

# Study of the Thermodynamic Parameters for Interaction of Ciprofloxacin Antibiotic with Bulk and Nanocopper Sulfate

Elsayed M. AbouElleef\* and Saleh D. Mekkey

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## Abstract

The association parameters of both bulk and nano-CuSO<sub>4</sub> salts in (EtOH-H<sub>2</sub>O) mixed solvents were estimated at room temperature (293.15K) using conductivity method by applying Fuoss-Shedlovsky calculation. The association parameters of nano-CuSO<sub>4</sub> was greater than bulk CuSO<sub>4</sub> salt. The interaction between the cation (Cu<sup>2+</sup>) with ligand (ciprofloxacin, CFL) in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15K) was determined by the conduct metric method. The formation Gibbs free energies change ( $\Delta G_f$ ) and transfer Gibbs free energies change ( $\Delta G_t$ ) were increased in negative signs with increasing in EtOH content in the binary solvent. Two stoichiometric complexes 1:2 and 1:1 (M:L) are formed and the formation constant and Gibbs free energy of the formed complexes follow the order:  $K_f$  (1:1) >  $K_f$  (1:2) and  $\Delta G_f$  (1:1) >  $\Delta G_f$  (1:2) for (M:L) ( in negative values), which indicate more favorable formation of (1:1) complex compared with (1:2) complex. Also there are a decrease in values of  $K_f$  and  $\Delta G_f$  in case of using nano-CuSO<sub>4</sub> than that of using bulk-CuSO<sub>4</sub> but in small difference due to the more solvation effect in case of using nanoparticles.

**Keywords:** Copper Sulfate, Ciprofloxacin, Association Parameters, Complexation, Formation Constant, Gibbs Free Energy. Mixed Solvents.

## Introduction

The investigation of the complexation formation reactions of the ligand with various cations in organic solvent is important for understanding the mechanism of biological transport, molecular recognition, and other analytical applications (Jose et al. 2009). Transition metal cations have a vital role in redox enzyme systems and bio-inorganic chemistry and also provide the basis of

### Elsayed M. AbouElleef\*

Chemistry Department, Faculty of Arts and Science, Northern Border University, 91911 Rafha, Kingdom of Saudi Arabia.  
Basic Science Department, Delta Higher Institute for Engineering & Technology, 35681-Dakhliya, Mansoura, Egypt.

### Saleh D. Mekkey

Chemistry Department, Faculty of Arts and Science, Northern Border University, 91911 Rafha, Kingdom of Saudi Arabia.  
Department of Chemistry, Faculty of Science, Al-Azhar University, Cairo, Egypt.

\*Email: s.abouelleef@yahoo.com

models biological systems (Angelusiu et al. 2010). It is helpful to consider the free energy, enthalpy and entropy change contributions to complexation reactions to obtain a good understanding of the thermodynamics of the complexation formation reactions (Gomaa et al. 2014a; Helmy et al. 2016).

The different techniques like polarography, spectrophotometry and conduct metric depends on physical and chemical properties of a material solution have been used to determine the complex formation between different metal cations within the ligand in the solutions (Nezhadali et al. 2009 & 2008). The conduct metric is an electrochemical technique, which is an extremely widespread and useful tool with a highly sensitive, simple and inexpensive experimental arrangement, that is used for studying the formation of complex between transition metal cations and ligand in solution (Harwood et al. 1989). It is very important to study complexation formation between different metal cations and ligand in a various solvent systems and their effect on solute's solvation by the solvent mixtures (Christopher et al. 2004; Nezhadali et al. 2011).

Thermodynamics parameters were used in understanding many systems and have vital importance for learning about the spontaneity of a given process at a certain temperature (Gomaa et al. 2013 a; Gomaa et al. 2013 b; El-Hady et al. 2012). Determination of stability constant is fundamental for understanding the behavior of the metal cations in a solution in the presence of some chelating agents and is best explained in terms of thermodynamics. Conductivity technique can be used to estimate the stability constant values, and also makes available the thermodynamics parameters of metal-ion complex formation.

Ciprofloxacin (generic name) is an antibiotic prescribed for treating a number of infections caused by susceptible bacteria including infections of bone, joint, lung, skin, intra-abdominal infections, certain type of infectious diarrhea, typhoid fever, and urinary tract infections, among others. It is used in addition to other antibiotics for some infections (Grabe et al. 2013; Baddour et al. 2005).

It is therefore necessary to study the effect of ciprofloxacin antibiotic on the properties of copper sulfate salt by determining the formation constant and the free energy change of interaction

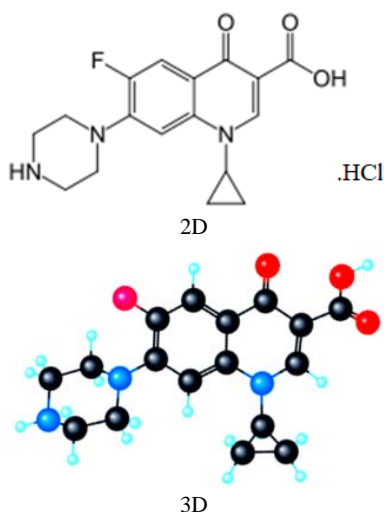
between them to find the extent of benefit of the ciprofloxacin antibiotic.

In this work, the association parameter for bulk and nano-copper sulphate salt in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15K) was determined by using the conduct metric method. The complex formation constant and stoichiometry of the complexation were elucidated between the metal cation (Cu<sup>2+</sup>) and the ligand (ciprofloxacin, CFL) in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15K) by using the conduct metric method to study the effect of the solvent mixture properties on the stabilities of the complexes.

## Experimental

### Materials and solutions

Copper sulfate salt (CuSO<sub>4</sub>·5H<sub>2</sub>O) and ethanol were obtained from Merck as analytical reagent grade materials and used without further purification while ciprofloxacin antibiotic (CFL) was from ["SANDOZ" a Novartis company].



