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## Synthesis and Characterization of Cu(I)-Folic Acid Complex A Theoretical and Experimental Study

*Salah Aldin Jassim Humadi\**  
*Kafa Khalaf Hammud\*\**

*Faliah Hassan Ali Al-Jeboori\*\**  
*Thaera A. Mussa\*\**

*Ahmed A. Alwan\*\**

\*Department of Chemistry, College of Science, University of Diyala, Iraq.

\*\*Material research Directorate, Ministry of Science and Technology, Baghdad, Iraq

E-mail: [drsalahalmula@gmail.com](mailto:drsalahalmula@gmail.com)

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### Abstract:

Copper (I) complex containing folic acid ligand was prepared and characterized on the basis of metal analyses, UV-VIS, FTIR spectroscopies and magnetic susceptibility. The density functional theory (DFT) as molecular modeling calculations was used to determine the donor atoms of folic acid ligand which appear clearly at oxygen atoms binding to hydrogen. Detection of donation sights is supported by theoretical parameters such as geometry, mulliken population, mulliken charge and HOMO-LUMO gap obtained by DFT calculations.

**Key words:** Folic Acid, DFT, Copper, Complex, Computational Chemistry.

### Introduction:

Copper is one of the essential trace elements in human body as a composition element of many enzymes such as tyrosinase, superoxide dismutase and cytochrome oxidase that are responsible for regulating the intracellular redox potential. Folic acid has a potential anticancer activity on some important cases such as breast, colorectal and ovarian carcinomas [1]. The absorption of metal – folic acid complexes as drugs are higher than the folic acid itself [2]. Many researchers report that the biological activity of NSO derivatives including folic acid and their copper complexes [3-7]. Due to

Tweedy's theory, partial sharing of positive metal ion charge with donor atom lead to reduce the polarity of metal cation through metal–ligand chelation [8]. According to overtone's concept, antimicrobial activity mechanisms of metal complexes can be explained by its ability to pass through the lipid cell membrane that need good lipo-solubility to be effective inside the cell [9]. Anticancer activity of copper complexes is due to their ability to produce reactive oxygen species (ROS) by REDOX reactions. Monovalent copper ion ( $\text{Cu}^{1+}$ ) can reduce  $\text{H}_2\text{O}_2$  to hydroxyl radical ( $\text{OH}^\bullet$ ), while divalent is reduced to mono by superoxide anion according to the following redox reactions [10]:



Several studies for the evaluation of copper complexes for antibacterial and antifungal activities test against different types of organisms were carried out. It is found that positive results have been obtained for some of these complexes and the activity is proportional to complexes concentration, more concentration means more inhibition of fungal and bacterial growth [11]. Prior to the implementation of practical experiments in ligand metal complexation field, theoretical calculations are recommended to gain view about some needed parameters. Molecular modeling is a term that refers to mathematical calculations used to simulate various chemical parameters at the molecular level. To verify their findings, many chemical researchers support their laboratory experiments through this modeling.

By molecular modeling, several method levels (ranging from semi empirical methods to high accuracy methods like density functional theory–DFT with different basis set) are required to study (metal – ligand complexation) to get full theoretical view about some important parameters within this field such as HOMO-LUMO, total energy, ionization energy, infrared frequencies, molecular geometry, ...etc. One of the important parameters used in this job is mulliken population. This parameter is so important to determine the donor atoms of ligand [12,13].

The aim of this study is to prepare new copper (I) complex with important biological compound that is folic acid and characterize it with elemental and spectroscopic techniques then compare the obtained spectral data with the theoretical calculations.

## Materials and Methods:

All chemicals used are of the reagent grade and used without further purification. Metal content is measured by using atomic absorption spectrometer (AAS) Shimadzu (Japan) instrumentation. FTIR spectra are recorded on a IRPrestige-21. Shimadzu, Japan spectrometer in the range (4000–400)  $\text{cm}^{-1}$ .

Synthesis of copper (I)-folic acid complex is performed by mixing (0.1mole) of the metal chloride with (0.2 mole) of folic acid in 50 ml of distilled water, the mixture solution is heated at about 60 °C and pH adjustment at (7.6–7.8) by  $\text{KHCO}_3$ . The clear solution was obtained and the resulted volume was concentrated to about 25 ml, cooled in an ice-cold water and a yellowish green precipitate was obtained. The complex was filtered, washed with ethanol several times and recrystallized from warm water then washed with ethanol. The complex began to decompose at 320°C before it melts.

