Research Article

A Physical-Chemical Study of the Interference of Ceftriaxone Antibiotic with Copper Chloride Salt

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The nano-CuCl2.2H2O salt was prepared by the ball milling method. The association parameters for bulk and nano-CuCl2 salts in H2O are estimated at different temperatures using the conductivity method by applying the Fuoss–Shedlovsky equation and it was higher for nano-CuCl2 than bulk CuCl2 salt. The interaction between the cation (Cu2+) and ligand (ceftriaxone) in H2O was determined also by the conductometric method. Two stoichiometric complexes 1/2 and 1/1 (M/L) are estimated and 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) indicate the favorable of formation of (1/1) complex compared to the (1 : 2) complex. The Gibbs free energies change was increased in negativesignswithincreasingthetemperature. The antimicrobial activities of CFT, bulk Cu-CFT complex, and nano-Cu-CFT complex were studied on LB agar by the disc diffusion technique against clinical isolates of gram-negative bacteria (*Klebsiella pneumonia* and *Pseudomonas aeruginosa*) and Fungi (*Candida albicans*). It was observed that (CFT) has a higher zone of inhibition and antibacterial activity than that of bulk and nano-Cu-CFT complexes in *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (gram-negative bacteria). The nano-Cu-CFT complex showed a higher clear zone of inhibition and antifungal activity against candida than bulk Cu-CFT complex while the absence of the inhibition zone in CFT, so nano-Cu-CFT complex, can be used as an antifungal drug.

### 1. Introduction

Nanoparticles (NPs) are a wide class of materials that have a state between bulk and atomic or molecular structures in different shapes of 0D, 1D, 2D, or 3D and have a great scientific interest [1–5]. Bulk materials have constant physical properties, with size larger than one micrometer or micron. Nanoparticles can be used for various applications such as drug delivery purposes [6], diagnostics of cancer therapy, gene delivery purposes, chemical and biological sensing [7], gas sensing [8–10], CO2 capturing [11, 12], and other related applications [13–17]. Nanoparticles are often used to photocatalytically break down oil into biodegradable compounds, break down volatile organic pollutants in the air, and clean up carbon tetrachloride pollution in spring water [18, 19]. Nanoparticles (NPs) such as gold, silver, platinum, and palladium showed colors with the variation of shape and size and characteristic properties that can be utilized in bioimaging applications [20]. Another application of nanoparticles is the synthesis of photocatalysis S-doped TiO2 nanoparticles and the study of their photocatalytic, antimicrobial, and antioxidant activities under sunlight illumination [21].

Ceftriaxone [22–25] is an antibiotic that belongs to a category of medicine referred to as cephalosporin antibiotics, and it treats a variety of bacterial infections by stopping the growth of bacteria variety of bacterial infections (e.g., middle ear, lower tract, skin, and urinary tract), meningitis, gonorrhea, pelvic disease, and joint infections.
Thermodynamics parameters are an important tool for learning about the spontaneity of a given process at a particular temperature [26, 27]. Determination of the formation constant is fundamental for understanding the behavior of the metal cations in the presence of some chelating agent in a solution and is best explained using thermodynamics. A conductivity technique can be used to estimate the interaction between the metal cations and the chelating agent by estimating the thermodynamics parameters of metal-ligand complex formation [28–32].

It is therefore necessary to study the effect of antibiotic ceftriaxone on the properties of copper chloride salt by determining thermodynamics parameters of interaction between them using conductometric techniques to find the extent of benefit of the antibiotic ceftriaxone.

2. Experimental

2.1. Materials and Solutions. The purities and sources of the materials used are presented in Table 1. The structure of ceftriaxone is shown in Figure 1.

2.2. Apparatus. The conductance measurements are carried out with a conductometer A JENCO, Vision plus-EC3175 conductance instrument, and connecting with Kottermann ultra-thermostat-4130 (a deviation ±0.01 K) with a cell constant equal unity. The conductivity bridge was calibrated using standard potassium chloride solutions [33].

The Bruker $D_n$ Advance X-ray diffractometer is a powder XRD instrument used to record X-ray diffraction (XRD) patterns of bulk and nanosamples. The Bruker diffractometer with CuKα anode radiation ($\lambda = 0.1542$ nm) as a source is operating at 40 kV and 30 mA. The scanning range of over an angular range was between 4° and 80° at a temperature of 25°C, and the scan mode was applied with a step width of 0.02° per step and step time of 0.4 s.

IR instrument of the type Thermo Scientific Nicolet is10 FTIR spectrometer is operating in the spectral range of 7800 to 400 cm$^{-1}$ with a resolution of 4 cm$^{-1}$, midinfrared KBr beamsplitter 4000 to 400 cm$^{-1}$.

Solid samples can be prepared by grinding about 5 mg of sample mixed with 100 mg of spectroscopic grade KBr. This powder mixture is then compressed into a pellet using a mechanical press between 4 and 8 ton/cm$^2$. The powdered mixture is then compressed into a pellet using a sample mixed with 100 mg of spectroscopic grade KBr.

