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Synthesis and characterization of norfloxacin-transition metal complexes (group 11, IB): Spectroscopic, thermal, kinetic measurements and biological activity

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Abstract

The investigation of the new structures of Ag(I), Cu(II) and Au(III) complexes, $[Ag_2(Nor)_2](NO_3)_2$, $[Cu(Nor)_2(H_2O)_2]SO_4\cdot 5H_2O$ and $[Au(Nor)_2(H_2O)_2]Cl_3$ (where, Nor = norfloxacin) was done during the reaction of silver(I), copper(II) and gold(III) ions with norfloxacin drug ligand. Elemental analysis of CHN, infrared, electronic, ^1H NMR and mass spectra, as well as thermo gravimetric analysis (TG and DTG) and conductivity measurements have been used to characterize the isolated complexes. The powder XRD studies confirm the amorphous nature of the complexes. The norfloxacin ligand is coordinated to Ag(I) and Au(III) ions as a neutral monodentate chelating through the N atom of piperidyl ring, but the copper(II) complex is coordinated through the carbonyl oxygen atom (quinolone group) and the oxygen atom of the carboxylic group. The norfloxacin and their metal complexes have been biologically tested, which resulted in norfloxacin complexes showing moderate activity against the gram positive and gram negative bacteria as well as against fungi.

Keywords: Norfloxacin; Gold(III) complex; Biological activity; Kinetic data; Infrared spectra

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1. Introduction

Norfloxacin, a fluoroquinolone, is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Norfloxacin belongs to the family of molecules known as the Fluoroquinolones, and is a wide-ranging drug used in treating bacterial infections of the urinary tract, the respiratory tract, and the skin, amongst others. It is also known to be effective in treating diarrhea and can in addition treat conjunctivitis when it is administered in the form of eye drops. Norfloxacin is not, however, effective against infections involving anaerobic bacteria (e.g., yeast, athlete's foot).

When dealing with the interaction between drugs and metal ions in living systems, a particular interest has been given to the interaction of metal ions with antibiotics. Antibiotics that interact with metal ions constitute a class of drugs which have been widely used in medicine both towards human beings and animals [1,2]. In particular, the interaction between transition metals and β-lactamic antibiotics such as cephalexin has been recently investigated by several physicochemical and spectroscopic methods, and with detailed biological data [3–6].

Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most widely studied cation in this respect is Cu(II), since a host of low-molecular-weight copper complexes have been proven beneficial against several diseases such as tuberculosis, rheumatoid, gastric ulcers, and cancers [7–10]. There has been a tremendous growth of drugs from quinolone family, which began with the discovery of nalidixic acid some over 40 years ago. Since then, the exponential growth of this family has produced more than ten thousand analogues [11].

The coordination chemistry of these drugs with metal ions of biological and pharmaceutical importance is of considerable interest. Norfloxacin (Nor; Fig. 1) was considered the best of the third generation quinolone family. There have been several reports about the synthesis and crystal structure of metal complexes with quinolone derivatives [12–15].

Quinolone antibiotics can participate in the formation of complexes in a number of ways [16–20]. In case of isolated drugs, these complexes in acidic media usually contain singly and/or doubly protonated quinolones that are incapable of bonding to

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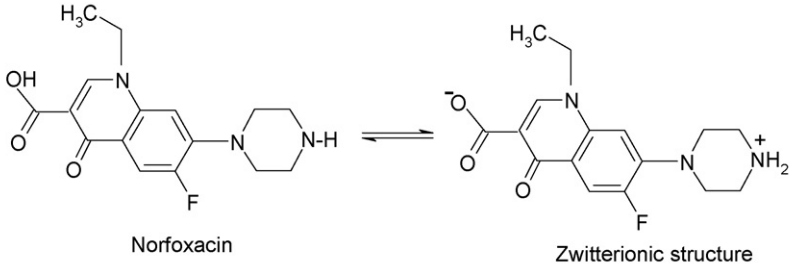


Fig. 1. Structure of norfloxacin (Nor) and zwitterionic structure.

the metal ions and in these cases only electrostatic interaction was observed between the drug and the metal ions [16–18]. On the other hand [19–21], it was found that neutral quinolones in the zwitterionic state are capable of forming simple complexes (bidentate chelating). The quinolones can also act as bridging ligands and thus are capable of forming polynuclear complexes [20,21].

A group 11 element is one in the series of elements in group 11 (IUPAC style) in the periodic table, consisting of transition metals which are the traditional coinage metals of copper (Cu), silver (Ag), and gold (Au). They are also known as the "noble metals"; the short-lived transactinide roentgenium (Rg) is also a member of group 11. They are all relatively inert, corrosion-resistant metals which have been used for minting coins, hence their name. These metals, especially silver, have unusual properties that make them essential for industrial applications outside of their monetary or decorative value. They are all excellent conductors of electricity. The most conductive of all metals are silver, copper, and gold in that order. Silver is also the most thermally conductive and the most light reflecting element. Silver also has the unusual property in that the tarnish that forms on silver is still highly electrically conductive. Copper is used extensively in electrical wiring and circuitry. Gold contacts are sometimes found in precision equipment for their ability to remain corrosion-free. Silver is used widely in mission-critical applications as electrical contacts and is also used in photography (because silver nitrate reverts to metal on exposure to light), agriculture, medicine, audiophile, and scientific applications.

The synthesis and characterization of new metal complexes with quinolone antibacterial agents are of great importance for understanding the drug-metal ion interaction and for their potential pharmacological use.

The isolation and characterization of the Ag(I), Cu(II) and Au(III) complexes is reported in this paper. Mid-infrared spectroscopy, ^{1}H NMR and mass spectra, and thermal analysis have been used to interpretation the proposed structures of the complexes that resulted from this interaction.

2. Experimental

2.1. Reagents

Norfloxacin used in this study were obtained from the Egyptian International Pharmaceutical Industrial Company (EIPICO). All chemicals used for the preparation of the complexes were of analytical reagent grade, commercially available from different sources. $AgNO_3$ (99%, Fluka Co.), $CuSO_4{\cdot}6H_2O$ (99.5%, Fluka Co.) and $KAuCl_4$ (99%, Aldrich Co.) were used without further purification.

2.2. Synthesis

All the complexes are prepared as following with different ratios dependent on the type of metal used.

2.3. $[Ag_2(Nor)_2](NO_3)_2$

A solution of 1.0 mmol (0.169 g) $AgNO_3$ in 5 ml of distilled water was added to a solution of 1.0 mmol (0.319 g) of norfloxacin ligand in 25 ml acetone. The resulting mixture was heated ∼50 °C under reflux on a water bath for about 12 h and then cooled. The resulted complex was separated from the reaction mixture by filtration, washed with boiling water then acetone and dried in *vacuo* over $CaCl_2$.

2.4. $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$

Norfloxacin (0.639 g, 2 mmol) in mixed solvent (50/50%) of methanol/water was stirred at room temperature for 20 min and $CuSO_4{\cdot}6H_2O$ (0.268 g, 1 mmol) was added. Upon continuous stirring the color of the heterogeneous mixture started to change from bluish white to green, and after 8 h a pale green solution and a light green precipitate were observed. Precipitation was completed in 20 h. The solid complex was filtered and washed with MeOH and dried in *vacuo* over $CaCl_2$.

2.5. $[Au(Nor)_2(H_2O)_2]Cl_3$

A hot aqueous solution (25 ml) of $KAuCl_4$ (0.378 g, 1 mmol) was added to a hot acetone (75 ml) solution of the norfloxacin ligand (0.957 g, 3 mmol). The resulted mixture was stirred under reflux for 24 h where upon the metal complex was precipitated. The pale yellow solid complex was filtered and washed several times with boiled water, then acetone, and dried in *vacuo* over $CaCl_2$.