**Figure 1.** Ciprofloxacin hydrochloride antibiotic (CFL).

Formula: C<sub>17</sub>H<sub>19</sub>ClFN<sub>3</sub>O<sub>3</sub>

Molar mass: 367.805 g/mol

The water and the binary mixed solvents of (EtOH-H<sub>2</sub>O) 0%, 20%, 40%, 60%, and 80% EtOH were used as the solvents under the study and were prepared by mixing EtOH and H<sub>2</sub>O (with error ± 0.01%).

### Apparatus

The conductance measurements were carried out with a conduct meter (OAKTON WD-35607-10,-20,-30) with platinum electrode and a cell constant equal 0.99. The temperature was adjusted on an ultra-thermostat (Kottermann 4130) with a constant temperature maintained within ±0.05°C.

### Procedure

### Preparation of Nano copper sulphate

The nano-CuSO<sub>4</sub> salt was prepared by using ball milling method, by shaking CuSO<sub>4</sub> salt in ball-milling apparatus of the type Retsch MM 2000 swing mill at 20225 Hz at room temperature for a period of one hour. The mill has 10 cm<sup>3</sup> stainless steel double-walled tubes. Two balls made from stainless steel of 12 mm diameter were used.

### Transmission electron microscopy (TEM) analysis

The TEM images of Nano copper sulphate sample in distilled water were measured using electron microscope model Joel 2010.

### Preparation of solutions

Solutions of Cu<sup>2+</sup> all at 10<sup>-3</sup> M were prepared by dissolving the accurately weighed amount of salt in proper volume of binary solvents. 10<sup>-3</sup> M solutions of ligand (CFL) were prepared by dissolving the accurately weighed amount of (CFL) in the proper volume of binary solvents.

### Conduct metric measurement

-To calculate the association parameters of bulk and nano-CuSO<sub>4</sub>·5H<sub>2</sub>O in the (EtOH-H<sub>2</sub>O) mixed solvent, a solution of metal cation (10<sup>-3</sup> M, 20 mL) was placed in a conductance cell, and the conductance was measured. The conductance of solution was measured after each addition of the mixed solvent using a microburette after stirring. The conductance reading, taken after 1.0 min of each addition, was corrected for dilution.

-To calculate the formation constants between CuSO<sub>4</sub>·5H<sub>2</sub>O and a ligand (Ciprofloxacin, CFL) in (EtOH-H<sub>2</sub>O) mixed solvents, a solution of CuSO<sub>4</sub>·5H<sub>2</sub>O salt (10<sup>-3</sup> M, 20 mL) was placed in a conductance cell, and the conductance was measured. The ligand (10<sup>-3</sup> M) (CFL) was transferred step by step to the conductance cell using a micropipette and the conductance was measured after each addition. The temperature used is room temperature (293.15K).

## Results and Discussion

### X-ray diffraction (XRD)

X-ray diffraction of investigated bulk and nano-CuSO<sub>4</sub> samples where nano samples prepared by ball mill method are shown in Figures 2 & 3. This new peaks at 2θ= 15.508, 16.322, 18.734, 22.364, 24.102, 27.035, 29.225, 32.825, 36.757, 47.096, 49.815, 56.364, 60.717, 67.086 may be due to elimination of water molecules by ball mill method. The nano-CuSO<sub>4</sub>·5H<sub>2</sub>O is better crystallized than bulk-CuSO<sub>4</sub>·5H<sub>2</sub>O and new faces are formed as clear in X-ray figs (3). The observed peaks are related to triclinic structure of CuSO<sub>4</sub>·5H<sub>2</sub>O as indexed in the standard data (Varghese et al. 1985).

By using Scherrer's Formula, the crystalline sizes of the samples have been estimated.

$$d_{XRD} = k\lambda/\beta\cos\theta \quad (1)$$

Where  $k$  is a shape factor which is taken to be 0.9,  $\lambda$  is the used wavelength of x-rays used (1.5405 nm),  $\beta$  is the full width at half maximum and  $\theta$  is the angle of diffraction. The obtained crystalline sizes are found to be in the nanometer scale range. The average crystal size is obtained in Table (1).

Table 1: XRD data of bulk and nano-CuSO<sub>4</sub>.5H<sub>2</sub>O samples.

Sample	Crystal size $d_{XRD}$ (nm)
Bulk CuSO <sub>4</sub> .5H <sub>2</sub> O	141.45
Nano CuSO <sub>4</sub> .5H <sub>2</sub> O	163.76