2.3. Procedure

2.3.1. Preparation of Nanocopper Chloride. The nano-CuCl$_2.2$H$_2$O salt was prepared by the ball milling method by shaking CuCl$_2.2$H$_2$O salt in a ball milling apparatus of the type Retsch MM 2000 swing mill at 20225 Hz at room temperature for one hour. The mill has 10 cm$^3$ stainless steel double-walled tubes. Two balls made from stainless steel of 12 mm diameter were used.

2.3.2. Preparation of Bulk Cu-CFT Complex and Nano-Cu-CFT Complex. Bulk Cu-CFT complex and nano-Cu-CFT were prepared according to a traditional method by refluxing 1 mmol of CFT under investigation with 1 mmol of bulk CuCl$_2.2$H$_2$O or nano-CuCl$_2.2$H$_2$O salts in an ethanolic solution for 2-3 h close to the boiling point of the solvent. The precipitate was filtered off, washed several times with absolute ethanol, and finally dried in vacuum desiccators over anhydrous calcium chloride.

2.3.3. Conductance Measurements. To calculate the association parameters of CuCl$_2.2$H$_2$O solutions, a solution of metal cation ($10^{-3}$ M, 20 mL) was placed in a double jacket glass conductance cell, and the conductance was measured after each addition of the solvent and stirring at a specific temperature.

To calculate the formation constants between CuCl$_2.2$H$_2$O and a ligand (ceftriaxone) in the solvents, a solution of CuCl$_2.2$H$_2$O ($10^{-3}$ M, 20 mL) was placed in a conductance cell, and the conductance was measured. The ligand ($10^{-3}$ M) (ceftriaxone) was added step by step to the conductance cell using a micropipette and the conductance was measured after each addition.

2.3.4. Biological Activity. The antimicrobial activities of CFT, bulk Cu-CFT complex, and nano-Cu-CFT complex were studied on LB agar by the disc diffusion technique against clinical isolates of gram-negative bacteria (Klebsiella pneumonia and Pseudomonas aeruginosa) and fungi (Candida albicans).

Sterile filter paper discs (6 mm) were individually immersed in dimethyl sulfoxide (DMSO) extract of CFT, bulk Cu-CFT complex, and nano-Cu-CFT complex, and DMSO was used as control. All the discs were dried, placed on the surface of the test bacterial and fungal, and incubated for 18 to 24 h at 37°C. The standard antibiotic used is ceftazidime (30 mg) and finally, the zones of inhibition were examined.

3. Results and Discussion

3.1. X-Ray Diffraction (XRD). The X-ray diffraction (XRD) pattern for the bulk and nano-CuCl$_2.2$H$_2$O salt is shown in Figure 2. The positions of the main peaks and their relative intensities as measured by powder diffraction are listed in Table 2.

The mean size of nanocrystals was determined from the diffraction peaks corresponding to the most intensive reflections according to the Joint Committee on Powder Diffraction Standards database. Scherrer’s equation was used to determine the average crystallite size for nanoparticles from the XRD diffraction pattern measured [34, 35]:

$$d = \frac{K\lambda}{\beta \cos \theta}$$

where $K$ is Scherrer’s constant (about 0.9), $\lambda$ is the wavelength ($\lambda = 0.154$ nm), $\beta$ is the line broadening at half the maximum intensity in radians, $\theta$ is the Bragg angle, and $d$ is the averaged dimension of crystallites in nanometers. Groth...
assigned CuCl₂·2H₂O to the bipyramidal class of the orthorhombic crystalline system with the axial ratios $a:b:c = 0.9179:1:0.4627$. Layer line measurements give the identity distances $a_0 = 7.38 \text{ Å}$, $b_0 = 8.04 \text{ Å}$, $c_0 = 3.72 \text{ Å}$. These lead to the ratios $a:b:c = 0.918:1:0.462$, in good agreement with the crystallographic data [36]. The mean crystal size (nm) of bulk and nano-CuCl₂·2H₂O salts obtained by XRD are mentioned in Table 2 [37].

A little difference was observed between bulk and nanosalts in peaks other than their intensities. Also, it was found that the salt remains in the crystalline form by converting it to nanoparticles. The main difference between the bulk and nanosalt was in the crystal size, as shown in Table 3.

3.2. Infrared Analysis (IR). Infrared spectra (IR) were used to identify the structure of ceftriaxone (CFT), as shown in Figure 3, and its complexes with bulk and nano-CuCl₂·2H₂O salts as their functional groups give rise to characteristic bands in terms of both intensity and position (frequency), as shown in Figures 4 and 5.

It was observed from the IR spectra of ceftriaxone (CFT) ligand that amidic N-H stretching vibrations mean strong intensity bands occurring at 3440 and 3261 cm⁻¹ are due to N-H asymmetric and symmetric stretching, respectively [38]. Amidic C=O stretching vibrations mean a strong intensity band identified at 1649 cm⁻¹ is due to C=O stretching vibrations [38]. Amidic N-H deformation and C-N stretching mean the strong bands observed at 1608, 1537, and 1500 cm⁻¹ are due to amide N-H deformation vibrations [38, 39]. C-H stretching vibrations mean the weak bands occurring at 2891 cm⁻¹ are assigned to CH₃ symmetric stretching. The bands appearing at 2934 cm⁻¹ in the IR spectra are due to CH₃ asymmetric stretching vibrations [40]. C-H deformation vibrations mean the weak bands observed at 822, 804, and 730 cm⁻¹ are allotted as C-H out-of-plane deformation vibrations and medium-to-weak intensity bands present at 1104 and 1033 cm⁻¹ are allotted as C-H in plane deformation vibrations. A strong band occurring at 1399 cm⁻¹ is due to the -CH₂- deformation vibration. Weak bands present at 1243 and 760 cm⁻¹ are due to CH₃ wagging and CH₂ rocking vibrations, respectively [40].