3. Measurement methods

Elemental analysis was carried out by standard micro methods using a Perkin-Elmer CHN 2400, and the metal contents were determined gravimetrically by ignition weighted samples in atmospheric air to constant weight and definite structures. IR spectra were recorded on a Genesis II FT-IR spectrophotometer (KBr discs) in the $\upsilon = 400\text{–}4000\,\mathrm{cm}^{-1}$ range. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using DMSO-d_6 as solvent. Mass spectra (MS) were taken on a AEI MS 30 mass spectrometer at 70 eV. TG-DTG measurements were made in an N_2 atmosphere between room temperature and 800 °C using a Shimadzu TGA-50H. Electronic spectra were obtained using a Shimadzu UV-spectrophotometer model 1601 PC with a 1 cm quartz cell. Molar conductivities in DMSO at $10^{-3}\,\mathrm{mol\,dm^{-3}}$ concentration were measured on a Jenway 4010 conductivity meter. The X-ray diffraction patterns of the copper(II) complex were recorded with a Rikagu diffractometer using Cu Kα radiation.

Decomposition of complexes was performed in concentrated HNO_3; after decomposition, the samples were diluted with water to 100 ml, and qualitative presence of Cl^- and SO_4^- ions in the samples Au(III) and Cu(II)) was determined by means of $AgNO_3$ and $BaCl_2$, respectively. The decomposition of gold compound was found to contain Cl^- ions, and their concentration was determined with an ion selective electrode.

3.1. *Antibacterial investigation*

For these investigations the filter paper disc method was applied. The investigated isolates of bacteria were seeded in tubes with nutrient broth (NB). The seeded NB ($1\,\mathrm{cm}^3$) was homogenized in the tubes with $9\,\mathrm{cm}^3$ of melted (45 °C) nutrient agar (NA). The homogeneous suspensions were poured into Petri dishes. The discs of filter paper (diameter 5 mm) were ranged on the cool medium. After cooling on the formed solid medium, $2 \times 10^{-5}\,\mathrm{dm}^3$ of the investigated compounds were applied using a micropipette. After incubation for 24 h in a thermostat at 25–27 °C, the inhibition (sterile) zone diameters (including disc) were measured and expressed in mm. An inhibition zone diameter over 8 mm indicates that the tested compounds are active against some of the bacteria and fungi under investigation.

The antibacterial activities of the investigated compounds were tested against *Escherichia Coli*, *Bacillus subtilis*, and *Pseudomonas aerruginosa* as well as some kinds of fungi *Aspergillus flavus*, *Fusarium solani*, and *Penicillium verrcosum*. At the same time with the antibacterial and antifungal investigations of the Ag(I), Cu(II), and Au(III) complexes, the ligand was also tested, as well as the pure solvent. The concentration of each solution was $1.0 \times 10^{-3}\,\mathrm{mol\,dm}^3$. Commercial DMSO was employed to dissolve the tested samples.

4. Results and discussion

The analytical data and physical properties of the Nor ligand and coordination compounds are listed in Table 1.The results from Table 1 show that the ligand coordinate to the Ag(I) and (Cu(II) and Au(III)) ions in a 1:1 and 1:2 molar ratio, respectively. All compounds are stable in air. The melting points of the complexes are higher than that of the ligand revealing that the complexes are much more stable than ligand. The molar conductance values (Table 1) of the complexes lay in the range $13.31\text{–}34.00\,\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (at 25 °C), which indicates that the compounds are of slightly increasing in electrolytic nature than ligand [22]. The products were insoluble in water, ethanol, chloroform, acetone, cyclohexane, and 2-propanol.

4.1. *Infrared spectra*

The assignments of IR bands (Fig. 2 and Table 2) were made by comparing the spectra of the complexes with those of the free ligand Norfloxacin.

Brown powdered solid of silver(I)-Nor compound was prepared in 75% yield by refluxing of 1:1 mixture of $AgNO_3$ and H-Nor in acetone/water at ~50 °C for 12 h (Scheme 1).

The infrared spectrum of the new complex, $[Ag_2(Nor)_2](NO_3)_2$, in KBr disc is shown in Fig. 2A and its band assignments are given in Table 2. The IR spectrum of silver compound shows distinct bands of υ(C=O); (COOH), and υ(C=O), which are similar to those of free norfloxacin, indicating the presence of uncoordinated $O_{\mathrm{carboxylate}}$ and O_{keto} in Ag(I) compound. The molecular structure of $[Ag_2(Nor)_2](NO_3)_2$ consists of cationic mononuclear units of $2[Ag(H\text{-}Nor)]^+$ and weekly coordinated anionic $2NO_3^-$. The H-Nor ligand in Ag(I) compound acts as a neutral monodentate to coordinate to Ag atom by N atom of piperidyl ring, and 4-oxo and 3-carboxylate oxygen atoms do not take in the coordination. Unlike in other known complexes of H-Nor ligand [23–25], only N of the piperidyl ring in H-Nor coordinates to the silver ion in Ag-Nor compound. This bonding mode was unexpected and, to this knowledge, unprecedented in quinolone drug interactions

Table 1
Elemental analyses and physical properties of the compounds

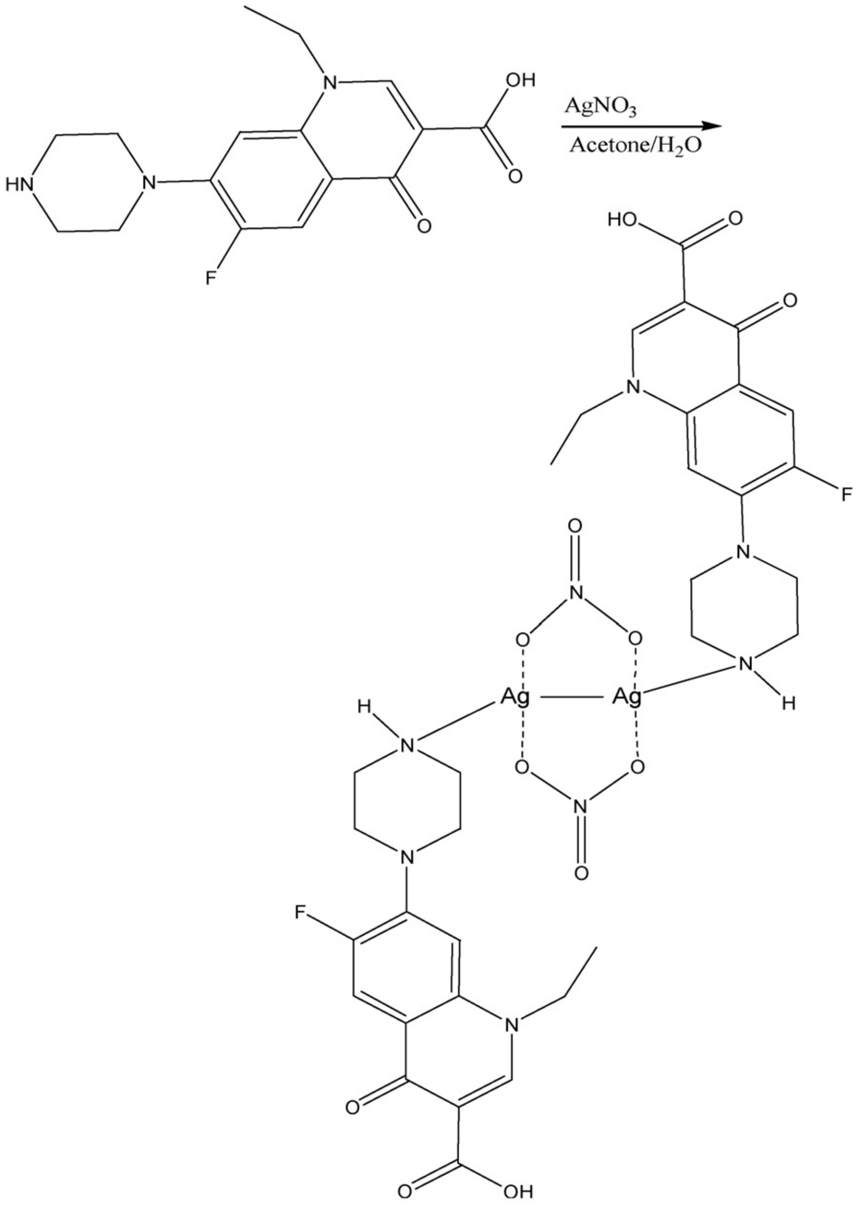
Complexes	Molecular weight	Yield (%)	Color	mp (°C)	Analysis (%) found (calculated)			Λ^{a} ($\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$)
					C	H	N	
Nor, $C_{16}H_{18}FN_3O_3$	319	–	Yellow	232	59.45 (60.18)	5.54 (5.68)	12.89 (13.16)	10.16
$[Ag_2(Nor)_2](NO_3)_2$, $C_{32}H_{36}F_2N_8O_{12}Ag_2$	978	75	Brown	247	40.62 (39.26)	4.41 (3.68)	11.30 (11.45)	34.00
$[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$, $C_{32}H_{50}F_2N_6O_{17}SCu$	924	77	Light green	265	41.22 (41.56)	5.46 (5.41)	8.93 (9.09)	19.73
$[Au(Nor)_2(H_2O)_2]Cl_3$, $C_{32}H_{40}F_2N_6O_8Cl_3Au$	978	73	Pale yellow	318	40.38 (39.26)	4.13 (4.09)	8.77 (8.59)	13.31