## Computational Methods:

Density functional theory (DFT) and B3LYP method at 3-21G levels was established. The energy minimization, molecular geometry, total energy and mulliken populations were calculated for folic acid ligand and its complex with  $\text{Cu}^{1+}$ . ChemBio3D Ultra package is used to carry out the calculations with time consuming processing reaching more than 48 hours for some runs.

## Results and Discussion:

The newly prepared and characterized copper (I)- folic acid complex with high melting point and 1:2 (metal : ligand), supported by atomic absorption measurements of the copper metal content which is found about 6.9%. The UV-VIS spectrum of folic acid (Figure (1)) shows three absorption bands at (256, 283, and 364) nm

assigned to ( $\pi \rightarrow \pi^*$ ), ( $\pi \rightarrow \pi^*$ ), and ( $n \rightarrow \pi^*$ ) transitions respectively. The UV-VIS spectrum of Cu(I) complex (Figure 2) exhibits a high intense absorption band at 283 nm and a shoulder at 363 nm which may be assigned to ligand field and charge transfer transitions respectively [14].

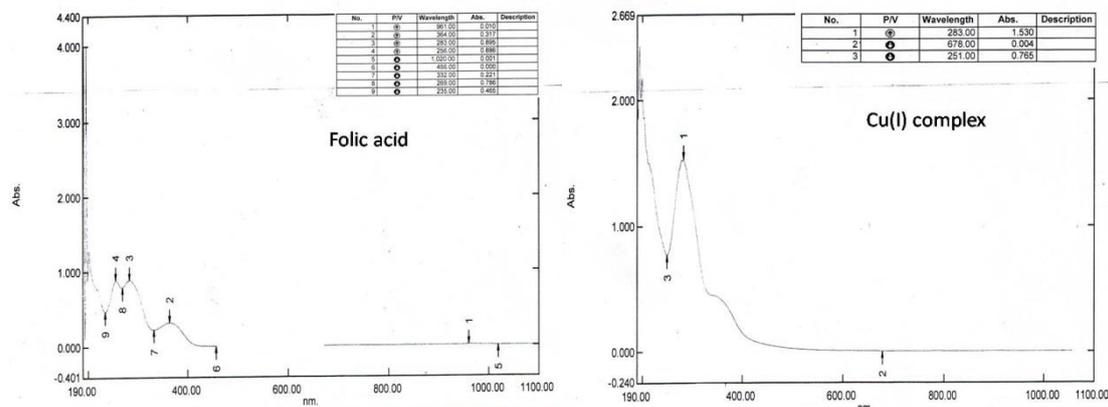


Fig. (1): Uv-vis spectrum of Folic acid

Several FTIR absorption bands of folic acid are shown in Figure(2) and Table -1. The spectrum showed two bands at (3545, 3417)  $\text{cm}^{-1}$  due to (OH, H<sub>2</sub>O). The bands appear at (3321, 3241, 3101)  $\text{cm}^{-1}$  assigned 1<sup>o</sup>, 2<sup>o</sup> amines and NH amide group respectively. The same spectrum shows two weak bands at (3101 and 2927)  $\text{cm}^{-1}$  assigned to aromatic and aliphatic CH stretching, while band at (2835)  $\text{cm}^{-1}$  is assigned to symmetrical C-H vibration. Two weak bands appear at (1340 and 1294)  $\text{cm}^{-1}$  are assigned to C-OH of the carboxylic groups. Additional absorption bands appear in folic acid as shown in Figure 2.

Copper (I) complex with folic acid (Fig. 2) shows disappearance of OH bands that reflect the deprotonation of folic acid from both sides of carboxylic groups and confirm coordination sites from each of the deprotonated oxygen of carboxylic groups. Bands at (3263 and 3194)  $\text{cm}^{-1}$  are due to amine groups. Appearance of a medium band 835  $\text{cm}^{-1}$  suggesting the presences of coordinated water in complex[15,16]. Broadening of

Since this metal ion belongs to  $d^{10}$  system, there is no presence of (d-d) transitions. Magnetic measurements show that the complex is diamagnetic material. Therefore, the stereochemistry of the prepared complex cannot be derived from the electronic spectra.