Lactam C=O stretching vibrations mean a strong band observed at 1741 cm⁻¹ in the IR spectrum of ceftriaxone is allotted to be due to C=O stretching vibration [41]. C-O-C stretching vibrations mean strong bands present at 1033 and 1243 cm⁻¹ are assigned as C-O-C symmetric and asymmetric stretching vibrations, respectively [41]. C-S stretching vibrations mean weak bands observed at 646 and 616 cm⁻¹ are due to C-S stretching vibrations [42]. C-N stretching vibrations mean the medium band present at 1285 cm⁻¹, weak band at 1243 cm⁻¹, and medium band present at 1185 cm⁻¹ are due to C-N stretching vibrations. C=C and C=N stretching vibrations mean very strong intensity bands present at 1608, 1537, and 1500 cm⁻¹ are assigned to C=C and C=N stretching vibrations [43]. O-H stretching vibrations mean strong intensity bands identified at 3440 and 3261 cm⁻¹ are allotted as O-H stretching vibrations [44], C-C and C=C-C bending vibrations mean a very weak band occurring at 507 cm⁻¹ in is due to C-C out-of-plane bending vibrations. The weak bands occurring at 646 and 606 cm⁻¹ are due to C-C-C in plane and out of plane deformation vibrations, respectively [45].

In the IR spectra of bulk Cu-CFT complex, as shown in Figure 4, after ceftriaxone coordination to copper ion, the frequencies of the (C=O) lactam shifted from 1741 cm⁻¹ to higher wavenumber 1775 cm⁻¹, one amidic (C=O) shifted from 1649 to lower wavenumber 1624 cm⁻¹, and also another amidic (C=O) triazine shifted from 1608 to lower wavenumber 1553 cm⁻¹. There are three functional groups participating in the formation of a complex. The increase in the vibrational frequencies of carbonyl groups can be explained by oxygen of lactam and triazine coordinating to Cu(II) indicates the formation of a chelate complex [46, 47]. These intramolecular interactions between oxygen and copper ion result in a more rigid molecular structure around the oxygen and shift of carbonyl (C=O) vibrational frequencies to higher wavenumbers. The frequency of the symmetric stretching mode $v_s$(COO⁻) shifts from 1391 to 1398 cm⁻¹. These shifts indicate that the carboxylate group (COO⁻), the lactam carbonyl group (C=O), and the oxo group of the triazine ring are involved in the formation of [Cu(CFT)]·3H₂O. This analysis is in agreement with previous studies where ceftriaxone is described as a polydentate chelating ligand [46, 47]. The broadband in the [Cu(CFT)]·
Table 2: Intensity (%) and crystal size (nm) of bulk and nano-CuCl$_2$·2H$_2$O salt.

| Angle (2-theta °) | d value (angstrom) | Intensity (count) | Intensity % | Crystal size (nm) | Angle (2-theta °) | d value (angstrom) | Intensity (count) | Intensity % | Crystal size (nm) |
|-------------------|-------------------|-------------------|------------|-------------------|-------------------|-------------------|-------------------|------------|-------------------|
| 16.375            | 5.40883           | 241               | 100        | 158.2             | 16.171            | 5.47654           | 28.5             | 76.8       | 16.171            |
| 22.097            | 4.01957           | 80                | 33.2       | 58.4              | 21.937            | 4.04841           | 20.4             | 55         | 21.937            |
| 26.76             | 3.32876           | 29.9              | 12.4       | 101.5             | 28.825            | 3.09476           | 24.5             | 65.9       | 28.825            |
| 28.938            | 3.08295           | 21.2              | 8.8        | 58.4              | 33.954            | 2.63614           | 37.1             | 100        | 33.954            |
| 32.916            | 2.71891           | 40.8              | 17         | 111.3             | 34.727            | 2.58114           | 13.3             | 35.9       | 34.727            |
| 35.491            | 2.52733           | 19.8              | 8.2        | 52.1              | 35.349            | 2.53715           | 13.3             | 35.8       | 35.349            |
3H₂O spectrum at 1624 cm⁻¹ has a high intensity and a low resolution due to the overlap of several vibrational modes, including ν(C=O)-amide, ν(C=O)-triazine, νₓ₋ₓ(COO⁻), ν(C=C), and ν(C=N). A new band appearing at the frequency 468 cm⁻¹ in the complex that is absent in the free ligand is due to ν(Cu-N) stretching vibration also giving strong evidence for the coordination of tertiary nitrogen atom with copper ion [47].