[a] Measured in 10^{-3} M DMSO solutions at room temperature.

Table 2
IR frequencies (cm^{-1}) and assignments for: Nor and Ag(I), Cu(II), and Au(III) compounds

Nor	Ag(I)	Cu(II)	Au(III)	Assignments
3399 ms	3428 s, br	3399 vs, br	3463 vs, br	υ(N—H) + υ_{as}(O—H); H_2O
3267 vw, 3228 vw, 3189 vw, 3130 vw, 3021 w, 2927 m, 2823 w, 2796 w 2764 w, 2723 m, 2696 vw, 2654 w, 2617 w, 2511 w, 2468 m	3246 w, br, 3122 w, br 3058 vw, 2990 vw, 2925 mw, 2852 mw, 2759 vw, 2644 vw, 2510 w	3197 s, br, 3114 sh, 2991 mw, 2918 w, 2851 mw, 2765 w, 2720 sh, 2653 w, 2544 mw, 2495 w	3162 ms, 3040 vw, 2991 w, sh, 2927 w, 2856 w	υ_s(O—H); H_2O, υ (C—H), υ (—NH_2^+)
1727 sh, 1716 ms	1716 s	–	1725 s	υ(C═O): (COOH)
–	–	1619 vs	–	υ_{as}(COO^-)
1630 vs, 15 1552 w	1628 vs, 1584 ms 1547 ms	1582 s, 1549 sh	1629 vs, 1580 vw	υ(C═O) + δ_b(H_2O) Phenyl breathing modes
1482 vs, 1454 m	1497 s, 1462 s	1483 vs	1483 vs, 1460 sh	CH; deformation of —CH_2— υ(N═O): NO_3^-
1396 s	1384 vs	1397 sh, 1386 s	1397 s	υ_s(COO^-) + υ(N—O): NO_3^-
1307 vw	1338 w, sh	1336 s	1348 w, 1326 vw	δ_b(CH_2)
1277 vw, 1263 s, 1248 vw	1274 s, 1250 w, sh	1266 vs	1268 vs	υ(C—C)
1201 m, 1192 m	1192 s	1179 s, 1142 w	1183 w	υ(C—O) υ(C—N)
1153 vw, 1142 w 1132 w, 1115 w, 1095 m, 1076 m, 1051 vw, 1036 ms, 1024 w, 1005 m, 982 m	1126 w, 1109 w 1031 s	1122 mw, 1096 w 1030 s, 962 vw	1128 w, 1097 vw 1087 ms, 1025 s	δ_r(CH_2) υ(N—O): NO_3^-
972 w, 935 ms, 916 m, 899 m, 887 m, 858 w, 823 ms, 804 ms	926 s, 899 sh, 827 s, 804 s	923 vs, 814 vs, 782 mw	958 w, 924 s, 900 mw, 819 vw, 809 s	CH-bend; phenyl
750 s, 706 m	758 m, 738 w, 700 w	732 s, 700 ms	747 ms, 677 w	δ_b(COO^-) + δ(NO_2): NO_3^-
667 w, 631 w, br, 569 ms, 524 w, 499 m, 474 m, 453 vw, 430 ms	663 m, 623 s, 556 w, 525 w, 501 w, 436 w	652 vw, 619 vs 562 w, 544 w 515 w, 483 w, 408 mw	614 ms, 554 vw, 530 vw, 499 w, 453 w	υ(M–O) + υ(M–N) ring deformation

(a): s = strong, w = weak, m = medium, sh = shoulder, v = very, br = broad; (b): υ, stretching; δ, bending.

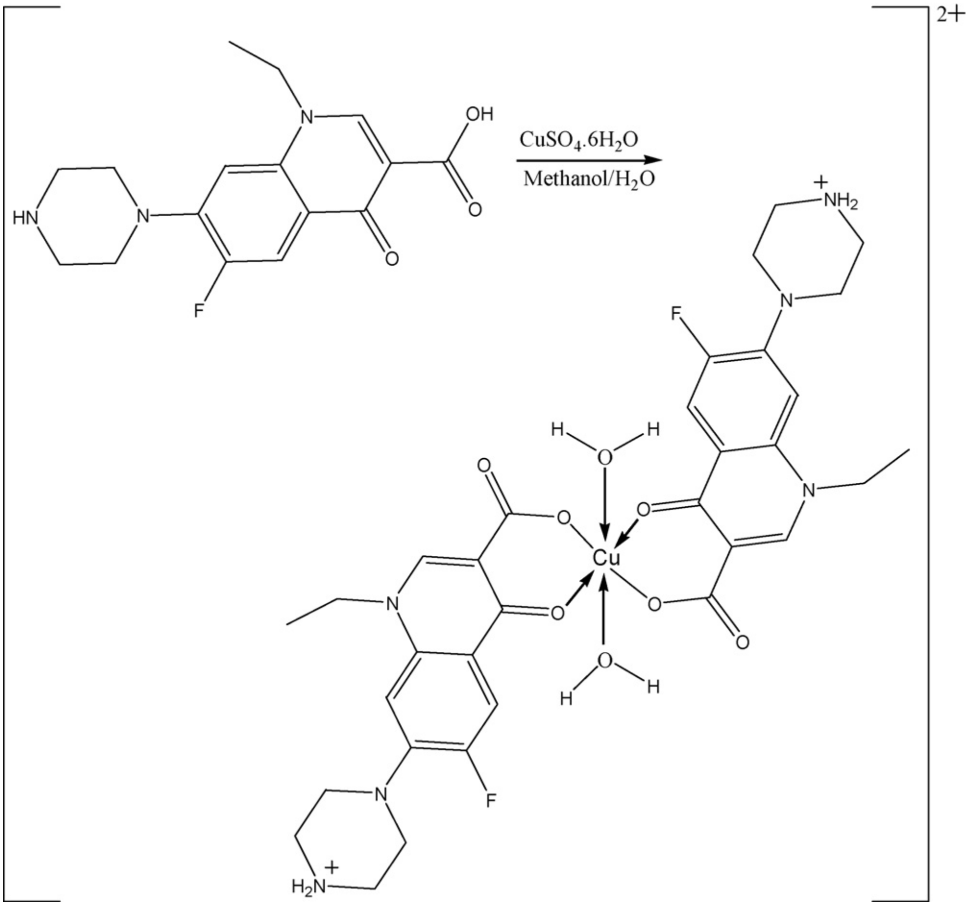


Scheme 1. $[Ag_2(Nor)_2](NO_3)_2$ compound.

