toxicity and benefit for biological application is coordinating them with metal ion. Based on this, using various mathematical calculations the quantum chemical parameter values were obtained. Their chemical and biological properties and comparison of 1, 10-phenanthroline and adenine ligands were reported as generating evidence for education.

4. Conclusion

In this review, the two heterocyclic ligands were characterized by FT-IR, UV-Vis Spectrometry and the Gaussian calculation such as electronegativity, electronic chemical potential, global hardness, global softness, global electrophilicity index, and nucleophilicity index were derived from the energy of HOMO – LUMO band gaps and these are important to analyze the chemical reactivity of the compounds also reported. Based on the calculation values 1, 10-phenanthroline is better chemical reactivity than adenine. In vitro antibacterial tests and in quantum chemical calculated results confirms that 1, 10-phenanthroline have better biological activity than adenine ligand. However, in the experimental study, both of compounds were found to be biologically active in all tested pathogens. Moreover, the experimental and calculated results were found to be agreed and hence we suggest in vivo biological evaluations to further confirm and consider the ligands for medicinal applications.

Author Contribution

Tadesse Bizuayehu has in the contribution of all the manuscript preparation, analyzed the data, and writing-review & editing the final manuscript.

Abebaw Agegne also contribute in reviewing the final manuscript.

Data Availability Statement

The raw data of the research are not available for this review paper.

Acknowledgments

The authors acknowledged the staff members of Debark University for their moral support and assisting to review this paper.

Conflicts of Interest

The authors declare no conflicts of interest.

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