Also, the IR spectra of nano-Cu-CFT complex asym.(NH₂) shifted from 3440 to lower wavenumber 3427 cm⁻¹, carboxylic (-OH) group appeared at wavenumber 2924 cm⁻¹, carboxylic (C=O) appeared at wavenumber 1742 cm⁻¹, one amicid (C=O) shifted from 1649 to lower wavenumber 1638 cm⁻¹ and also another amicid (C=O) shifted from 1608 to lower wavenumber 1553 cm⁻¹, as in Figure 5. This indicates the formation of a complex between CuCl₂.2H₂O salt and CFT antibiotic.

### 3.3. Conductometric Measurements

#### 3.3.1. Calculation of Association Parameters for Bulk and Nano-CuCl₂.2H₂O Salts in Distillate H₂O.

The specific conductance values (Kₛ) of different concentrations of bulk and nano-CuCl₂.2H₂O salt in distillate H₂O were measured experimentally in absence of (CFT) at different temperatures (288.15, 293.15, 298.15, and 303.15 K). The molar conductance (Λₘ) values were calculated [48–50] using

\[ \Lambda_m = \frac{(K_s - K_{solv}) \times 1000}{C}, \]

where Kₛ and Kₛolv are the specific conductance of the solution and the solvent (distillate H₂O), respectively, and C is the concentration of the bulk and nano-CuCl₂.2H₂O solutions.
The experimental data for conductance measurements were analyzed using Fuoss–Shedlovsky extrapolation techniques [51–53] which follow equations (3)–(12):

\[
\frac{1}{\Delta S(z)} = \frac{1}{\Lambda_o} + \frac{K_A}{\Lambda_o^2} (C_A \gamma_z^2, S(z)).
\]  (3)

The results obey the Fuoss–Shedlovsky equation and can be applied to obtain the value of limiting molar conductivity \((\Lambda_o)\) and association constant \((K_A)\) by plotting a graph between \(1/\Delta S(z)\) and \((C_A \gamma_z^2, S(z))\), which is presented in Figure 6, giving straight line with intercept \((1/\Lambda_o)\) and slope \((K_A/\Lambda_o^2)\):

\[
S(z) = 1 + Z + \frac{Z^2}{2} + \frac{Z^3}{3} + \ldots,
\]  (4)

\[
Z = \frac{S(A_C)^{1/2}}{\Lambda_o^{3/2}},
\]  (5)

\[
S = a\Lambda_o + b,
\]  (6)

\[
a = \frac{8.2 \times 10^5}{(\varepsilon T)^{3/2}};
\]  (7)

\[
b = \frac{82.4}{\eta(\varepsilon T)^{1/2}};
\]  (8)

\[
(a) = \frac{\Lambda S(z)}{\Lambda_o};
\]  (9)

\[
\log \gamma_z = \frac{-A(aC)^{1/2}}{[1 + Br^\sigma (aC)^{1/2}]},
\]  (10)

\[
A = 1.824 \times 10^6 (\varepsilon T)^{-3/2},
\]  (11)

\[
B = 50.29 \times 10^8 (\varepsilon T)^{-1/2},
\]  (12)

\[
K_A = \frac{C[MX_n] \cdot \gamma[MX_n]}{C_{M^n+} \cdot \gamma_{M^n+} \cdot C_{X^-} \cdot \gamma_{X^-}}.
\]  (13)

where \((S)\) is the Onsager slope; \((\varepsilon)\) is the dielectric constant of the solvent; \((\eta_o)\) is the viscosity of the solvent; \((T)\) is the temperature; \((\alpha)\) is the degree of dissociation; \((\gamma_o)\) is the mean activity coefficients; \((z^+, z^-)\) are the charges of ions in solutions; \((A, B)\) are the Debye–Hückel constant; \((\rho)\) is the solvated radius; and \((K_A)\) is the association constant.

The dissociation constant \((K_D)\) is calculated by the following equation:

\[
K_D = \frac{1}{K_A};
\]  (14)

The Walden product \((\Lambda_o\eta_o)\) values were calculated from the values of limiting molar conductance \((\Lambda_o)\) [54]:

\[
\text{Walden product} = \Lambda_o \eta_o.
\]  (15)

The triple ion association constant \((K_3)\) can be calculated from

\[
\frac{(A_C)^{1/2}}{(1 - (\Lambda/\Lambda_o))^{1/2}} = \frac{\Lambda_o}{K_A^{1/2}} + \frac{\lambda_3^3 C}{K_3 (K_A)^{1/2}} \left(1 - \frac{\Lambda}{\Lambda_o}\right).
\]  (16)

The values of free energy of association \((\Delta G_A)\) of bulk and nano-CuCl_2·2H_2O salt in H_2O at different temperatures of 288.15, 293.15, 298.15, and 303.15 K were calculated from the association constant \(K_A\) values [55] by using

\[
\Delta G_A = -2.303RT \log K_A.
\]  (17)

The activation energy of the transfer process can be estimated depending on the relation between conductance of ion, ion mobility, and temperature degree, as in the Arrhenius equation:

\[
\Lambda_o = Ae^{-E_a/RT},
\]  (18)
where \( A \) is the frequency factor and \( E_a \) Arrhenius activation energy of the transport process.

\[
\log \Lambda_o = \log A - \frac{E_a}{2.303RT} \tag{17}
\]

By plotting \( \log \Lambda_o \) versus \( 1/T \), as shown in Figure 7, the activation energy of transfer processes values can be calculated from the slope [56].