towards metal ions. Accordingly, the most probable geometrical structure of this complex is shown in Scheme 1, where NO_3^- acts as a bridged bidentate ligand while the two Nor molecules exist as monodentate ligands. A related mononuclear complex of norfloxacin with silver(I), $[Ag(H\text{-}Nor)_2]NO_3$, was reported by Li et al. [26] to be formed in the reaction of silver nitrate with norfloxacin by 1:2 ratio in concentrated aqueous NH_3 at 100 °C for 8 h. The characteristic stretching vibrations of bridged bidentate nitrato group, NO_3^-, is observed at 1384 and $1031\,cm^{-1}$ attributed to $\upsilon_{as}(NO_2)$ and $\upsilon_s(NO_2)$, respectively, [27,28]. The stretching motion of $\upsilon(N{=}O)$ is observed at $1462\,cm^{-1}$ as a strong band, while the two bending motion of the type $\delta(NO_2)$ are well resolved and observed at 758 and $663\,cm^{-1}$ as medium bands.

Concerning the $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ complex, (Scheme 2) the most important region in the infrared spectra of the copper(II) complex and the norfloxacin free ligand ($\sim$1700–$1300\,cm^{-1}$) is selected and assigned, as shown in Fig. 2B. In contrast to the assignments data of Nor and Cu(II)/Nor complex shows no absorption band at $\sim 1700\,cm^{-1}$, characteristic of the $\upsilon(C{=}O)$ vibration of the carboxylic group, that is indicative of the involvement of the carboxyl group in the coordination with copper ion. The peak at $1619\,cm^{-1}$ is absent in the spectrum data of the free Nor and can be assigned to the asymmetric stretching vibration of the carboxylate group, $\upsilon_{as}(COO^-)$. The spectrum of $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ complex also has strong intensity band at $1386\,cm^{-1}$. This band is absent in spectrum of Nor and interpretive to the symmetric vibration of the $\upsilon_s(COO^-)$ group.

Deacon and Phillips [29] have studied the criteria that can be used to distinguish between the three binding states of the carboxylate complexes. These criteria are: (i) $\Delta\upsilon > 200\,cm^{-1}$



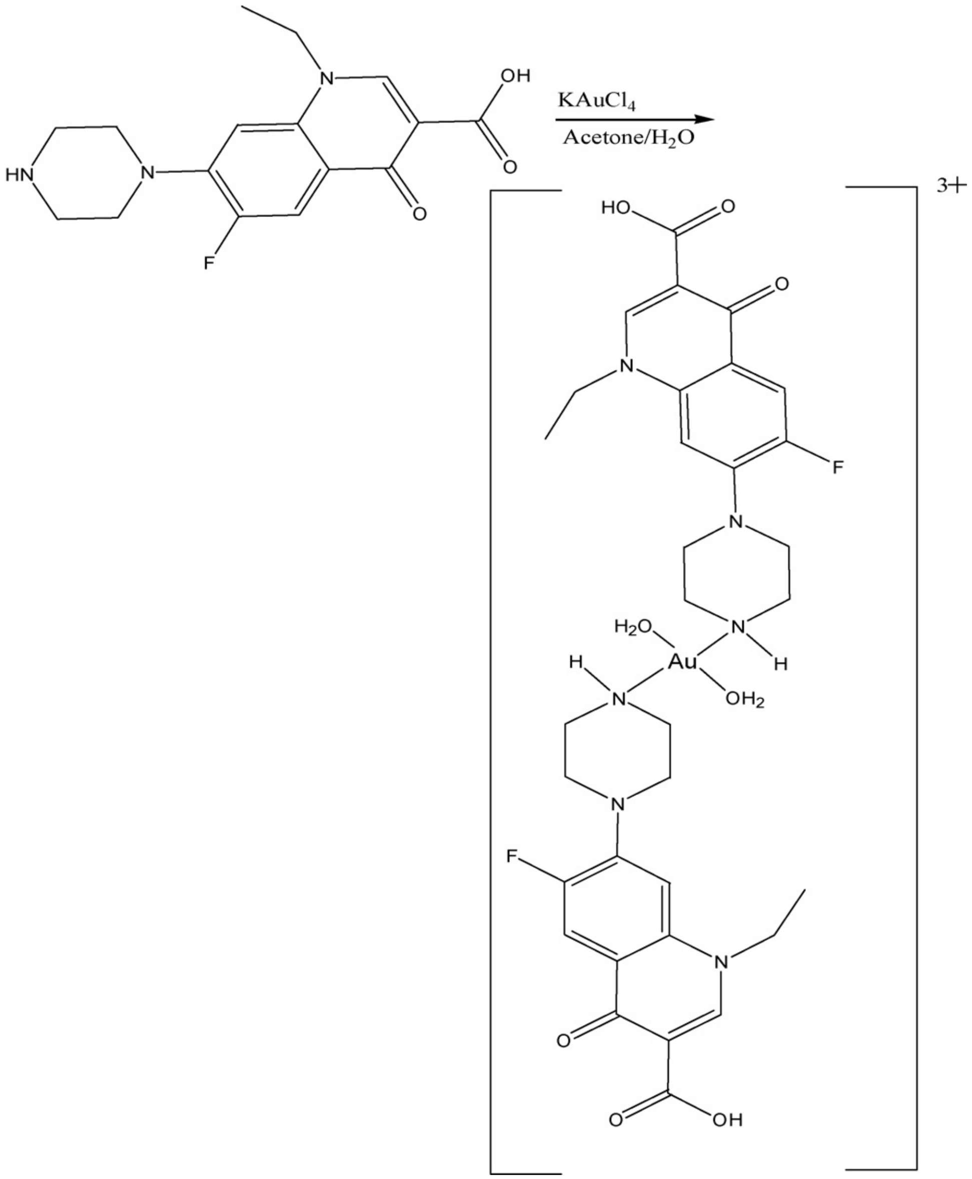
Scheme 2. $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$.

(where $\Delta\upsilon = [\upsilon_{as}(COO^-) - \upsilon_{as}(COO^-)]$) this relation was found in case of unidentate carboxylato complexes, (ii) bidentate or chelating carboxylato complexes exhibit $\Delta\upsilon$ significantly smaller than ionic values ($\Delta\upsilon < 100\,cm^{-1}$), and finally, (iii) bridging complexes show $\Delta\upsilon$ comparable to ionic values ($\Delta\upsilon \sim 150\,cm^{-1}$). The observed $\Delta\upsilon$ for the copper complex is $233\,cm^{-1}$, which confirm a unidentate interaction of the carboxylate group. The infrared spectral data of the Cu/Nor complex show a very strong broad band at $3399\,cm^{-1}$ and medium weak to weak bands at 2851 and $2495\,cm^{-1}$. These bands can be assigned to the vibrations of the quaternized nitrogen of the piperazinyl group, which indicated that the zwitterionic form of Nor is involved in the coordination to the copper ion investigated [30]. However, the vibrations of the free sulphate group [27] in this complex $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$, can be assigned as follows: two bands with strong intensities occur in the region above $1000\,cm^{-1}$ at 1179 and $1030\,cm^{-1}$, and very strong band at $923\,cm^{-1}$ are assigned to the different symmetric and antisymmetric bond vibrations, $\upsilon(SO_4{}^{2-})$, while the bending motion of $\delta(SO_4{}^{2-})$ is assigned to the band at $619\,cm^{-1}$.

