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Quantum Chemical Calculation, Hemolytic Effect and Anti-Denaturation Activity of Schiff Base Ligand

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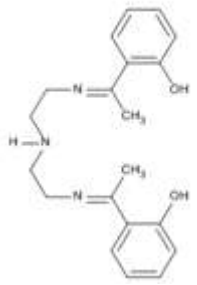
***Abstract*—** *A Schiff base ligand 2-[(1E)-N-{2-[(2-{(Z)-[1-(2-hydroxyphenyl) ethylidene] amino}ethyl)amino]ethyl}ethanimidoyl]phenol was selected for quantum chemical calculations and biological effects evaluations. The quantum calculation showed stability and reducing character of the Schiff base. In addition, in vitro hemolytic and anti-denaturation activities were evaluated. The Schiff base showed no toxic effect (hemolytic activity) in vitro. For anti-denaturation effect, the Schiff base exhibited significant activity against denaturation of egg proteins with I% decreasing with increase of temperature. In conclusion, results of the present investigation indicate that the ligand can be a potential anti-denaturant agent.*

***Keywords*—** *Schiff base, hemolytic, denaturation, quantum.*

I. INTRODUCTION

Schiff bases are a special class of ligands and represent an important class of organic compounds, which had got wide applications in various fields. These Schiff bases display activities such as antibacterial, anticonvulsant, anti-inflammatory, anticancer, anti-hypertensive, anti-fungal, antipyretic, antimicrobial, anti-HIV, cytotoxic activity, hypnotic, and herbicidal. On the basis of the above discussion and owing to the bioactivity of Schiff bases, we sought to undertake in vitro hemolytic and anti-denaturation effects of the Schiff base 2-[(1*E*)-*N*-{2-[(2-{(*Z*)-[1-(2-hydroxyphenyl) ethylidene] amino}ethyl)amino]ethyl} ethanimidoyl] phenol. In addition, the quantum chemical calculations were investigated.



Scheme 1. The Schiff base ligand.

II. EXPERIMENTAL

Computational studies

Experimental and calculated vibration was carried out HyperChem 08 software[1], with molecular mechanic force field (MM+) and semi-empirical AM1, PM3 methods. The optimized structure and chemical reactivity descriptors HOMO and LUMO energies calculated using Software Gaussian 03[2]. Each one of the following parameters such as Ionization Potential (IP), Electron Affinities (EA), global hardness (η), global softness (σ), electronegativity (χ), chemical potential (μ) and electrophilicity index (ω) was calculated by using the following equations[3]:

$$IP = -EHOMO \quad (1)$$

$$EA = -ELUMO \quad (2)$$

$$\eta = E\,LUMO - E\,HOMO \quad (3)$$

$$\sigma = (1/\ \eta) \quad (4)$$

$$\chi = -(\frac{EHOMO - ELUMO}{2}) \quad (5)$$

$$\mu = (\frac{EHOMO - ELUMO}{2}) \quad (6)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

In vitro hemolytic Assay

To 285µL of 0.5% (v/v) erythrocytes/ Thyrode, 15µL of different concentrations of the ligand (0.025-1.0 mg/mL) were added. The mixture was incubated at 37ºC for 1 h or 4 h. After centrifugation at 10000 g over 5 min, absorbance of the supernatant was measured in 96-well plates using a microplate reader at 570 nm[4]. Triton X100, which induces 100% hemolysis, was used as a positive control.

Anti-inflammatory activity

In vitro inhibition of proteins denaturation

The anti-inflammatory activity of the Schiff base *via* inhibition of proteins denaturation was explored according to the method of Akkouche et al. [5]. A volume of 100 µL of the tested compound (dissolved in acetone 4% in a buffered solution) was added to 2 mL of egg white protein solution (pH 6.6). Acetylsalicylic acid (0.562 mg / mL) was used as standard. The control consists of 2 mL of egg white protein solution and100µL of acetone. The samples were heated at 55, 60, 65, 70, and 75°C for 10 min and then cooled for 15 min. The transmittance (T %) was determined at 650 nm, and the inhibition % of denaturation was calculated using the following formula:

$$\text{Inhibition}(\%) = (\text{Tsample}\% / \text{T\%Acetylsalicylic acid}) \times 100$$

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III. Results and Discussion

Quantum chemical calculation

In this study, chemical reactivity descriptors and the optimized structure were calculated using Gaussian software. The optimized structure of the Schiff base as shown in Figure 1.