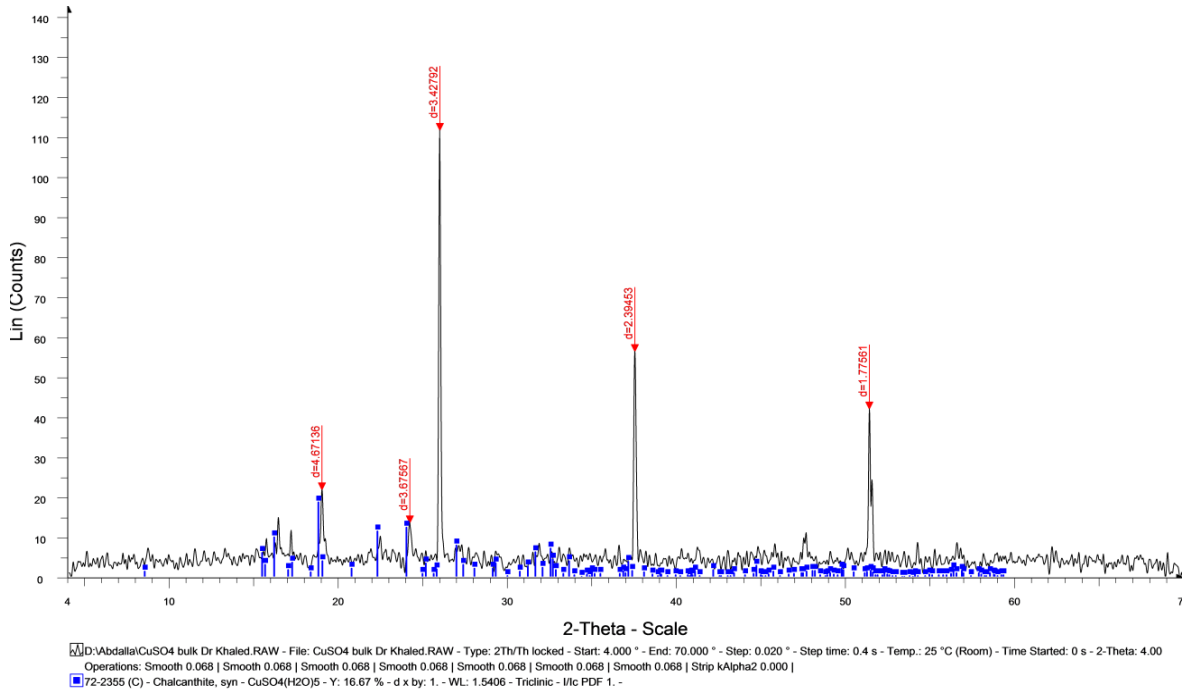


Figure 2: X-ray diffraction of bulk-CuSO<sub>4</sub>.5H<sub>2</sub>O.

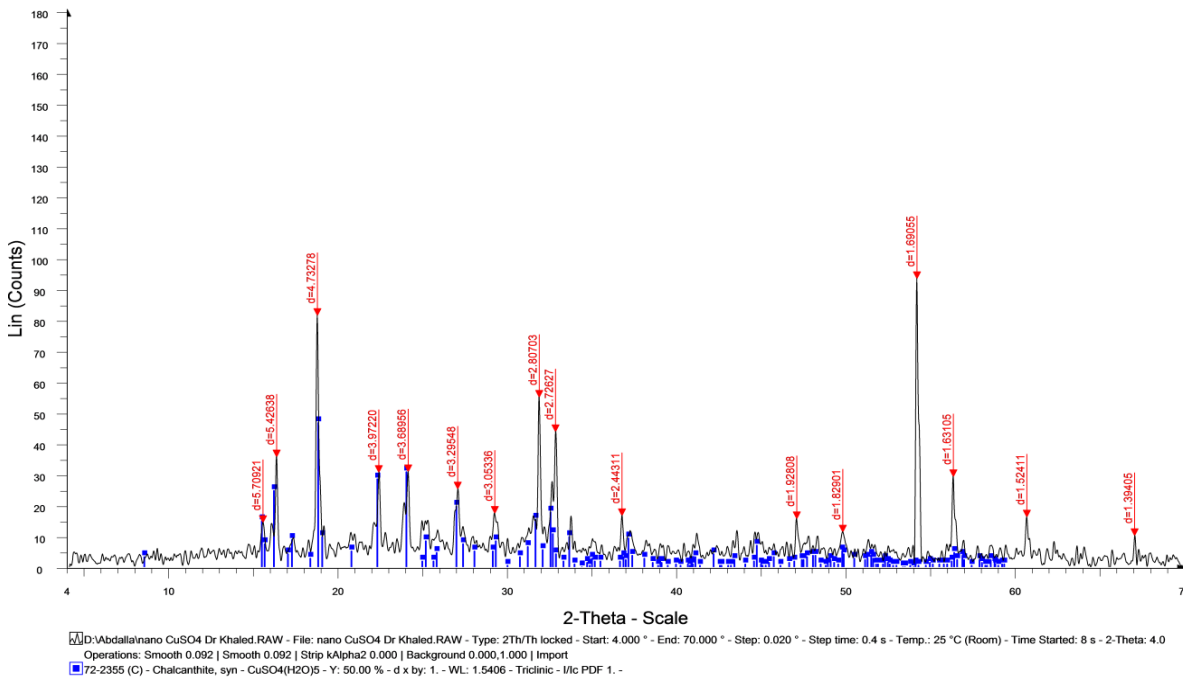


Figure 3: X-ray diffraction of nano-CuSO<sub>4</sub>.5H<sub>2</sub>O.

Scanning & Transmission electron microscope (SEM) & (TEM)

Transmission electron microscope (TEM) is a special kind of electron microscope for imaging of different objects. In TEM the electrons pass through with atoms of the sample and interact with the atoms and the electrons are therefore being scattered.

Their size and morphology of nano-CuSO<sub>4</sub>.5H<sub>2</sub>O are studied by TEM and CEM analysis. Fig. (4) shows the nanoparticles that obtained in ethanol are sphere like. The Nano particles are in the size ranging 5.027 – 49.33 nm. The all shapes are separated with defined boundaries. The diffraction image of TEM shown in Fig. (5) supported the X-ray diffraction; the nano-CuSO<sub>4</sub>.5H<sub>2</sub>O is better crystallized. The images are also indicated by SEM measurements in Fig. (6).

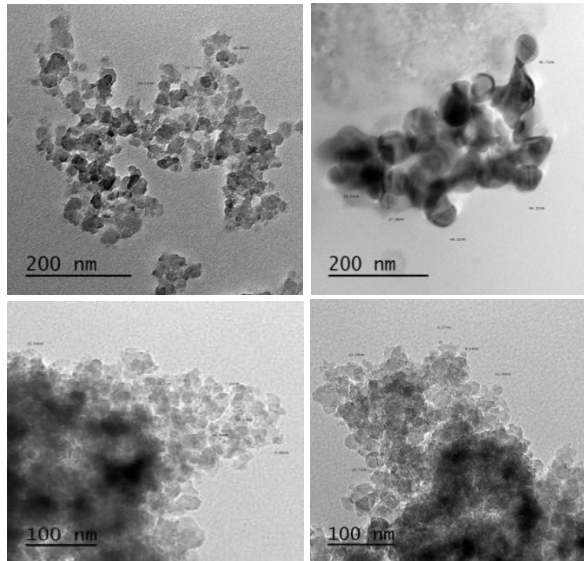


Figure 4: TEM images of nano-CuSO<sub>4</sub>.5H<sub>2</sub>O.