Fig. 2C shows the IR spectra of $[Au(Nor)_2(H_2O)_2]Cl_3$ complex. On comparing the main IR frequencies of gold complex with that of Nor, the following were found: (1) there were two absorption peaks in the ligand Nor, i.e., $1716\,cm^{-1}$(ms) and $1630\,cm^{-1}$(vs); (2) the band at $1717\,cm^{-1}$, due to the carboxylic group, was detected in the spectrum of the gold complex, indicating that this moiety does not participate in the bonding to metal ion; (3) however, the technique permitted a definitive conclusion about the participation of the ketone group in the bonding to the metal, the corresponding band was recorded at $1630\,cm^{-1}$ in the spectrum of Nor, and a band close to this position ($1629\,cm^{-1}$) in the spectrum of the complex could be due to the ketone group uncoordinated to the metal ion. Similar to $[Ag_2(Nor)_2](NO_3)_2$ compound, the N atom of the piperidyl ring takes part in the coordination to metal ion (Au(III)) (Scheme 3 and Table 2).

4.2. Electronic spectra

Electronic spectra of the three complexes and Nor were recorded in the 200–800 nm region in DMSO (Fig. 3). Two peaks appear at 285 nm (band I) and 335 nm (band II) in the ligand, attributed to n-π^* and π–π^* transitions (these transitions occur in case of unsaturated hydrocarbons which contain carbon atom attached with oxygen atom as in carboxylic and ketone groups). The electronic spectra of complexes Ag^+ and Au^{3+} are similar to each other and are also similar to that of ligand; these facts show that after formation of the complexes, the two bands I and II in the electronic spectra are not affected, obviously suggesting that the ligand has not changed to the zwit-



Scheme 3. $[Au(Nor)_2(H_2O)_2]Cl_3$ compound.

terionic form. In the copper(II) complex, the peak at 285 nm has hyperchromic effect to high absorbance than the ligand, and it should be assigned that carboxylic group and ketone groups are involved in the complexation.

4.3. Mass spectra

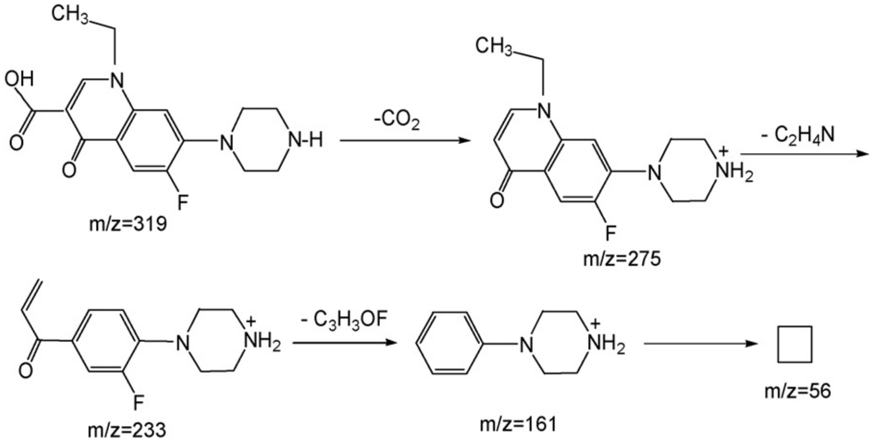
In the mass spectra of $[Ag_2(Nor)_2](NO_3)_2$, intense mass peaks at m/z 319, 275, 233, 161, 107, and 56 were observed (Fig. 4). The first mass peak corresponds to the $[H\text{-}Nor]^+$ ion and the second one proceeds by loss of CO_2 from the molecular ion at m/z 275 with intensity 72%, then the elimination of C_2H_4N, leads to the formation of an ion at m/z (%), 233 (100%), which is the base peak of the spectrum (Scheme 4). On comparison between the Nor (ligand) and Ag–Nor complex, it is clearly obvious that the peak that refers to molecular ion m/z 319 of Nor ligand is present in the silver(I) complex, and the new peak that appears at m/z 108 should be assigned to silver metal Ag^+. These results are again consistent with the presence of direct metal–ligand bonding in silver complex.

4.4. Powder X-ray diffraction

X-ray patterns of the copper(II) complex recorded at $2\theta = 0$–90 range were shown in Fig. 5. All the complexes are powder solids (amorphous). The resulted complexes are slightly soluble in DMF and DMSO and are decomposed in diluted solutions of all strong acids. Attempts to prepare single crystals were unsuccessful.

4.5. ^1H NMR spectra

The ^1H NMR spectra presented the persuasive confirmation of the coordination modes. Thus, the ^1H NMR spectrum



Scheme 4. Mass fragmentation route of Norfloxacin ligand.

of Cu(II) complex on comparing with that of the free norfloxacin indicates that Nor acts as bidentate ligand through the ring carbonyl oxygen atom and one of the oxygen atoms of the carboxylic group. On the other hand, the reaction of norfloxacin with $KAuCl_3$ yields an unusual mononuclear complex $[Au(Nor)_2(H_2O)_2]Cl_3$ in which the local coordination environment around Au(III) ion with N–Au–N coordinated feature. Fig. 6 shows ^{1}H NMR spectra of copper(II) and gold(III) complexes, which were carried out in DMSO-d$_6$ as a solvent. Concerning $[Cu(Nor)_2(H_2O)_2]SO_4.{\cdot}5H_2O$ complex, the data obtained are in agreement with the suggested coordination through the carboxylic group (absent the hydrogen signal of (COOH) in this case), and due to different chemical environments two signals are recorded for the quaternized nitrogen ($-^+NH_2$) at δ 2.51 and 2.75 ppm. The peak at δ 3.55 ppm was assigned to water molecules within the complex, which was not detected in the spectra of free norfloxacin ligand. Table 3 summarizes the ^{1}H NMR spectral data of free Nor, $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ and $[Au(Nor)_2(H_2O)_2]Cl_3$ compounds. The $-CH_2-$ group quartet has a total intensity of two units with the values of δ 4.56, 4.67, 4.70, and 4.78 ppm, while the $-CH_3$ group (triplet) has three units of intensity with the value of δ 1.41, 1.43 and 1.46 ppm. The ^{1}H NMR spectrum of a solution of $[Au(Nor)_2(H_2O)_2]Cl_3$ solid complex in DMSO-d$_6$ showed frequencies at δ 1.33, 2.00, 3.45, 2.82, 4.48, 4.51, 7.03, 7.07, 7.75, 7.78, 7.82, and 8.85 ppm and these are the same places as those of free donor, Nor (the signal of carboxylic group not affected and the presence of δH; –NH signal) located at δ 1.13, 2.00, 3.55, 2.78, 3.10, 3.47, 5.93, 7.12, 8.01, and 11.00 ppm, respectively, except an increasing/decreasing in the chemical shift of protons of piperazine and aromatic rings compared with the donor alone. This shift is due to the complexation and difference in the configuration of complexes than ligand.

4.6. Thermal studies

The norfloxacin of Ag(I), Cu(II), and Au(III) complexes are stable at room temperature and can be stored for several months without any changes. Ag(II), Cu(II), and Au(III) complexes of norfloxacin were studied by thermogravimetric analysis from ambient temperature to 800 °C N_2 atmosphere. The TG curves were redrawn as mg mass loss versus temperature (TG) curves and also as the rate of loss of mass versus temperature (DTG) curves. Typical TG and DTG curves are presented in Fig. 7, and the temperature ranges and percentage mass losses of the decomposition reaction are given in Table 4, together with evolved moiety and theoretical percentage mass losses.

The overall loss of mass from the TG curves is 97.74% for Nor, 71.25% for $[Ag_2(Nor)_2](NO_3)_2$, 82.39% for $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ and 80.35% for $[Au(Nor)_2(H_2O)_2]Cl_3$. All the complexes show two or three stages of mass loss in their TG/DTG curves. The first mass loss corresponds to the formation of their respective anhydrous compounds. While the second, third, and fourth mass loss is due to the decomposition of counter ions and Nor molecules. The end-products were confirmed with infrared spectra.