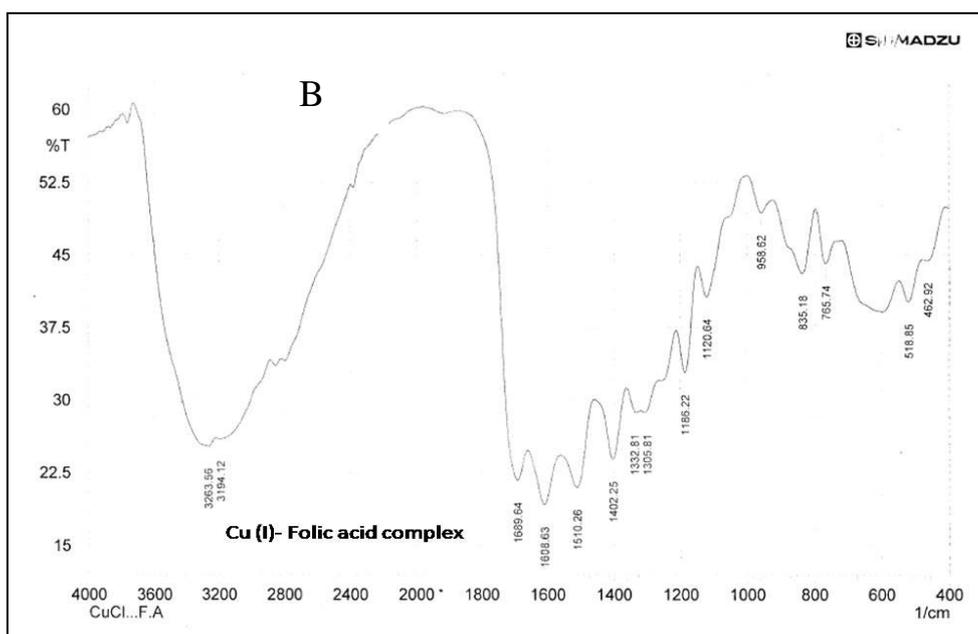
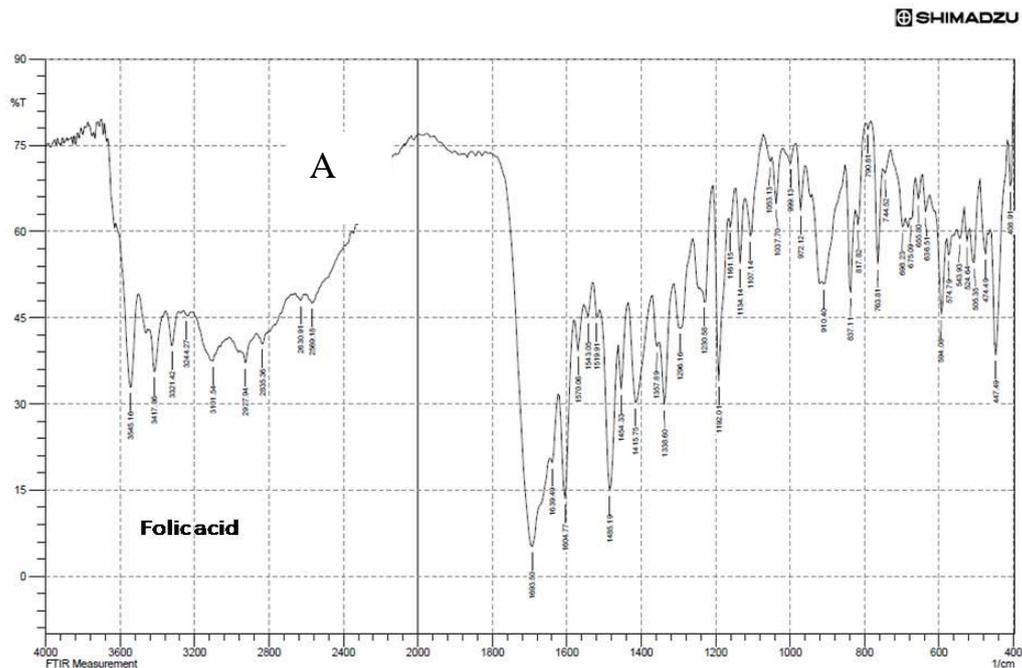
OH confirm the presence of H<sub>2</sub>O as two coordination and two hydrate molecules [3,17]. The appearance of M-O group at (518)  $\text{cm}^{-1}$  is a good evidence of complexation. This conclusion suggest that the geometrical structure of the complex is the octahedral shape. The appearance of this new band supports the involvement of oxygen atom in complexation with the metal ion under investigation.

