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Synthesis, characterization, crystal structure and antimicrobial studies of a novel Cu(II) complex based on itaconic acid and nicotinamide

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ABSTRACT

A novel complex was synthesized from Cu(II), nicotinamide and itaconic acid and is formulated as $[Cu(C_5H_4O_4)_2(C_6H_6N_2O)_2(H_2O)_2\cdot 2(H_2O)]$ (**1**). The compound was characterized by elemental analysis, FTIR spectroscopy, UV-Vis and single crystal X-ray diffraction. The complex crystallizes in the triclinic *P*-1 space group, with $a = 7.5111(2)$ Å, $b = 9.8529(3)$ Å, $c = 10.5118(4)$ Å, $\alpha = 116.244(3)^\circ$, $\beta = 90.291(3)^\circ$, $\gamma = 103.335(3)^\circ$, $V = 673.81(4)$ Å^3, $Z = 1$.The octahedral geometry around the copper(II) ion is of the form CuN_2O_4 consisting of two molecules of nicotinamide acting as monodentate ligand through the nitrogen atoms, two molecules itaconate ligand and two coordinated water molecules each coordinating through the oxygen atoms. The structure of **1** showed infinite chains build up linking the molecules together via strong O—H···O and N—H···O intermolecular hydrogen bonds generating a two dimensional network sheet along *c* axis. The antimicrobial study of the synthesized complex **1** was investigated and showed higher antibacterial activity against all the organisms comparing with Copper(II) nicotinamide **2** and Copper(II) itaconate **3**.

1. Introduction

Transition metal complexes, such as metal carboxylates, have received extensive attention due to their great biological and industrial applications [1–9]. As an important class of organic ligands, those containing the carboxyl groups that have been applied in the preparation of many advanced functional materials such as metal-organic frameworks (MOFs) [10–12], due to the affinity of carboxylate anions to metal cations. In particular, we focused our research on the dicarboxylate organic linker itaconic acid (ITA) that exhibits tetra-, penta-, and hexadentate coordination modes [13–15]. Nitrogen based ligands have received some attention for the synthesis of metal complexes due to the ease of coordination of the nitrogen donor atom to the metal ions [16,17]. Among them, nicotinamide that may be mono [18] or bidentate [19], it is considered as one form of vitamin B_3, the deficiency of this vitamin leads to loss of copper from the body, known as pellagra diseases. Victims of pellagra show usually high serum and urinary copper levels. So this compound acts as interesting potential medicinal substance. Transition metals are the most famous cations to be used in preparation of metal-organic complex due to the electrical, magnetic, catalytic and luminescence properties of such metal centers [20–26]. Copper was chosen for its importance in biological and physiological activities that mediate a multitude of chemical reactions needed for life [27–29]. To the best of our knowledge, studies on Copper-nicotinamide-itaconic system have not been reported to date. Herein, we report the synthesis, crystal structure and characterization of the first complex assembled from Cu(II), nicotinamide and itaconic acid, formulated as $[Cu(C_5H_4O_4)_2(C_6H_6N_2O)_2(H_2O)_2\cdot 2(H_2O)]$ **1**. Furthermore, antimicrobial studies of the synthesized complex **1** were investigated and showed higher antibacterial activity against all the organisms comparing with Copper(II) nicotinamide **2** and Copper(II) itaconate **3**.

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2. Experimental section

2.1. Materials

The Itaconic acid and Nicotinamide were commercially obtained and used without further purification. Hydrated metal salts ($Cu(NO_3)_2 \cdot 3H_2O$), $CuCl_2 \cdot 2H_2O$ and $Cu(CH_3COO)_2 \cdot H_2O$ for complexation were obtained from British Drug House (BDH) Poole, England.

2.2. Synthesis of $[Cu(C_5H_4O_4)_2(C_6H_6N_2O)_2(H_2O)_2 \cdot 2(H_2O)]$ **1**

Complex **1** was synthesized by mixing a solution of Itaconic acid (0.260 g, 2 mmol) in methanol (10 ml), a solution of Nicotinamide (0.244 g, 2 mmol)in ethanol (10 ml) and a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (0.242 g, 1 mmol) in ethanol (10 ml). The mixture was stirred for 1 h; a clear blue solution was obtained and left standing for slow evaporation at room temperature (Scheme 1). Single blue crystals suitable for X-ray analysis was obtained after 10days. The blue crystal formed was separated out by filtration and washed with mixture of methanol and ethanol in ratio 1:2 and dried at room temperature.