Norfloxacin melts at 232 °C with simultaneous decomposition. The first mass loss was observed at 125 °C in the TG

Table 3
^{1}H NMR spectral data of free Nor, $[Cu(Nor)_2(H_2O)_2]SO_4.5H_2O$ and $[Au(Nor)_2(H_2O)_2]Cl_3$ compounds

Nor	$[Cu(Nor)_2(H_2O)_2]SO_4.{\cdot}5H_2O$	$[Au(Nor)_2(H_2O)_2]Cl_3$	Assignments
1.13	1.41, 1.43, 1.46	1.33	δ H, $-CH_3$
2.0	–	2.00	δ H, $-NH$; Piperazine
–	2.51, 2.75	–	δ H, $-^+NH_2$
–	3.55	3.45	δ H, H_2O
2.78, 3.10, 3.47	4.56, 4.67, 4.70, 4.78	2.82 4.51, 4.48	δ H, $-CH_2$; Piperazine δ H, $-CH_2$; $-CH_2CH_3$
5.93, 7.12, 8.01	7.20, 7.29, 7.92, 7.95	7.03, 7.07, 7.75, 7.78, 7.82	δ H, $-CH$ aromatic
11.00	–	8.85	δ H, $-COOH$

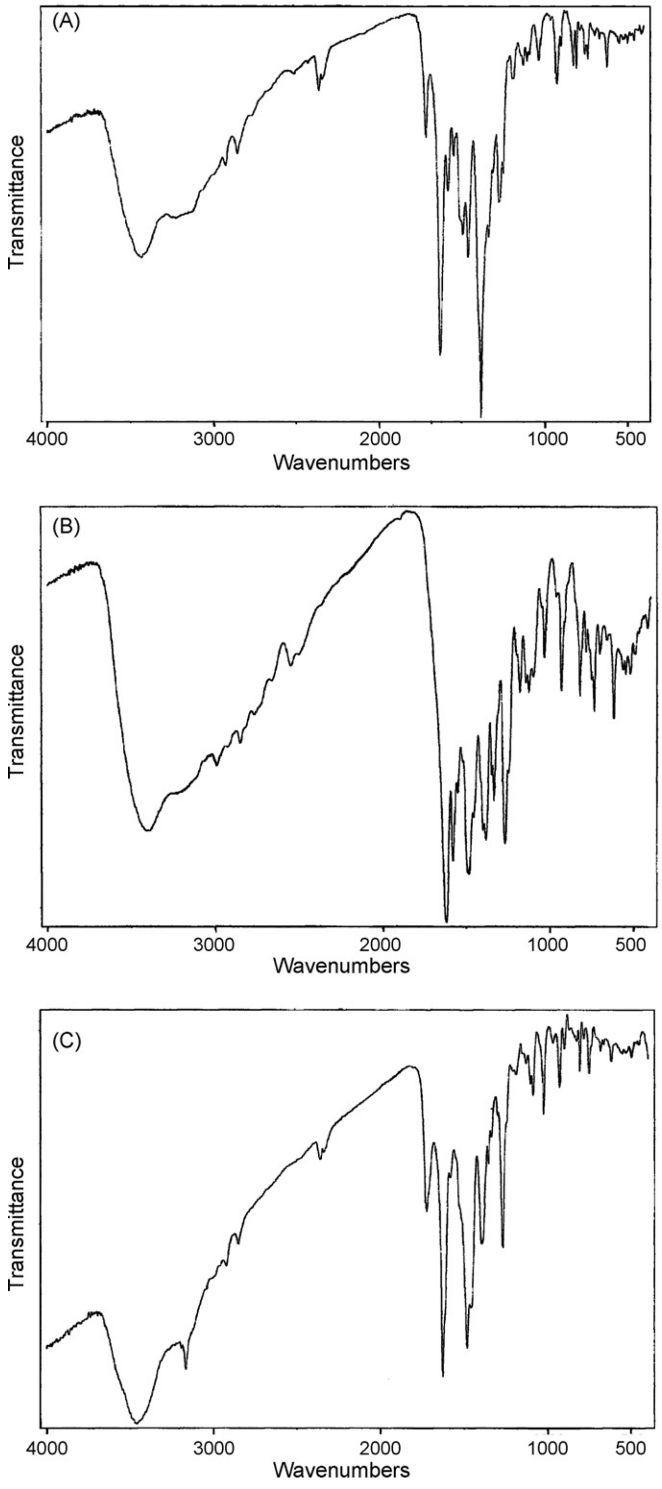


Fig. 2. Infrared spectra of: (A) $[Ag_2(Nor)_2](NO_3)_2$ compound; (B) $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ compound; (C) $[Au(Nor)_2(H_2O)_2]Cl_3$ compound.

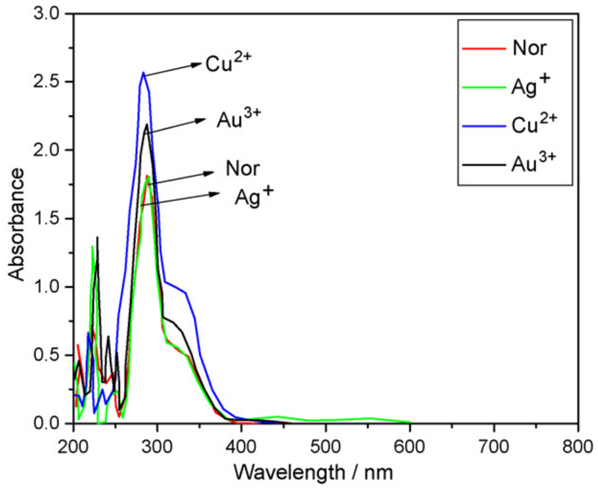


Fig. 3. Electronic spectra of: $[Ag_2(Nor)_2](NO_3)_2$; $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ and $[Au(Nor)_2(H_2O)_2]Cl_3$ compounds.

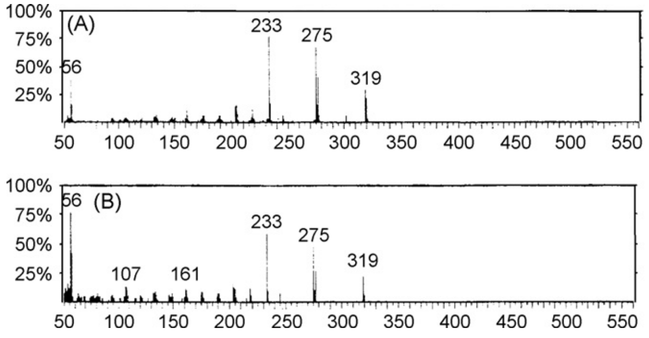


Fig. 4. Mass spectra of (A): Nor ligand and (B): $[Ag_2(Nor)_2](NO_3)_2$ compound.

profile. The TG/DTG profiles of ligand are shown in Fig. 7. From TG curves, it appears that the sample decomposes in three stages over the range 25–726 °C. The first decomposition occurs between 25 and 270 °C with a mass loss of 8.38% and the second decomposition starts at 270 °C and ends at 575 °C with a 69.80% mass loss. The next decomposition step occurs in the range 575–726 °C with a maximum at 650 °C and is accompanied by a weight loss of 19.56%, and may be attributed to the loss of pyrrole ring, $2C_2H_2 + 1/2N_2 + 1/2H_2$, in reasonable agreement with the theoretical value of 21.00%.