### Computational Results:

Table -2- shows mulliken populations for each atom of the ligand that possess unshared electron pair donor (oxygen and nitrogen atoms) showing that O7 and O32 atoms have the highest value of mulliken populations compared to the other atoms and this means that the mentioned atoms represent the best donors to the cationic metal [18]. As observed in (Table 3 ), the interactions of Cu(I) with folic acid ligand in both cases (protonated and deprotonated forms) show that all calculated parameters prefer the deprotonated folic

- copper complex due to Cu-O32 and Cu-O7 bond shortening compared to

protonated one from 1.791Å<sup>o</sup> to 1.765Å<sup>o</sup> and from



**Fig(2): FTIR Spectra of both Folic Acid (A) and its Complex with Copper (I) Metal ion (B).**

**Table (1): Infrared Spectral Data of the prepared Folic Acid and its Cu(I) Complex**

Compound name	Wavelength (cm <sup>-1</sup> )- note
Folic acid	(OH, H <sub>2</sub> O) (3545,3417), 1 <sup>o</sup> and 2 <sup>o</sup> amines (3321,3241), NH amide (3101), CH aromatic and aliphatic respectively (3101,2927), aliphatic CH (2835), CO amide (1693).
Cu(I) complex	Amines (3263,3194), CO amide (1689), Cu(I)-O (518).

and from 1.818A<sup>o</sup> to 1.7714A<sup>o</sup> respectively which reflects the strong interaction upon the deprotonated form. The higher energy gap between HOMO-LUMO levels of the deprotonated complex indicates the highly stability of complex compared to the smaller gap of the protonated complex [19]. Finally, the low mulliken charges of copper in deprotonated complex confirm the donor ability of ligand to Cu(I) center [20]. As seen in (Fig.3-5), optimized structures of folic acid ligand and its complex with Cu(I) are observed with both options. All the experimental FTIR

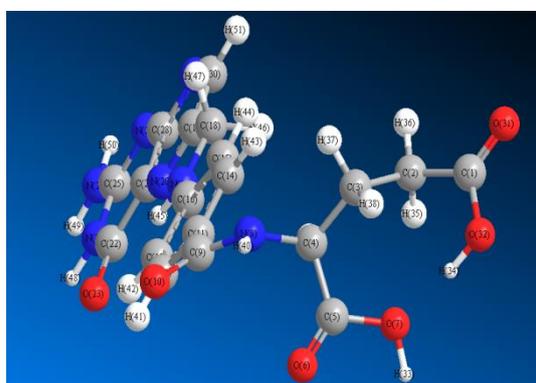
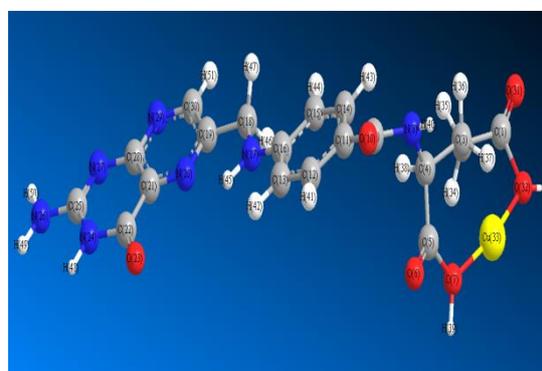
and theoretical obtained values confirm that the deprotonated folic acid ligand interact with (protonated and deprotonated forms of the ligand). The two atoms (O7 and O32) due to complexation. Based on the foregoing informations, an octahedral geometry has been suggested as seen in Fig-6.