M.wt: 638.05 g mol^{-1}, Yield: 75.6%, M. pt: 120 °C, Anal. Calc for $C_{22}H_{28}CuN_4O_{14}$ (%): C 41.54; H, 4.41; N 8.81; Found %: C, 41.00; H, 4.57; N, 8.60. IR (KBr pellet, cm^{-1}) 3524, 3429, 3385, 3308, 1712, 1780, 1680, 1649, 1604, 1220, 692, 443. UV-Vis (distilled water) nm(cm^{-1}): 220(45,455), 348(28,736), 660(15,152).

2.3. Synthesis of copper (II) – nicotinamide$[Cu(Nic)_2(H_2O)_2]$ **2**

$[Cu(Nic)_2(H_2O)_2]$ was prepared according to published procedure [30]. Nicotinamide (0.244 g, 2 mmol) dissolved in10 ml methanol was gradually added to 5 ml of stirred methanol solution of $CuCl_2 \cdot 2H_2O$ (0.068 g, 1 mmol). The mixture was stirred for 3 h. Blue precipitate obtained was filtered, washed and dried in a desiccator.

M.pt: 281 °C. Anal. Calc. for $C_{12}H_{16}CuN_4O_4$.; C, 41.86%; H, 4.65%; N, 16.28%. Found, C, 42.00%; H, 4.76%; N, 16.10%. IR(KBr pellet, cm^{-1}): 3402, 3161, 1708, 1403, 1381, 1151,688; solid UV-vis spectra (nm): 211,661.

2.4. Synthesis of copper (II) – itaconate $[Cu(Ita)_2(H_2O)_2]$ **3**

$[Cu(Ita)_2(H_2O)_2]$ was prepared according to published procedure [31]. Itaconic (0.260 g, mmol) dissolved in 10 ml ethanol was gradually added to 10 ml of methanol solution of $Cu(OAC)_2$ H_2O (0.199 g, 1 mmol). The mixture was stirred for 2hr. Green precipitate obtained was filtered, washed and dried in a desiccator.

M.pt:.>300 °C. Anal. Calc. for $C_{10}H_{14}CuO_{10}$ C, 33.52%; H, 3.91%; O; 44.69%. Found, C, 33.67%; H, 4.16%; O, 44.10%. IR(KBr pellet, cm^{-1}): 3446, 1610, 2924, 2372, 1610, 419, 1238, 1168,671, 464; solid UV-vis spectra (nm): 226, 510.

2.5. Physical measurement

The C, H and N analyses were performed on Carlo Erba Model EA1108 elemental analyzer. IR spectra on the range of 4000–400 cm^{-1}were obtained from samples in the form of KBr pellets using FTIR-8501 Schimadzu Spectrometer. Electronic absorption spectra (200–1100 nm) were recorded using JENWAY 6405UV/Vis spectrophotometer. The melting points were determined on MPA100 Optimelt Automated Melting Point System.

2.6. Crystal structure determination

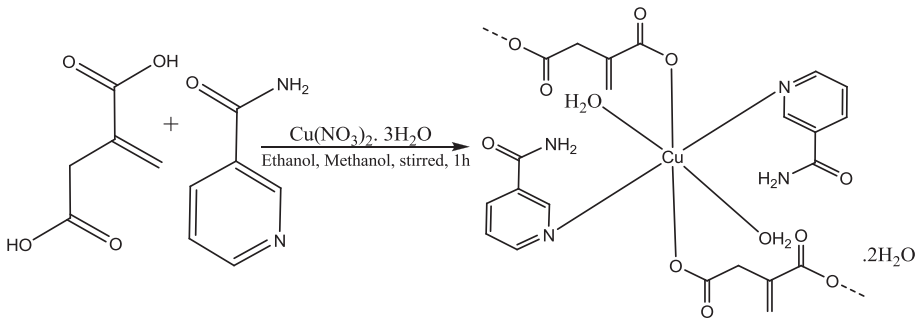
Data collection was performed at 293 K on an Agilent GeminiCCD diffractometer using MoKα radiation. Images were collected at a 55 mm fixed crystal–detector distance, using theoscillation method, with 1° oscillation and variable exposuretime per image. The crystal structure was solved by directmethods. The refinement was performed using full-matrixleast squares on F2. All non-H atoms were anisotropically refined. All H atoms were either geometrically placed riding ontheir parent atoms or located from the difference Fourier map,with isotropic displacement parameters set at 1.2 times the Ueq of the atoms to which they are attached. Crystallographic calculations were carried out using the following programs: CrysAlis CCD [32] for data collection; CrysAlis RED [33] for cell refinement, data reduction and empirical absorption correction; SHELXS-97 [34] for structure solution; XABS2 [35] forrefined absorption correction; SHELXL-97 for structure refinement and preparing materials for publication; PLATON [36] for the geometrical calculations; Diamond [37] for molecular graphics.