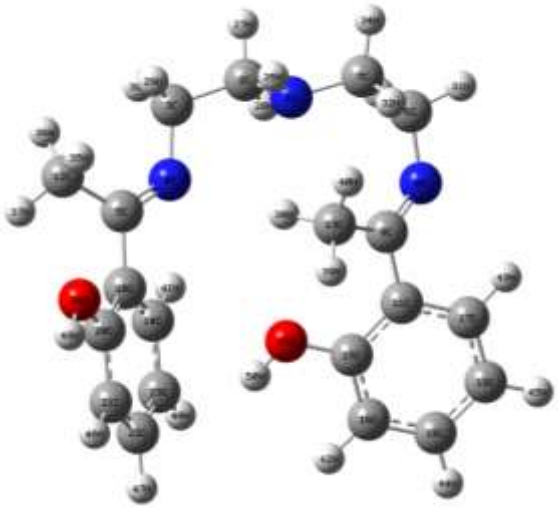

Fig. 1. The optimized structure of the ligand

The chemical reactivity descriptors including the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) were calculated for L, as shown in Figure 2. In addition, results presented in TABLE I, give information from the reactivity of the ligand L, (nucleophilic or electrophilic character) like L polarization and its ability to accept or to attract electrons by the compute of global hardness, global softness, Electronegativity and Electrophilicity index. The difference between HOMO and LUMO energies, $\Delta E = (E_{LUMO} - E_{HOMO})$ which is an important factor for the stability of molecules. In our results, E HOMO = -5.517927 eV and E LUMO = -0.191309 eV. The energy gap between LUMO and HOMO = 4.606618 eV. In this study, result indicates the highest stability of the synthesized Schiff base **L**, this result is in best agreement with the result reported in literature, that large HOMO–LUMO energy gaps indicate the stability of molecules[6]. On the other hand, and according to the previous results of Salihović et al.[7], we predict that our Schiff base ligand **L** has the properties of a reducing agent in oxidation-reduction reactions.

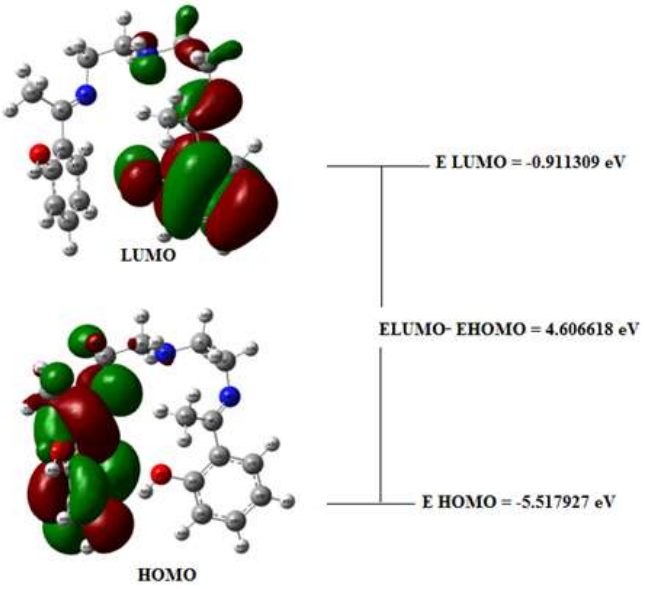

Fig. 2. HOMO and LUMO populations of the ligand.

TABLE I. Calculated global scalar properties of **L**

Ionization Potential (IP)	Electron Affinities (EA)	Global hardness (η)	Global softness (σ)	Electronegativity (χ)	Chemical potential (μ)	Electrophilicity index (ω)
5.517927	0.191309	2.303309	0.434157	-2.854615	2.854615	1.768938

For the IR vibrational spectrum of the ligand L and the complex, the results obtained in Figure 3 indicate the good correlation between experimental and calculated IR vibration in the both methods, AM1 and PM3, with correlation coefficient values of 0.9875 and 0.9930 for the ligand. These results are in good agreement with the results reported in the literature, that PM3 method gives highest correlation between experimental and calculated vibration[1].