The TG of the $[Ag_2(Nor)_2](NO_3)_2$ complex reveals a mass loss in the temperature range 25–275 °C corresponding to the formation of 2Ag(Nor). The next decomposition step occurs in

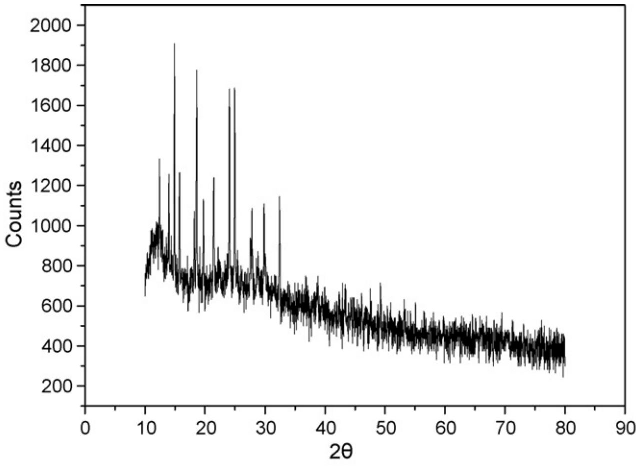


Fig. 5. X-ray powder diffraction of $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ complex.

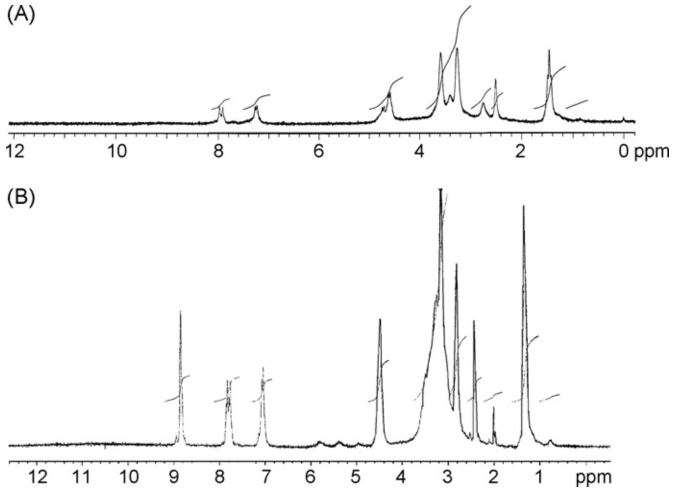


Fig. 6. ^{1}H NMR spectra of: (A) $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$; (B) $[Au(Nor)_2(H_2O)_2]Cl_3$.

the temperature range 275–525 °C and corresponds to the thermal decomposition of 2Ag(Nor) to (AgF + Ag(Nor)). The last decomposition step occurs in the temperature range 525–773 °C and corresponds to the formation of 2AgF.

The TG curve of $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$ complex shows an initial mass loss in the temperature range 25–275 °C corresponding to the decomposition of the complex to anhydrous complex by the loss of five uncoordinated water molecules. This is followed by another mass loss in the temperature range 275–470 °C due to the thermal decomposition of $[Cu(Nor)_2(H_2O)_2]SO_4$ to $[Cu(Nor)]SO_4$. The mass loss at the last stage in the temperature range 470–657 °C is due to the decomposition of $[Cu(Nor)]SO_4$ to copper(II) sulfate by the decomposition of the second norfloxacin molecule.

The $[Au(Nor)_2(H_2O)_2]Cl_3$ complex is thermally stable up to 265 °C. The mass loss at the first stage in the temperature range 25–350 °C corresponds to the decomposition of the complex to $[Au(Nor)_2]Cl_3$. The mass loss at the second stage in the temperature range 350–700 °C is due to the decomposition of $[Au(Nor)_2]Cl_3$ to metallic gold. A horizontal plateau on the TG curve for the complex indicate the decomposition of organic part of the chelate in the last step leaving residue of metallic at the final temperature. The final weight of residues correspond to the corresponding metallic or/and metal oxides [31] as end-products. The decomposition temperatures of the complexes are higher than that of the ligands (Table 4) and indicate that the thermal stability of the complexes are increased due to

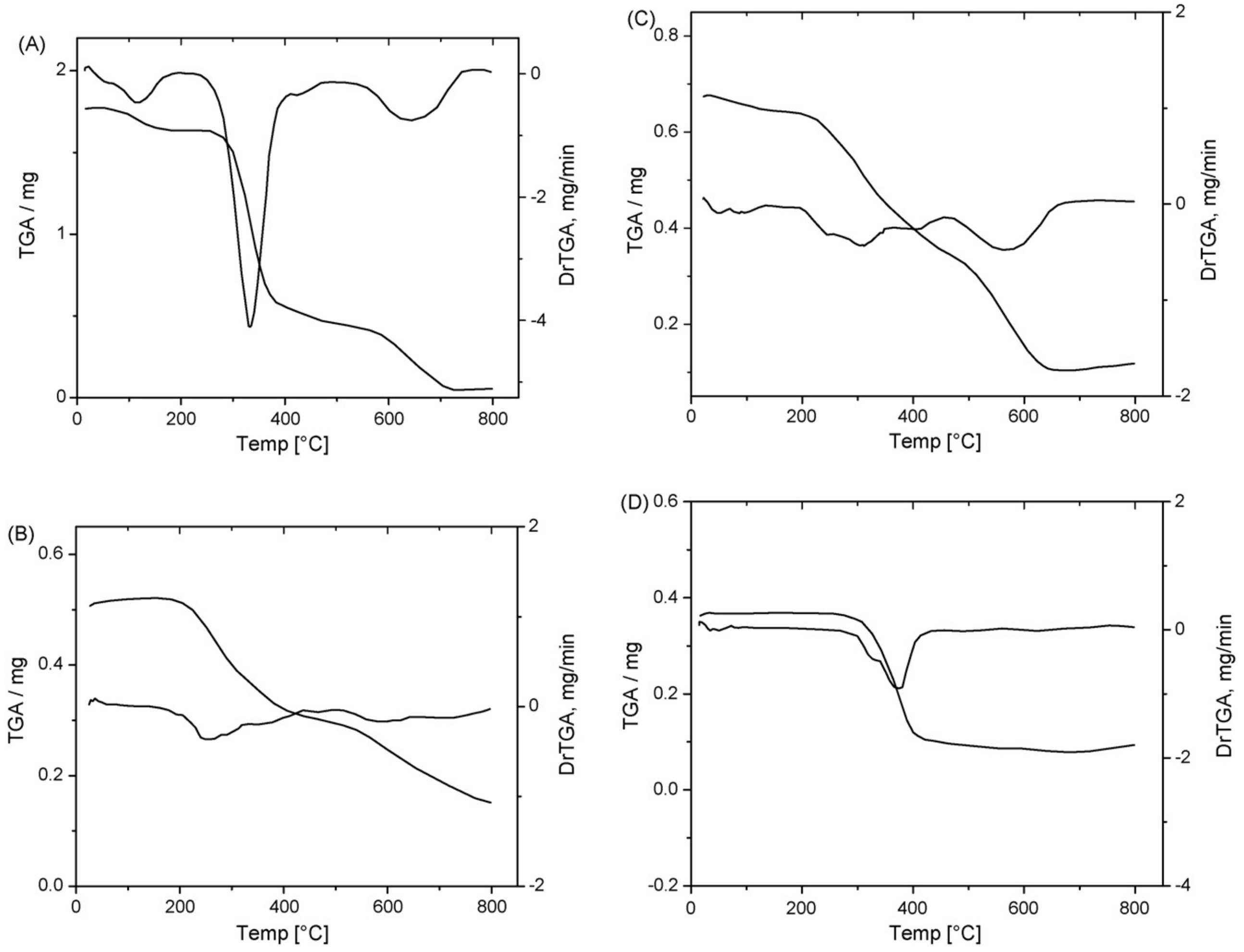


Fig. 7. TG and DTG curves of: (A) Norfloxacin ligand; (B) $[Ag_2(Nor)_2](NO_3)_2$; (C) $[Cu(Nor)_2(H_2O)_2]SO_4{\cdot}5H_2O$; (D) $[Au(Nor)_2(H_2O)_2]Cl_3$.