2.7. Antibacterial experiments

Three clinical bacteria isolates: *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were collected from University of Ilorin Teaching Hospital (UITH) Nigeria, for antibacterial screening. Standardized sensitivity text agar (Lab M, UK) was used for the antibacterial assay. The three clinical bacteria isolates were challenged with varying concentrations of the metal complex using the agar diffusion technique and zones of inhibition were interpreted using standard recommendation National Committee for Clinical Laboratory Standards (NCCLS, 2006) [38].

2.8. Minimum inhibitory concentration MIC

MIC of the samples was determined using the broth dilution technique. Nutrient broth was seeded with standardized inocula of the test organisms. These were challenged with varying



Scheme 1. Synthesis of **1**.

concentrations of the complexes **1**, **2**, **3**, nicotinamide and itaconic acid samples. For the antimicrobial susceptibility testing, nine clinical antibiotics with their concentrations given in parentheses were used as control as recommended by the National Committee for Clinical Laboratory Standards (NCCLS, 2006) [38]. The antibiotics used to challenge *P. aeruginosa* and *E. coli* being gram negative organisms were ciprofloxacin (10 μg), gentamycin (10 μg) and perfloxacin (30 μg).Those used for *S. aureus* a gram positive organism were erythromycin (30 μg), gentamycin (10 μg), augumentin (30 μg), chloramphenicol (10 μg), cotrimoxazole (10 μg), streptomycin (30 μg) and ciprofloxacin (10 μg).

3. Results and discussions

The complex is soluble in cold DMSO and warm water, but insoluble in common organic solvents. The elemental analysis result of the complex clearly shows the formation of $[Cu(C_5H_4O_4)_2(C_6H_6N_2O)_2(H_2O)_2\cdot 2(H_2O)]$ **1** and confirmed by X-ray crystal structure.Determination of stoichiometric ratio using Job's method suggested mole ratio 1:2:2 Cu to ITA to NIC. The complex consists of metal ion which coordinates through the nitrogen atom of the Pyridine ring in nicotinamide and oxygen atom of the carboxylate groups on the itaconic acid with two water molecule to form octahedral structure.The carboxylic moiety is deprotonated to form COO^-, with the coordination of the metal at the nitrogen atom of the second ligand. The formula of the structure gives a net formula charge of zero (0). There is no excess charge on the compound as given in the formula.

3.1. Structure description

The detailed crystallographic data and the structure refinement parameters are summarized in Table 1. Selected bond distances and angles are given in Table 2. The asymmetric unit of complex **1** comprises one Cu^{2+}, one itaconate, one nicotinamide, two coordinated water molecule, and two water molecules acting as solvent of crystallization (Fig. S1). The complex crystallizes in a triclinic space group *P*-1 in which the copper(II) ion is octahedrally coordinated by two O atoms of two itaconate ligand, two O atoms of water molecules and two N atoms of nicotinamide molecules (Fig. 1a,b). The Cu–N distance has the average of 2.019 Å in good agreement with the value of reported Cu–N bond lengths for Cu(II)- nicotinamide complexes [39–42]. The Cu–O distance has the average of1.944 Å and it is favourably similar to those found in copper complexes of related dicarboxylate ligands [43–46]. It can be observed that the Cu(1)–O(2) is slightly shorter than Cu(1)–N(1) and Cu(1)–O(6), this indicates that the coordination ability of oxygen atom of the itaconate ligand is stronger than that of the nitrogen atom of the pyridine from nicotinamide and oxygen atom from the water molecules (O6) which could be ascribed to the Jahn–Teller effects in the copper(II) complexes, this consequently leads to the distorted octahedral geometry of the compound [47]. Cu(1)–O(6) aqua distances are longer than those reported in literature, this is probably due to hydrogen bonding and other non-covalent interactions between one aqua and acceptor groups [48]. The bond angles N(1)–Cu(1)–N(1), O(2)–Cu(1)–O(2) and O(6)–Cu(1)–O(6) are 180° which are comparable to other copper (II) complexes with similar ligands [47]. The other bond angles N(1)–Cu(1)–O(2), O(2)–Cu(1)–O(6) and O(6)–Cu(1)–N(1), are ranged between 87 and 92° near ideal 90°. The structure of **1** showed infinite chains build up linking the molecules together via strong O–H···O and N–H···O intermolecular hydrogen bond generating a two dimensional network sheet along *c*-axis. The structure is stabilized by these strong intermolecular hydrogen bonds in addition to the intramolecular hydrogen bonds within each molecule (Fig. 2), Table 3.