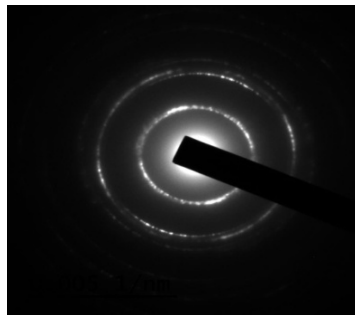


Figure 5: TEM diffraction image of nano-CuSO<sub>4</sub>.5H<sub>2</sub>O.

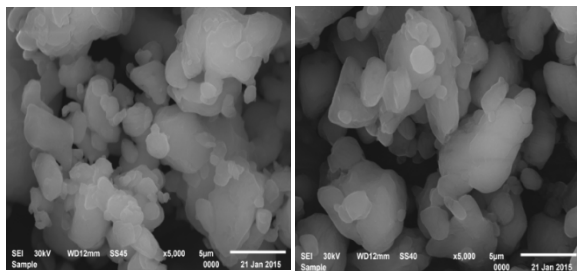


Figure 6: SEM images of nano-CuSO<sub>4</sub>.5H<sub>2</sub>O.

Calculation of association parameters for CuSO<sub>4</sub>.5H<sub>2</sub>O

The values of specific conductance (K<sub>s</sub>) for different concentrations of CuSO<sub>4</sub>.5H<sub>2</sub>O solution in (EtOH-H<sub>2</sub>O) mixed solvents were measured experimentally at room temperature (293.15 K). Also, the values of molar conductance (Λ<sub>m</sub>) can be calculated using equation (2) (Gryzybkowski et al. 1980; Gomaa et al. 2014b):

$$\Lambda_m = \frac{(K_s - K_{solv})K_{cell} \times 1000}{C} \quad (2)$$

where, K<sub>s</sub> and K<sub>solv</sub> are the specific conductance of the solution and the solvent, respectively; K<sub>cell</sub> is the cell constant, equal to 0.99 and C is the concentration of the CuSO<sub>4</sub>.5H<sub>2</sub>O solution in molar.

The limiting molar conductance (Λ<sub>0</sub>) at infinite dilutions was estimated by extrapolating the relation between Λ<sub>m</sub> and C<sub>m</sub><sup>1/2</sup> to zero concentration (Fig. 7).

The experimental data for conductance measurements were analyzed using Fuoss-Shedlovsky (Shdlovsky et al. 1956) extrapolation techniques which follows equation (3-12): -

$$\frac{1}{\Lambda S_{(z)}} = \frac{1}{\Lambda_0} + \left( \frac{K_A}{\Lambda_0^2} \right) (C \Lambda \gamma_{\pm}^2 S_{(z)}) \quad (3)$$

where, S<sub>(z)</sub> = 1 + Z + Z<sup>2</sup>/2 + Z<sup>3</sup>/8 + ..... etc. and

$$Z = \frac{S(\Lambda C)^{1/2}}{\Lambda_0^{3/2}} \quad (4)$$

The Onsager slope (S) can be calculated by knowing the value of (Λ<sub>0</sub>) from the equation (5):

$$S = a\Lambda_0 + b \quad (5)$$

$$\text{where, } a = 8.2 \times 10^5 / (\epsilon T)^{3/2} \quad (6)$$

$$b = 82.4 / \eta ((\epsilon T)^{1/2}) \quad (7)$$

where, (ε) is the dielectric constant of the solvent, (η<sub>0</sub>) is the viscosity of the a binary solvent and (T) is the temperature. Using the values of (ε) and (η<sub>0</sub>), the value of (S) were easily estimated. Using the data of (Λ), S<sub>(z)</sub> and (Λ<sub>0</sub>), the degree of dissociation (α) was calculated by equation (8):

$$(\alpha) = \Lambda S_{(z)} / \Lambda_0 \quad (8)$$

Using these (α) and (ε) values, the mean activity coefficients (γ<sub>±</sub>) were calculated by equation (9) (Debye et al. 1923):

$$\log \gamma_{\pm} = - A(\alpha C)^{1/2} / [1 + B r^0 (\alpha C)^{1/2}] \quad (9)$$

where, (z<sup>-</sup> z<sup>+</sup>) are the charges of ions A & B are the Debye-Hückel constant.

$A = 1.824 \times 10^6 (\epsilon T)^{-3/2}$ ;  $B = 50.29 \times 10^8 (\epsilon T)^{-1/2}$  and  $(r^o)$  is the solvated radius.

The association constant ( $K_A$ ) is given by equation (10):

$$K_A = \frac{C_{[MX_n]} \cdot \gamma_{[MX_n]}}{C_{M^{n+}} \cdot \gamma_{M^{n+}} \cdot C_{X^-} \cdot \gamma_{X^-}} \quad (10)$$

Using the values of association constant ( $K_A$ ), the values of the dissociation constant ( $K_D$ ) were easily calculated by means of the following equation (11):

$$K_D = 1/K_A \quad (11)$$

The triple ion association constant ( $K_3$ ) were calculated (Hirsch et al. 1956; Fuoss et al. 1959 a) by using the equation (12):

$$\frac{\Lambda C^{1/2}}{(1 - \frac{\Lambda}{\Lambda_o})^{1/2}} = \frac{\Lambda_o}{(K_A)^{1/2}} + \frac{\lambda_3^o C}{K_3 (K_A)^{1/2}} (1 - \frac{\Lambda}{\Lambda_o}) \quad (12)$$

Equation (12) was derived by Fuoss and using Walden approximation ( $\Lambda_o = 3\lambda_o$ ).

The values of free energy change of association ( $\Delta G_A$ ) of  $CuSO_4 \cdot 5H_2O$  solution in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15 K) were calculated (Popuych et al. 1972; Isabel et al. 1996) from the association constant ( $K_A$ ) values by using equation (13) (Atkins 1978; Ives 1971).

$$\Delta G_A = -2.303 RT \log K_A \quad (13)$$

From the calculated ( $\Delta G_A$ ) values, the free energies change of transfer ( $\Delta G_t$ ) from water (w) as a reference solvent to the (EtOH-H<sub>2</sub>O) mixed solvent (s) were calculated using equation (14).

$$\Delta G_t = \Delta G_{A(s)} - \Delta G_{A(w)} \quad (14)$$

Where  $\Delta G_{A(s)}$  and  $\Delta G_{A(w)}$  are the free energies of association in mixed solvents and in water, receptively.