Table 4
Thermo analytical results for the investigated compounds

Samples	Stage	TG results temp peak (°C)	DTG results temp. range (°C)	Weight loss(%)		Evolved moiety
				Found	Calculated	
Nor	I	25–270	125	8.38	8.78	C_2H_4
	II	270–575	335	69.80	70.22	$HF + 4C_2H_2 + CO + CO_2 + N_2$
	III	575–726	650	19.56	21.00	$2C_2H_2 + 0.5H_2 + 0.5N_2$
Ag/Nor	I	25–275	250	11.97	12.68	$2NO_2 + O_2$
	II	275–525	375	30.54	30.67	$8C_2H_2 + 0.5N_2 + 2NO + H_2O$
	III	525–773	600	28.74	30.67	$8C_2H_2 + 0.5N_2 + 2NO + H_2O$
	Residue	>773		28.75	25.97	2AgF
Cu/Nor	I	25–275	45, 90, 240	9.55	9.75	$5H_2O$
	II	275–470	290, 425	38.21	38.44	$2H_2O$ + Nor
	III	470–657	575	34.63	34.53	Nor
	Residue	>657		17.61	17.28	$CuSO_4$
Au/Nor	I	25–350	320	3.74	3.68	$2H_2O$
	II	350–700	375	76.16	76.61	$3/2Cl_2$ + 2Nor
	Residue	>700		19.65	20.16	Au

the ligand coordinating with metal ions to form stable complexes (Table 4).

4.7. Kinetics data

Coats–Redfern [32] and Horowitz–Metzger [33] are the two methods mentioned in the literature related to decomposition kinetics studies; these two methods are applied in this study. From the TG curves, the activation energy, E, pre-exponential factor, A, entropies, ΔS, enthalpy, ΔH, and Gibbs free energy, ΔG, were calculated by well-known methods; where $\Delta H = E - RT$ and $\Delta G = \Delta H - T\Delta S$.

The linearization curves of Coats–Redfern and Horowitz–Metzger methods are shown in Fig. 8. Kinetic parameters for the first stages, calculated by employing the Coats–Redfern and Horowitz–Metzger equations, are summarized in Table 5, together with the radii of metal ions. The results show that the values obtained by various methods are comparable.

The kinetic data obtained with the two methods are in harmony with each other. The activation energy of Ag(I), Cu(II), and Au(III) compounds is expected to increase in relation with decrease in their radii [34]. The smaller size of the ions permits a closer approach of the ligand. Hence, the E value in the first stages for the Cu(II) complex is higher than that for the other complexes [35,36].

4.8. Biological activities

The results of antibacterial activities *in vitro* of the ligand and the complexes are shown in Table 6. From the results we can see that when the content of the ligand and the complexes was 1.0×10^{-3} mol dm^3, they had no inhibitory activity against G(−) *Escherichia coli*. The ligand showed no inhibitory activity against G(−) *Pseudomonas aeruginosa*, while the complexes showed obvious inhibitory activity. The inhibitory activity of the three complexes in comparison with ligand against G(+) *Bacillus subtilis* was decreased.

The norfloxacin ligand and their Ag(I), Cu(II), and Au(III) complexes have been evaluated for their antifungal activity. The minimal inhibitory concentration values listed in Table 7 show that all the test compounds have lower antifungal activity against *Aspergillus flavus* and *Fusarium solani* types except for *Penicillium verrcosum* type, which have higher antifungal activity comparable to the respective ligand.

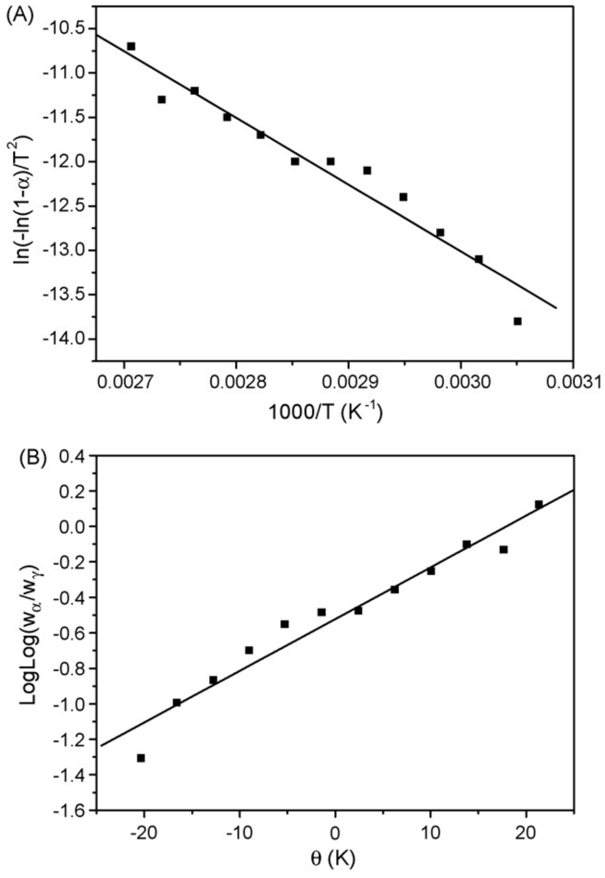


Fig. 8. Kinetic parameter of $[Cu(Nor)_2(H_2O)_2]SO_4 \cdot 5H_2O$ compound.

Table 5
Kinetic data on the studied compounds for stage I

Compounds	Ionic radius/pm	Parameters[a]	From Coats–Redfern eq.	From Horowitz–Metzger eq.
Nor	–	E	9.36×10^{4}	9.66×10^{4}
		A	2×10^{1}	8.68×10^{1}
		ΔS	-5.01×10^{1}	-3.79×10^{1}
		ΔH	9.03×10^{4}	9.33×10^{4}
		$\Delta \mathrm{G}$	1.10×10^{5}	1.08×10^{5}
		r	0.9853	0.9817
Ag/Nor	126	E	4.70×10^{4}	4.89×10^{4}
		A	3.74×10^{4}	2.24×10^{2}
		ΔS	-1.62×10^{2}	-2.05×10^{2}
		ΔH	4.24×10^{4}	4.43×10^{4}
		ΔG	1.31×10^{5}	1.57×10^{5}
			0.9815	0.9822
Cu/Nor	73	E	6.26×10^{4}	6.77×10^{4}
		A	2.67×10^{7}	2.37×10^{8}
		ΔS	-1.04×10^{2}	-8.59×10^{1}
		ΔH	5.97×10^{4}	6.48×10^{4}
		ΔG	9.59×10^{4}	9.47×10^{4}
			0.9737	0.9768
Au/Nor	85	E	5.23×10^{4}	5.39×10^{4}
		A	2.67×10^{26}	3.40×10^{27}
		ΔS	-2.55×10^{2}	-2.76×10^{2}
		ΔH	3.18×10^{5}	3.25×10^{5}
		ΔG	1.66×10^{5}	1.61×10^{5}
			0.9878	0.9863

[a] Units of parameters: E in kJ mol^{-1}, A in s^{-1}, ΔS in J mol^{-1} k^{-1}, ΔH and ΔG in kJ mol^{-1}.

Table 6
Antibacterial activity data for Nor and its compounds

Compound	*Bacillus subtilis*	*P. aeruginosa*	*E. coli*
Nor	++++	+	−
Ag/Nor	+++	++	−
Cu/Nor	+++	+++	−
Au/Nor	+++	++	−

(−) NO antibacterial activity, (+) mild activity, (++) moderate activity, (+++) marked activity, (++++) strong marked activity.

Table 7
Antifungal activity data for Nor and their compounds

Compound	*Aspergillus flavus*	*Fusarium solani*	*Penicillium verrcosum*
Nor	−	−	++
Ag/Nor	−	−	+++
Cu/Nor	−	−	+++
Au/Nor	−	−	++++

(−) NO antibacterial activity, (+) mild activity, (++) moderate activity, (+++) marked activity, (++++) mtrong marked activity.

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