The calculated values of \( \Lambda_o, S_{(Z)}, \alpha, \gamma_z, K_A, K_D \), and \( K_3 \) for the solutions of bulk and nano-CuCl₂·2H₂O salt with distillate H₂O at different temperatures of 288.15, 293.15, 298.15, and 303.15 K are calculated and reported in Tables 4 and 5.

Table 4 shows that the limiting molar conductivity \( (\Lambda_o) \) increases with increasing temperature due to the increase in mobility of ions and increasing kinetic energy which increases the separation among the oppositely charged ions while the Walden product \( (\Lambda_o\eta) \) decreases with increasing the temperature due to the decrease in viscosity; also, the association constant \( (K_A) \) decreases with increasing the temperature due to the decrease in the association of ions and the increase in mobility of ions; and similarly, the triple ion association constant \( (K_3) \) decreases with increasing the temperature due to the decrease for the same reason.

Table 5 shows the same trend, that is, the limiting molar conductivity \( (\Lambda_o) \) increases with increasing the temperature while the Walden product \( (\Lambda_o\eta) \) decreases with increasing the temperature; also association constant \( (K_A) \) decreases with increasing the temperature; and similarly, the triple ion association constant \( (K_3) \) decreases with increasing the temperature.
The enthalpy ($\Delta H_A$) for bulk and nano-CuCl$_2$·2H$_2$O salts with distillate H$_2$O at different temperatures were calculated by using Van ’t Hoff equation:

$$\log K = -\frac{\Delta H_A}{2.303R} \left( \frac{1}{T} \right) + \text{constant.}$$ (18)

By drawing the relation between $\log K_A$ and 1/T, $\Delta H_A$ can be calculated from the slope of each line which equals ($-\Delta H_A/2.303 \, R$), as shown in Figure 8. The entropy ($\Delta S_A$) for bulk and nano-CuCl$_2$·2H$_2$O salts were calculated by using

$$\Delta G_A = \Delta H_A - T\Delta S_A,$$ (19)

where (S) is the entropy of the system. The calculated values of $\Delta H_A$ and $\Delta S_A$ for bulk and nano-CuCl$_2$·2H$_2$O salts are presented in Table 6. It is obvious that the limiting molar conductance ($\Lambda_o$) increased as the temperature increased while the dissociation degree decreased as the temperature increased indicating a higher solvation process. The values of the association constant ($K_A$) and the triple ion association constant ($K_3$) were decreased by increasing the temperature. Gibbs free energies change of association ($\Delta G_A$) was decreased with negative signs by increasing the temperature indicating that association is favored with lowering of dielectric constant of solvent mixture. The decrease in the values of activity coefficient, limiting molar conductance, association constant, Gibbs free energy change of association, and Walden product for nano-CuCl$_2$·2H$_2$O in comparison to bulk CuCl$_2$·2H$_2$O indicates that the association of nano-CuCl$_2$·2H$_2$O is greater than bulk CuCl$_2$·2H$_2$O salt, due to the high surface to volume ratio of nanoparticles which leads to a greater ability for ion-pair formation.

### Table 4: Different association parameters (limiting molar conductance ($\Lambda_o$), Fuoss–Shedlovsky parameter $S_{o/z}$, degree of dissociation (z), activity coefficient ($\gamma_o$), association constant ($K_A$), dissociation constant ($K_1$), triple ion association constant ($K_3$)) for bulk CuCl$_2$·2H$_2$O in distillate H$_2$O at 288.15, 293.15, 298.15, and 303.15 K in absence of CFT.

| T (K) | $\Lambda_o$ S·cm$^{-2}$·mol$^{-1}$ | $\Lambda_{o/z}$ S·cm$^{-2}$·MPa·s·mol$^{-1}$ | z | $\gamma_o$ | $K_A$ dm$^{-3}$·mol$^{-1}$ | $10^{-3}K_1$ mol·dm$^{-3}$ | $10^6K_3$ (dm$^{-3}$·mol$^{-1})^2$ |
|-------|-------------------------------|---------------------------------|---|-----------|-------------------------|---------------------|-----------------------------|
| 288.15 | 270.00 | 307.43 | 0.9806 | 0.9022 | 99.74 | 0.0100 | 1.322 |
| 293.15 | 281.69 | 282.14 | 0.9668 | 0.9013 | 93.39 | 0.0107 | 1.273 |
| 298.15 | 284.90 | 254.16 | 0.9755 | 0.9005 | 82.79 | 0.0120 | 1.190 |
| 303.15 | 292.39 | 233.09 | 0.9912 | 0.8995 | 78.32 | 0.0127 | 1.154 |