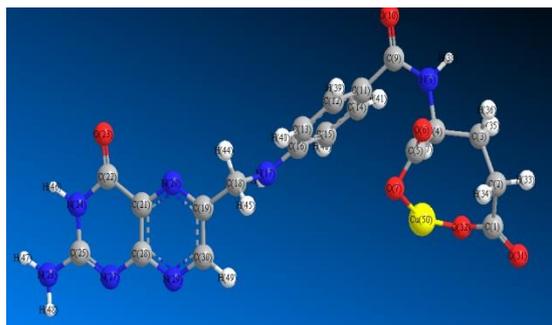
**Table-2:- Mulliken Popoulations of ligand calculated at DFT- B3LYP/3-21G**

Atom	Mulliken population
O6	8.437506
O7	8.560655
N8	7.652008
O10	8.484711
N17	7.801694
N20	7.615289
O23	8.473807
N24	7.806975
N26	7.777872
N27	7.640242
N29	7.532753
O31	8.468997
O32	8.588127

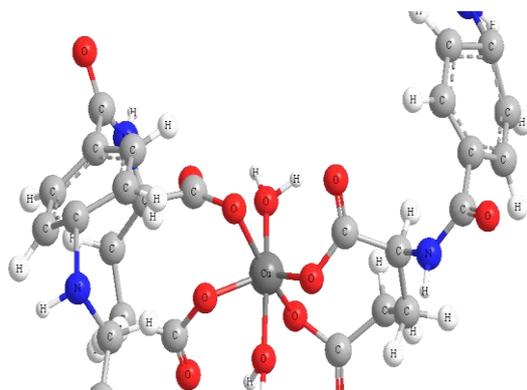
**Table 3: Theoretical Parameters calculated by DFT –B3LYP/3-21 G.**

	Folic acid ligand	Folic acid ligand+ Cu <sup>+1</sup>	Deprotonated folic acid ligand+ Cu <sup>+1</sup>
O32- Cu	.....	1.791	1.765
O7-Cu	.....	1.818	1.7714
HOMO	-7.076	-2.277	-6.582
LUMO	-2.836	-1.552	-2.298
HOMO- LUMO gap	-4.24	-0.725	-4.284
Total energy	-1560.6	-3192.8	-3191.7
Mulliken charge		0.860540	0.486165

**Fig. (3): Optimized Structure of Folic Acid Ligand calculated by DFT – B3LYP/3-21 G.****Fig. (4): Optimized Structure of Cu(I) –Folic Acid (protonated form) calculated by DFT–B3LYP/3-21G.**



**Fig. (5): Optimized Structure of Cu(I)-Folic Acid (deprotonated form) calculated by DFT-B3LYP/3-21G.**



**Fig. (6): The Suggested Octahedral Geometry for the synthesized Complex".**

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## دراسة نظرية وعملية لتحضير وتشخيص معقد النحاس الاحادي مع حامض الفوليك

صلاح الدين جاسم حمادي\*  
كفاء خلف حمود\*\*  
فليح حسن علي الجبوري\*\*  
ثائرة عبد الرضا موسى\*\*  
احمد عبد الرضا علوان\*\*

\*قسم الكيمياء ، كلية العلوم، جامعة ديالى، العراق  
\*\* دائرة بحوث المواد، وزارة العلوم والتكنولوجيا، بغداد ، العراق

### الخلاصة:

تم تحضير وتشخيص معقد النحاس الاحادي الحاوي على حامض الفوليك على أساس تحليل العناصر، (الامتصاص الذري)، مطياف الاشعة فوق البنفسجية – المرئية، تحت الحمراء والحساسية المغناطيسية. تم استخدام نظرية DFT كأساس للحسابات النظرية لتعيين الذرات المانحة من ليكاند حامض الفوليك والتي اظهرت بوضوح انها ذرات الاوكسجين المتأصرة بالهيدروجين. تم تأكيد مواقع الذرات المانحة من خلال المتغيرات الهندسية ومشاركة المليكان وشحنة المليكان وفرق الطاقة بين الهومو- لومو المستخرجة من حسابات DFT.

الكلمات المفتاحية: حامض الفوليك ، DFT ، النحاس ، المعقد ، الكيمياء النظرية.