Hemolytic Assay

In this test, the effect of L on red blood cells, which have been used as a model system for the study of interaction between drugs and biomembranes[8], was investigated. This interaction could lead to diverse effects, including cell damage, formation of complexes with macromolecules, and immune reactions[4]. In this method, the effect of L on hemolysis of human red blood cells suspension was evaluated using a UV–visible spectrophotometer. Results did not show changes in hemolytic activity when the mixture was incubated for 1 h and changes did not exceed 5% at the concentration of 1 mg/mL after 4 h of incubation. These results do not agree with previous studies that showed that hemolysis was observed for phenolic compounds which can interact with membrane lipids and proteins of erythrocytes and lead to membrane damage[9].

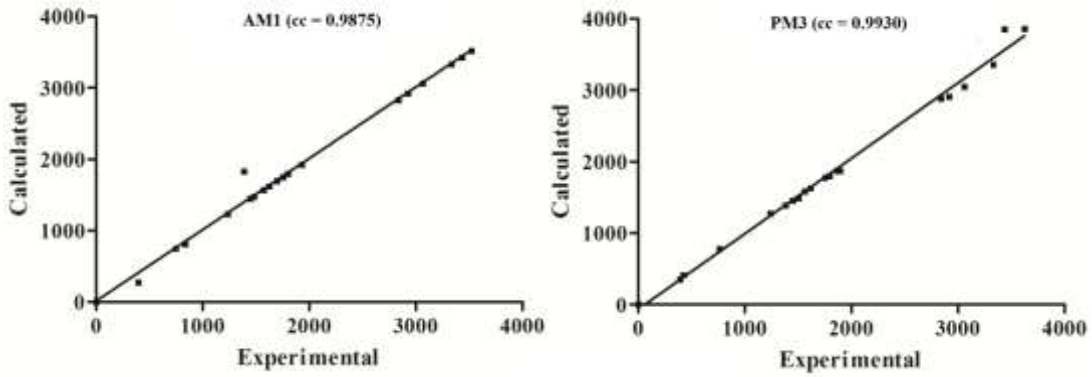

Fig. 3. Graphical correlations between the experimental and calculated IR vibration of L obtained by AM1 and PM3 semi-empirical methods (cc = correlation coefficient).

Anti-inflammatory activity
In vitro assay

In vitro anti-denaturation assay is used to predict the anti-inflammatory effect of a tested compound. Proteins lose their biological function when exposed to high stress or to a strong acid or base, a concentrated inorganic salt, an organic solvent, or heat[10]. Results of the present study show that the Schiff base L exhibits significant anti-inflammatory activity as presented in Figure 4. L protected egg white proteins from denaturation against increasing thermal treatment. Due to the structural similarities of L with nonsteroidal ant-inflammatory drugs (presence of aromatic ring and hydroxyl groups) **L** exhibits the same similar effect of these drugs against proteins denaturation.

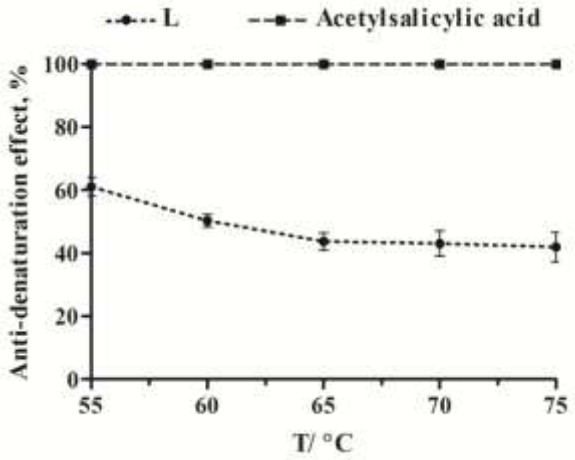

Fig. 4. Anti-denaturation effect of **L** and Acetylsalicylic acid at different heat treatments.

IV. Conclusions

Results of the present investigation indicate that the ligand can be a potential anti-denaturant agent.

Acknowledgments

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