### Table 5: Different association parameters (limiting molar conductance ($\Lambda_o$), Fuoss–Shedlovsky parameter $S_{o/z}$, degree of dissociation (z), activity coefficient ($\gamma_o$), association constant ($K_A$), dissociation constant ($K_1$), triple ion association constant ($K_3$)) for nano-CuCl$_2$·2H$_2$O in distillate H$_2$O at 288.15, 293.15, 298.15, and 303.15 K in absence of CFT.

| T (K) | $\Lambda_o$ S·cm$^{-2}$·mol$^{-1}$ | $\Lambda_{o/z}$ S·cm$^{-2}$·MPa·s·mol$^{-1}$ | z | $\gamma_o$ | $K_A$ dm$^{-3}$·mol$^{-1}$ | $10^{-3}K_1$ mol·dm$^{-3}$ | $10^6K_3$ (dm$^{-3}$·mol$^{-1})^2$ |
|-------|-------------------------------|---------------------------------|---|-----------|-------------------------|---------------------|-----------------------------|
| 288.15 | 266.21 | 302.58 | 0.9754 | 0.9022 | 60.60 | 0.0165 | 0.9949 |
| 293.15 | 271.73 | 282.14 | 0.9013 | 0.9005 | 56.35 | 0.0177 | 0.9546 |
| 298.15 | 277.00 | 247.11 | 0.9873 | 0.9005 | 46.16 | 0.0216 | 0.8499 |
| 303.15 | 282.48 | 225.19 | 0.9874 | 0.8995 | 34.47 | 0.0290 | 0.0714 |

3.3.2. Calculation of Formation Constants for Bulk and Nano-Cu-CFT Complexes in H$_2$O at Different Temperatures. Different lines were obtained with breaks indicating the formation of (1:2) and (1:1) ($M$: $L$) stoichiometric
Table 6: Gibbs free energy of association ($\Delta G_f$), enthalpy change ($\Delta H_f$), and entropy change ($\Delta S_f$) for bulk and nano-CuCl$_2$·2H$_2$O in distillate H$_2$O at different temperatures.

| T (K) | $\Delta G_f$ (kJ mol$^{-1}$) | $\Delta H_f$ (kJ mol$^{-1}$) | $\Delta S_f$ (kJ mol$^{-1}$K$^{-1}$) |
|-------|-----------------|-----------------|-----------------|
|       | Bulk | Nano | Bulk | Nano | Bulk | Nano | Bulk | Nano |
| 288.15 | -11.028 | -9.322 | -12.928 | -22.918 | 3.60 | 3.72 | -0.0496 | -0.0904 |
| 293.15 | -11.059 | -9.801 | -12.948 | -22.918 | 3.60 | 3.72 | -0.0487 | -0.0842 |
| 298.15 | -10.949 | -9.501 | -12.948 | -22.918 | 3.60 | 3.72 | -0.0477 | -0.0824 |
| 303.15 | -10.993 | -8.924 | -12.948 | -22.918 | 3.60 | 3.72 | -0.0468 | -0.0807 |

By drawing the relation between log $K_f$ and 1/T, different lines were obtained indicating the formation of (1:2) and (1:1) (M:L) stoichiometric complexes, as shown in Figure 10.

From the relation between log $K_f$ and 1/T, $\Delta H_f$ can be calculated for each type of complexes, from the slope of each line which equals $(-\Delta H_f/2.303 R)$. The entropy ($\Delta S_f$) for bulk and nano-CuCl$_2$·2H$_2$O complexes was calculated for each type of complexes (1:2) and (1:1) (M:L) by using

$$\Delta G_f = \Delta H_f - T\Delta S_f.$$  \hspace{1cm} (23)

The calculated values of ($\Delta H_f$) and ($\Delta S_f$) for bulk and nano-Cu-CFT complexes are presented in Tables 9 and 10.

It was observed that inflections at (1:2) M/L proportion and (1:1) M/L indicating the formation of both stoichiometric complexes in the solutions. These types of stoichiometric complexes are formed as a result of the interaction of bulk or nano-CuCl$_2$ with CFT in distillate H$_2$O at different temperatures. The complex formation parameters for (1:1) complexes are greater than those of (1:2) complexes indicating more favorable complexes. Also, the complex formation parameters ($K_f$, $\Delta G_f$) increased by increasing temperatures due to an increase in the kinetic energies. This trend was supported by entropies data which are greater for (1:1) M/L complexes than (1:2) M/L complexes.
4. Biological Activity

Many transition metals show arresting biological activity, working as active centers within important bioactive molecules in living systems. Copper (II) plays a significant function in cell metabolism and has proved beneficial in numerous diseases [58–60]. Ceftriaxone-metal complexes have both pharmacological and toxicological properties [61]. The interaction between metal ions and ceftriaxone can lead to precipitation resulting in serious adverse drug events [62]. Ceftriaxone complexes have antibacterial properties that can decrease or increase relative to pure ceftriaxone [61]. The antimicrobial activity was estimated based on the size of the inhibition zone formed around discs of bulk CuCl$_2$·2H$_2$O, nano-CuCl$_2$·2H$_2$O, CFT, and its bulk and nano-Cu complexes on a petri dish with Luria Bertani agar (LB-agar) plates as it measures the compound’s efficacy.