The Walden product ( $\Lambda_o \eta$ ) values (Walden, 1906; Kay, 1973; Kay, 1991; Kay et al., 1968 and Fuoss, 1959 b) were calculated for the solutions of  $CuSO_4 \cdot 5H_2O$  in pure (EtOH) solvent and also

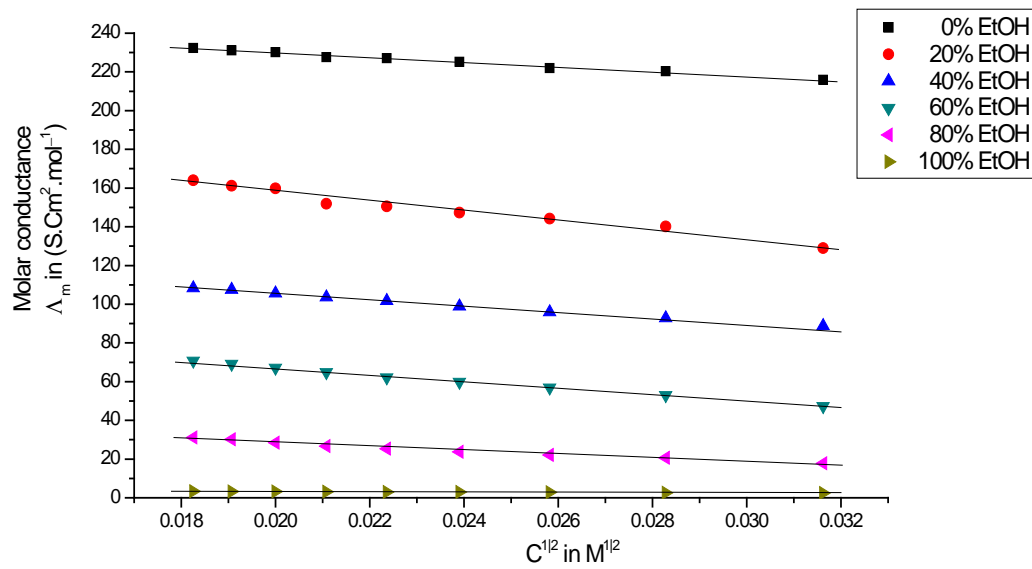
in (EtOH-H<sub>2</sub>O) mixtures. The Walden product values as computed from the limiting molar conductance values ( $\Lambda_o$ ) would be informative from the point of view of ion-solvent interactions.

The fluidity ratios (Bishopa et. al 1958) were also calculated by using equation (15).

$$R_x = \frac{\Lambda_o \eta_o (\text{in mixed solvent})}{\Lambda_o \eta_o (\text{in water})} \quad (15)$$

It was observed that the fluidity ratios ( $R_x$ ) values were decreased with increasing the organic solvent (EtOH) content in the (EtOH-H<sub>2</sub>O) mixtures; this is an indication of selective solvation of  $CuSO_4 \cdot 5H_2O$  or ion by the organic solvent molecules in this mixed solvent and is ascribed mainly to the decrease in the Zwanzig solvent relaxation effect (Zwanzig, 1963). In the other words, this decrease in Walden product ( $\Lambda_o \eta$ ) indicates strong solvent-solute interaction, as a result of which the solvent fails to decrease the mobility of ions and increases the viscosity of the medium. The strength of such interaction however increases with increase of the proportion of EtOH in (EtOH-H<sub>2</sub>O) mixtures. We see that Walden product is lower in water medium than in (EtOH-H<sub>2</sub>O) mixtures. This is explained by Frank and Wen (Franck et. al 1957) as follows: ions like quaternary ammonium salts that possess large hydrophobic side chains, a water molecule at the surface of these large ion is influenced very little by either the ionic charge or the inert hydrocarbon chain on its one side. Consequently, the water molecules on the hydrophobic surface can be oriented to a greater extent by their nearest neighbors and can, in effect, be oriented into cages about the hydrocarbon side chains that one similar in structure to polyhedral clathrate hydrates of this ion (Beurskens, et. al 1964). This clathrate like structures can be considered as a type of hydration, since increase the size of the moving entity. Ions experiencing this effect should have lower mobilities in aqueous solution than in non-aqueous solution, since only water appears able to form any appreciable amount of three-dimensional structure.

The calculated values of association parameters and Gibbs free energies change for the solution of bulk and nano- $CuSO_4 \cdot 5H_2O$  in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15 K), and were calculated and reported in Tables 2 & 3 and illustrated in Fig. (8).



**Figure 7:** Variation of the molar conductance  $\Lambda_m$  ( $S.cm^2.mol^{-1}$ ) with  $C^{1/2}$  for bulk  $CuSO_4.5H_2O$  in (EtOH- $H_2O$ ) mixed solvents at (293.15 K).