4.1. Antibacterial Activity. The antibacterial activities of bulk CuCl$_2$·2H$_2$O, nano-CuCl$_2$·2H$_2$O, bulk and nano-Cu-CFT complexes were compared with the activity of CFT and as presented in Table 11. Bulk CuCl$_2$·2H$_2$O provides an excellent antimicrobial activity, and such property is greatly improved when using nano-CuCl$_2$·2H$_2$O. It was observed also that CFT has a higher zone of inhibition than bulk and nano-Cu-CFT complexes in *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (gram-negative bacteria), Figure 11.

The antibacterial activity of Cu-CFT complexes depends on the bacterial species. The complexes and antibiotics presented inhibition zones of diameters larger than 20mm showing that they have good activity as bactericides [63]. The antibacterial effect against *Staphylococcus aureus* is present at the bulk and nano-Cu-CFT complexes (the inhibition zones are 21 and 16mm, respectively). These values are lower than the corresponding values for bulk CuCl$_2$·2H$_2$O and nano-CuCl$_2$·2H$_2$O and ceftriaxone. The data indicate that ceftriaxone ligand is more active than their metal complexes; this may be because the chelating ligands containing N and O donor atoms show wide biological activity through bonding to metal ions [64,65]. However, the synergetic effects of ceftriaxone and Cu ion may play an important function in the inhibition of bacterial growth after the complex decomposition. These effects are due to the different mechanisms of the action of antibiotics and heavy ions on the bacteria metabolism [66, 67].

### Table 7: Limiting molar conductance ($\Lambda_0$) and formation constant ($K_f$) for bulk Cu-CFT complex in distillate H$_2$O at different temperatures.

| T (K) | [M] : [L] | $\Lambda_0$ S cm$^2$·mol$^{-1}$ | $\Lambda_{obs}$ S cm$^2$·mol$^{-1}$ | log $K_f$ dm$^3$·mol$^{-1}$ |
|-------|-----------|-------------------------------|-------------------------------|-----------------|
| 288.15 | 1:2       | 912.11                        | 433.62                        | 4.211           |
|        | 1:1       | 554.03                        | 440.05                        | 4.424           |
| 293.15 | 1:2       | 958.50                        | 473.22                        | 4.186           |
|        | 1:1       | 584.60                        | 331.16                        | 4.375           |
| 298.15 | 1:2       | 966.40                        | 465.30                        | 4.179           |
|        | 1:1       | 594.50                        | 322.25                        | 4.342           |
| 303.15 | 1:2       | 985.30                        | 481.14                        | 4.174           |
|        | 1:1       | 593.40                        | 347.49                        | 4.275           |

### Table 8: Limiting molar conductance ($\Lambda_0$) and formation constant ($K_f$) for nano-Cu-CFT complex in distillate H$_2$O at different temperatures.

| T (K) | [M] : [L] | $\Lambda_0$ S cm$^2$·mol$^{-1}$ | $\Lambda_{obs}$ S cm$^2$·mol$^{-1}$ | Log $K_f$ dm$^3$·mol$^{-1}$ |
|-------|-----------|-------------------------------|-------------------------------|-----------------|
| 288.15 | 1:2       | 912.00                        | 439.56                        | 4.191           |
|        | 1:1       | 555.00                        | 290.00                        | 4.426           |
| 293.15 | 1:2       | 966.00                        | 473.22                        | 4.177           |
|        | 1:1       | 593.00                        | 331.16                        | 4.349           |
| 298.15 | 1:2       | 958.00                        | 485.10                        | 4.180           |
|        | 1:1       | 584.00                        | 335.61                        | 4.323           |
| 303.15 | 1:2       | 985.30                        | 481.14                        | 4.171           |
|        | 1:1       | 593.00                        | 348.98                        | 4.263           |

Figure 9: The relation between $\Lambda_m$ and the [M]/[L] molar ratio for (a) bulk Cu-CFT complex and (b) nano-Cu-CFT complex in distillate H$_2$O at different temperatures.
Table 9: Different formation parameters (Gibbs free energy of formation ($\Delta G_f$), enthalpy change ($\Delta H_f$), and entropy change ($\Delta S_f$)) for bulk Cu-CFT complex in distillate $H_2O$ at different temperatures.

| $T$ (K) | Complex ratio ($M:L$) | $\Delta G_f$ (kJ mol$^{-1}$) | $\Delta H_f$ (kJ mol$^{-1}$) | $\Delta S_f$ (kJ mol$^{-1}$K$^{-1}$) |
|---------|-----------------------|-----------------------------|-------------------------------|-----------------------------------|
| 288.15  | (1:2)                 | −23.23                      | −3.97                         | 0.0252                            |
| 293.15  | (1:2)                 | −23.50                      |                               | 0.0257                            |
| 298.15  | (1:2)                 | −23.86                      | −3.97                         | 0.0265                            |
| 303.15  | (1:2)                 | −24.23                      |                               | 0.0273                            |
| 288.15  | (1:1)                 | −24.41                      |                               | 0.0847                            |
| 293.15  | (1:1)                 | −24.56                      |                               | 0.0838                            |
| 298.15  | (1:1)                 | −24.79                      | −15.96                        | 0.0831                            |
| 303.15  | (1:1)                 | −24.82                      |                               | 0.0819                            |

Table 10: Different formation parameters (Gibbs free energy of formation ($\Delta G_f$), enthalpy change ($\Delta H_f$), and entropy change ($\Delta S_f$)) for nano-Cu-CFT complex in distillate $H_2O$ at different temperatures.

| $T$ (K) | Complex ratio ($M:L$) | $\Delta G_f$ (kJ mol$^{-1}$) | $\Delta H_f$ (kJ mol$^{-1}$) | $\Delta S_f$ (kJ mol$^{-1}$K$^{-1}$) |
|---------|-----------------------|-----------------------------|-------------------------------|-----------------------------------|
| 288.15  | (1:2)                 | −23.12                      | −1.82                         | 0.0208                            |
| 293.15  | (1:2)                 | −23.44                      | −1.82                         | 0.0215                            |
| 298.15  | (1:2)                 | −23.86                      | −1.82                         | 0.0226                            |
| 303.15  | (1:2)                 | −24.21                      |                               | 0.0234                            |
| 288.15  | (1:1)                 | −24.42                      |                               | 0.0847                            |
| 293.15  | (1:1)                 | −24.56                      |                               | 0.0833                            |
| 298.15  | (1:1)                 | −24.68                      | −17.13                        | 0.0828                            |
| 303.15  | (1:1)                 | −24.75                      |                               | 0.0816                            |

Table 11: Inhibition zones for antibacterial activity (gram-negative bacteria) and antifungal activity ($Candida albicans$).

| Compound                  | Types of gram-negative bacteria | Type of fungi $Candida albicans$ |
|---------------------------|---------------------------------|---------------------------------|
| Bulk CuCl$_2$·2H$_2$O     | $Klebsiella pneumonia$ 19        | 12                              |
| Nano-CuCl$_2$·2H$_2$O     | $Staphylococcus aureus$ 23      | 14                              |
| Ceftriaxone (CFT)         |                                 | 0                               |
| Bulk Cu-CFT complex       | $Klebsiella pneumonia$ 24        | 8                               |
| Nano-Cu-CFT complex       | $Staphylococcus aureus$ 25      | 9                               |
4.2. Antifungal Activity. The experimental antifungal activity data are presented in Table 11 which indicates that the nano-Cu-CFT complex showed a higher clear zone of inhibition against *Candida albicans* compared to the bulk Cu-CFT complex while there was an absence of the inhibition zone in CFT. So, the nano-Cu-CFT complex can be used as an antifungal drug, as shown in Figure 12. The zone of inhibition after treatment with bulk and nano-Cu-CFT complex was 8 and 9 mm, respectively. According to the standard criteria for evaluation of the drugs, the antifungal action such as a small zone of inhibition indicates that *Candida albicans* is stable with respect to CFT. The inhibition zones were completely absent, indicating the resistance of these fungi to CFT as well.

5. Conclusion

The nano-CuCl₂·2H₂O salt was prepared by ball milling method. The thermodynamic association parameters of both bulk and nano-CuCl₂·2H₂O salts in H₂O were calculated using the conductometric method by applying the Fuoss–Shedlovsky method at different temperatures. It shows that the association parameters of nano-CuCl₂·2H₂O are greater than bulk CuCl₂·2H₂O salt due to the high surface-to-volume ratio of the nanoparticles which leads to a greater ability for ion-pair formation.

The thermodynamic parameters of complexation between bulk and nano-CuCl₂·2H₂O salts and ceftriaxone antibiotic in H₂O were calculated from conductance measurement. It was found that the formation of Gibbs free.
energies change ($\Delta G_f$) was decreased in negative signs with increasing temperatures. Two stoichiometric complexes, 1/2 and 1/1 ($M/L$), are formed with the formation constant and Gibbs free energy of the formed complexes following 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) indicates the favorable of formation of (1:1) complex compared to (1:2) complex. Also, there is a decrease in values of $K_f$ and $\Delta G_f$ in case of using nano-CuCl$_2$·2H$_2$O compared to using bulk CuCl$_2$·2H$_2$O but in small difference due to the more solvation effect in case of using nanoparticles.

It was observed that CFT has a higher zone of inhibition and antibacterial activity than that of bulk and nano-Cu-CFT complexes in Klebsiella pneumonia and Pseudomonas aeruginosa (gram-negative bacteria). The nano-Cu-CFT complex showed a higher clear zone of inhibition and antifungal activity against candida compared to the bulk Cu-CFT complex while there was an absence of the inhibition zone in CFT, so the nano-Cu-CFT complex can be used as an antifungal drug. 

**Data Availability**

The data are available on request from the corresponding author.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

**Authors’ Contributions**

Elsayed M. AbouElleef conceptualized the study, supervised the study, wrote the original draft, reviewed and edited the article, developed the methodology, performed formal Analysis, performed data collection and analysis, performed investigation, performed visualization, and performed project administration. Mowafak M. Mahmoud performed investigation, developed the methodology, and wrote the manuscript. Sherine E. Salem performed data collection and analysis, provided the resources, performed investigation, and developed the methodology.

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