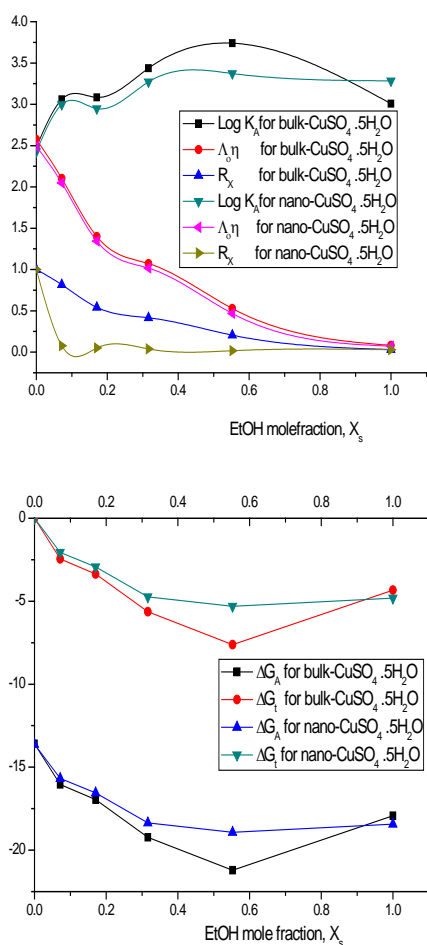
**Table 2:** The values of limiting molar conductance ( $\Lambda_o$ ), degree of dissociation ( $\alpha$ ), activity coefficient ( $\gamma_{\pm}$ ), dissociation constant ( $K_D$ ), triple ion association constant ( $K_3$ ), association constant ( $\log K_A$ ), Gibbs free energy change of association ( $\Delta G_A$ ), transfer free energy change ( $\Delta G_t$ ), Walden product ( $\Lambda_o \eta$ ) and fluidity ratios ( $R_x$ ) for bulk- $CuSO_4 .5H_2O$  in (EtOH- $H_2O$ ) mixed solvents at room temperature (293.15 K).

EtOH vol. %	$X_s$	$\Lambda_o$	$\alpha$	$\gamma_{\pm}$	$10^3 K_D$	$10^3 K_3$	$\log K_A$	$\Delta G_A$	$\Delta G_t$	$\Lambda_o \eta$	$R_x$
0	0	257.2	0.9209	0.9599	3.2953	1.8112	2.4821	-13.9320	0.0000	2.5761	1.0000
20	0.0716	207.3	0.7845	0.9572	0.8723	3.6223	3.0593	-16.0004	-2.0684	2.1022	0.8161
40	0.1706	135.6	0.7757	0.9592	0.8226	3.7044	3.0848	-17.3151	-3.3831	1.3988	0.5430
60	0.3163	101.6	0.6480	0.9583	0.3652	5.5745	3.4374	-19.2942	-5.3622	1.0732	0.4166
80	0.5523	48.2	0.5320	0.9514	0.1825	7.6645	3.7389	-20.9860	-7.0540	0.5281	0.2050
100	1	6.87	0.8452	0.7997	0.9835	1.3328	3.0072	-16.8795	-2.9475	0.0806	0.0313

**Table 3:** The values of limiting molar conductance ( $\Lambda_o$ ), degree of dissociation ( $\alpha$ ), activity coefficient ( $\gamma_{\pm}$ ), dissociation constant ( $K_D$ ), triple ion association constant ( $K_3$ ), association constant ( $\log K_A$ ), Gibbs free energy change of association ( $\Delta G_A$ ), transfer free energy change ( $\Delta G_t$ ), Walden product ( $\Lambda_o \eta$ ) and fluidity ratios ( $R_x$ ) for nano- $CuSO_4 .5H_2O$  in (EtOH- $H_2O$ ) mixed solvents at room temperature.(293.15 K).

EtOH vol. %	$X_s$	$\Lambda_o$	$\alpha$	$\gamma_{\pm}$	$10^3 K_D$	$10^3 K_3$	$\log K_A$	$\Delta G_A$	$\Delta G_t$	$\Lambda_o \eta$	$R_x$
0	0	248.7	0.9291	0.9597	3.7401	1.6921	2.4271	-13.6234	0.0000	2.4909	1.0000
20	0.0716	202.1	0.8035	0.9567	1.0027	3.3691	2.9988	-15.6839	-2.0604	2.0490	0.07641
40	0.1706	103.3	0.8180	0.9581	1.1258	3.1459	2.9485	-16.5501	-2.9266	1.3432	0.0501
60	0.3163	96.4	0.7116	0.9563	0.5354	4.5764	3.2712	-18.3615	-4.7381	1.0178	0.0379
80	0.5523	42.7	0.6777	0.9453	0.4246	4.9418	3.3720	-18.9270	-5.3036	0.4682	0.0174
100	1	4.2	0.7000	0.7726	0.5218	3.3472	3.2837	-18.4382	-4.8148	0.0728	0.0282

$\Lambda_o$  in ( $\Omega^{-1}.cm^2.mol^{-1}$ ),  $\Lambda$  in ( $\Omega^{-1}.cm^2.mol^{-1}$ ) and  $\Delta G_A$  in ( $kJ mol^{-1}$ ).

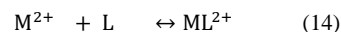


**Figure 8:** Variation of the association parameters ( $\log K_A$ ,  $\Lambda_{01}$ ,  $R_x$ ) and Gibbs free energy change ( $\Delta G_A$ ,  $\Delta G_i$ ) for bulk and nano- $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  in (EtOH- $\text{H}_2\text{O}$ ) mixed solvents at (293.15 K).

It is obvious that the values of the association constant ( $K_A$ ) and the triple ion association constant ( $K_3$ ) were found to be increased in increasing the EtOH content in the binary solvent. Gibbs free energies change of association ( $\Delta G_A$ ) and transfer Gibbs free energies change of association ( $\Delta G_i$ ) were increased with negative signs in increasing in EtOH content. On contrary the values of Walden product ( $\Lambda_{01}$ ), fluidity ratio ( $R_x$ ), activity coefficient ( $\gamma_{\pm}$ ), dissociation constant ( $K_D$ ) of the  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  solutions in the EtOH is less than in  $\text{H}_2\text{O}$ . The decrease in the values of activity coefficient, limiting molar conductance, association constant, Gibbs free energy change of association, Walden product and fluidity ratios for nano- $\text{CuSO}_4$  in comparison to bulk- $\text{CuSO}_4$  indicate that the association of nano- $\text{CuSO}_4$  is greater than bulk  $\text{CuSO}_4$  salt, due to the high surface to volume ratio of nanoparticles which lead to greater ability for ion-pair formation.

#### Calculation of formation constants for interaction of Ciprofloxacin antibiotic and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ solution in (EtOH- $\text{H}_2\text{O}$ ) mixed solvents

The binding of transition metal cation ( $\text{Cu}^{2+}$ ) with the ligand ciprofloxacin antibiotic (CFL) can be represented by following equilibrium equation:



where  $\text{M}^{2+}$ , L and  $\text{ML}^{2+}$  are the cation, ligand (CFL) and complex, respectively.

The formation constants ( $K_f$ ) for  $\text{CuSO}_4$  complexes in terms of molar conductivity were estimated by using equation (15) (Takeda et al. 1983 a; Nasrabadi et al. 2009).

$$K_f = \frac{[\text{ML}^{2+}]}{[\text{M}^{2+}][\text{L}]} = \frac{\Lambda_M - \Lambda_{\text{obs}}}{(\Lambda_{\text{obs}} - \Lambda_{\text{ML}})[\text{L}]} \quad (15)$$

and

$$[\text{L}] = [\text{L}]_t - \left\{ [\text{M}]_t \frac{\Lambda_M - \Lambda_{\text{obs}}}{(\Lambda_M - \Lambda_{\text{ML}})} \right\} \quad (16)$$

Where, [L] is the ligand concentration,  $\Lambda_M$  is the limiting molar conductance of the  $\text{CuSO}_4$  alone,  $\Lambda_{\text{obs}}$  is the apparent molar conductance of the solution during titration,  $\Lambda_{\text{ML}}$  is the molar conductance of the complex. The value of  $\Lambda_{\text{ML}}$  is determined from the value at point of large  $[\text{L}]_t$  to  $[\text{M}]_t$  ratios (Hakimi et al. 2008).

The variations of molar conductance ( $\Lambda_m$ ) versus the  $[\text{L}]_t / [\text{M}]_t$  mole ratio for  $(\text{Cu}-\text{CFL})^{2+}$  complex in binary EtOH- $\text{H}_2\text{O}$  mixture were studied at room temperature Fig. (9). Different lines were obtained with breaks indicating the formation of 1:2 and 1:1 (M:L) stoichiometric complexes (Zollinger et al. 1987). The molar conductance value ( $\Lambda_m$ ) always decreases with an increase in  $[\text{L}]_t / [\text{M}]_t$  mole ratio, showing that the metal cation ( $\text{Cu}^{2+}$ ) becomes less mobile upon complexation with ligand.

Valuable chemical information can be obtained between metal cations ( $\text{Cu}^{2+}$ ) and ligand (CFL) in in binary EtOH- $\text{H}_2\text{O}$  mixture. As it is shown in Table (4), the  $K_f$  value of the  $(\text{Cu}-\text{CFL})^{2+}$  complexes increases with increase in EtOH ratios. Insolvents with medium donicites, such as EtOH, a more stable complex is formed, while in strong solvating solvents, such as  $\text{H}_2\text{O}$ , the complex formation is poor. In general, in higher donor solvent, the metal ion is more strongly solvated.

The Gibbs free energy change of formation ( $\Delta G_f$ ) for each stoichiometric complex was calculated from equation (17) (Takeda et al. 1983 b):

$$\Delta G_f = -2.303 RT \log K_f \quad (17)$$



From the calculated ( $\Delta G_f$ ) values, the free energies change of transfer ( $\Delta G_t$ ) from water (w) as a reference solvent to the (EtOH-H<sub>2</sub>O) mixed solvent (s) were calculated using equation (14).

$$\Delta G_t = \Delta G_{f(s)} - \Delta G_{f(w)} \quad (18)$$

Where  $\Delta G_{A(s)}$  and  $\Delta G_{A(w)}$  are the free energies of association in mixed solvents and in water, respectively.

The obtained values ( $K_f$ ) for bulk and nano-CuSO<sub>4</sub> stoichiometric complexes and their calculated  $\Delta G_f$  and  $\Delta G_t$  values are presented in Tables (4 & 5).

It was found that formation Gibbs free energies change ( $\Delta G_f$ ) and transfer Gibbs free energies change ( $\Delta G_t$ ) were increased in negative signs with increasing in EtOH content in the binary solvent. Two stoichiometric complexes 1:2 and 1:1 (M:L) are formed and the formation constants and Gibbs free energies of the formed complexes follow the order:  $K_f$  (1:1) >  $K_f$  (1:2) for (M:L) and  $\Delta G_f$  (1:1) >  $\Delta G_f$  (1:2) for (M:L) (in negative values), which indicated the more favorable of formation of (1:1) complex compared with (1:2) complex. Also there are decrease in values of  $K_f$  and  $\Delta G_f$  in case of using nano-CuSO<sub>4</sub> than that of using bulk-CuSO<sub>4</sub> but in small difference due to the more solvation effect in case of using nanoparticles.

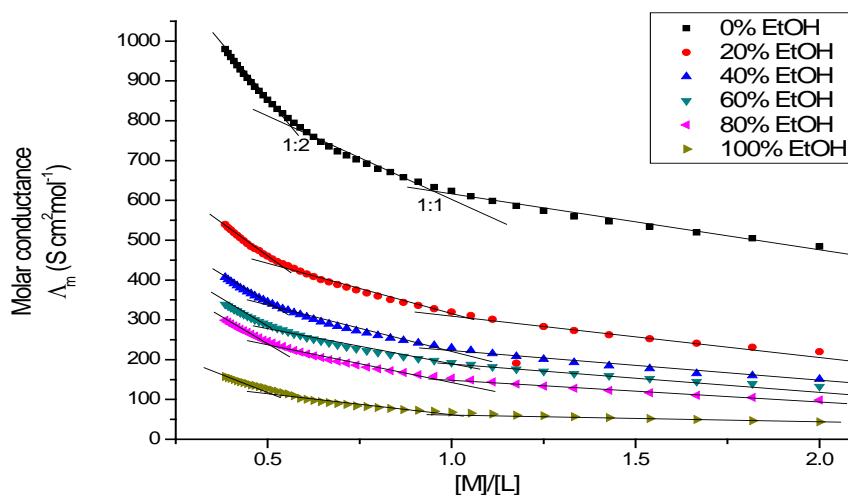
**Table 4:** Formation constants (log  $K_f$ ), Gibbs free energies change of formation ( $\Delta G_f$ ) and transfer free energies change ( $\Delta G_t$ ) for 1:2 and 1:1 (M/L) complex of bulk-CuSO<sub>4</sub> .5H<sub>2</sub>O with Ciprofloxacin, in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15 K).

EtOH vol. %	X <sub>s</sub>	Complex ratio (M:L)	log K <sub>f</sub>	ΔG <sub>f</sub>	ΔG <sub>t</sub>
0	0	(1:2)	2.384	-13.381	0.000
		(1:1)	3.022	-16.965	0.000
20	0.0716	(1:2)	2.453	-13.771	-0.390

40	0.1706	(1:1)	3.123	-17.530	-0.565
		(1:2)	2.466	-13.844	-0.463
		(1:1)	3.206	-17.993	-1.028
60	0.3163	(1:2)	2.469	-13.860	-0.488
		(1:1)	3.204	-17.985	-1.038
80	0.5523	(1:2)	2.559	-14.363	-0.982
		(1:1)	3.332	-18.702	-1.737
100	1	(1:2)	2.606	-14.628	-1.247
		(1:1)	3.450	-19.365	-2.400

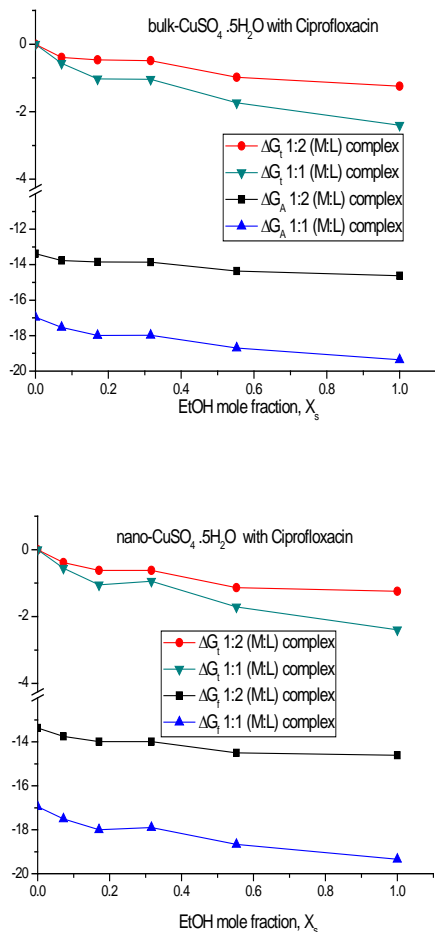
**Table 5:** Formation constants (log  $K_f$ ), Gibbs free energies change of formation ( $\Delta G_f$ ) and transfer free energies change ( $\Delta G_t$ ) for 1:2 and 1:1 (M/L) complex of nano-CuSO<sub>4</sub> .5H<sub>2</sub>O with Ciprofloxacin, in (EtOH-H<sub>2</sub>O) mixed solvents at room temperature (293.15 K).

EtOH vol. %	X <sub>s</sub>	Complex ratio (M:L)	log K <sub>f</sub>	ΔG <sub>f</sub>	ΔG <sub>t</sub>
0	0	(1:2)	2.382	-13.369	0.000
		(1:1)	3.020	-16.951	0.000
20	0.0716	(1:2)	2.450	-13.752	-0.383
		(1:1)	3.119	-17.507	-0.556
40	0.1706	(1:2)	2.492	-13.989	-0.620
		(1:1)	3.207	-18.002	-1.051
60	0.3163	(1:2)	2.492	-13.988	-0.620
		(1:1)	3.188	-17.896	-0.945
80	0.5523	(1:2)	2.584	-14.506	-1.137
		(1:1)	3.325	-18.665	-1.714
100	1	(1:2)	2.603	-14.612	-1.243
		(1:1)	3.447	-19.347	-2.396



**Figure 9:** Variation of the molar conductance ( $\Lambda_m$ ) with [M]/[L] for CuSO<sub>4</sub>.5H<sub>2</sub>O with CFL in (EtOH-H<sub>2</sub>O) mixed solvents at (293.15 K).





**Figure 10:** Variation of the Gibbs free energies change of formation ( $\Delta G_f$ ) and transfer free energies change ( $\Delta G_t$ ) for 1:2 and 1:1 (M:L) complex of bulk- and nano- $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  with Ciprofloxacin, in (EtOH- $\text{H}_2\text{O}$ ) mixed solvents at room temperature (293.15 K).

## Conclusion

The association constants of both bulk and nano- $\text{CuSO}_4$  salts in (EtOH- $\text{H}_2\text{O}$ ) mixed solvents were calculated using Fuoss-Shedlovsky method. It shows that the association parameters of nano- $\text{CuSO}_4$  is greater than bulk  $\text{CuSO}_4$  salt due to the high surface to volume ratio of nanoparticles which leads to greater ability for ion – pair formation.

The thermodynamic parameters of complexation reactions between bulk, nano- $\text{CuSO}_4$  salts and ciprofloxacin antibiotic in (EtOH- $\text{H}_2\text{O}$ ) mixed solvents were calculated from conductance measurement. It was found that the formation Gibbs free energies change ( $\Delta G_f$ ) and transfer Gibbs free energies change ( $\Delta G_t$ ) were increased in negative signs with increasing in EtOH content in the binary solvent. Two stoichiometric complexes 1:2 and 1:1 (M:L) are formed and the formation constant and Gibbs free energy of the formed complexes follow the order:  $K_f$  (1:1) >  $K_f$  (1:2) for (M:L) and  $\Delta G_f$  (1:1) >  $\Delta G_f$  (1:2) for (M:L) (in negative values),

which indicate the more favorable formation of (1:1) complex than (1:2) complex. Also there are decrease in values of  $K_f$  and  $\Delta G_f$  in case of using nano- $\text{CuSO}_4$  than that of using bulk- $\text{CuSO}_4$  but in small difference due to the more solvation effect in case of using nanoparticles.

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