Table 1
Crystal data and structure refinement for **1**.

Identification code	**1**
Empirical formula	$C_{22}H_{30}O_{14}N_4Cu_1$
Formula weight	638.05
Temperature/K	293.0
Crystal system	Triclinic
Space group	*P*-1
a/Å	7.5111(2)
b/Å	9.8529(3)
c/Å	10.5118(4)
α/°	116.244(3)
β/°	90.291(3)
γ/°	103.335(3)
Volume/Å^3	673.81(4)
Z	1
Calc. density/mg m^{-3}	1.572
μ/mm^{-1}	0.89
F(000)	331
Crystal size/mm	0.12 × 0.20 × 0.36
θ range for data collection/°	3.8 to 28
Index ranges	$-11 \le h \le 11$, $-14 \le k \le 14$, $-15 \le l \le 15$
Reflections collected	31,039
Independent reflections	4680[R(int) = 0.069]
Data/restraints/parameters	4331/0/211
Goodness-of-fit on F^2	1.09
Final R indexes [I ≥ 2σ (I)]	$R_1 = 0.042$, $wR_2 = 0.094$
Final R indexes [all data]	$R_1 = 0.0605$, $wR_2 = 0.1337$
Largest diff. peak/hole/e Å^{-3}	0.37/−0.43

Table 2
Selected bond lengths (Å) and angles (°) for **1**.

Bond lengths (Å)		Bond angles (°)	
Cu1–O2	1.944(1)	O2–Cu1–O2^i	180(1)
Cu1–N1	2.019(1)	N1–Cu1–N1^i	180
Cu1–O6	2.605(1)	O6–Cu1–O6^i	180
		N1–Cu1–O2	89.89(6)
		02–Cu1–O6	92.73
		06–Cu1–N1	88.61

Symmetry code: (i) −x, −y+1, −z.

3.2. Infra-red spectra studies

The infrared spectrum of the complex **1** was compared with those of the ligands as shown in (Fig. 3). The infra-red spectrum of the metal carboxylate was found to be different from those of the ligands and showed either a shift or disappearance of some

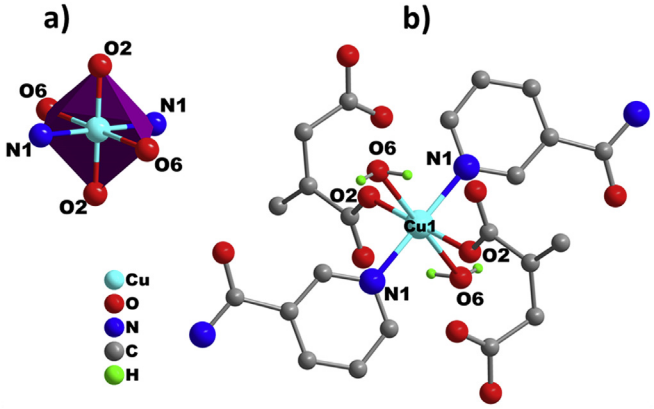


Fig. 1. Perspective view of the coordination environments of Cu^{2+} in **1**.

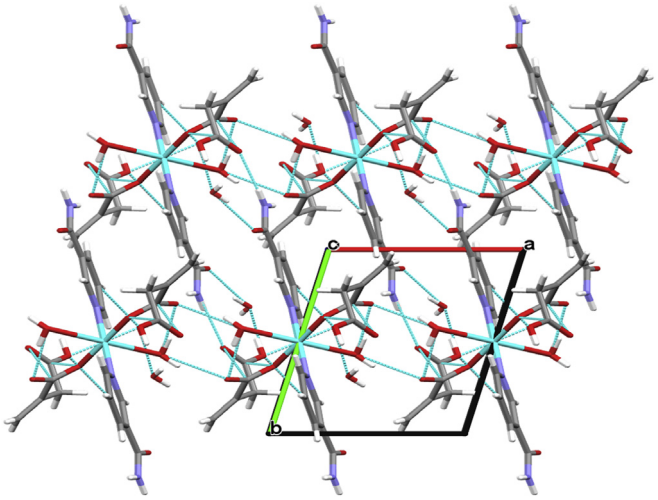


Fig. 2. Projection of the structure along *c* axis for **1** with the relevant hydrogen bonds.

Table 3
Hydrogen-bond geometry (Å, °) for **1**.

D—H···A	D—H	H···A	D···A	D—H···A
N(2)—H(1N)···O(4)^{I}	0.83(2)	2.04(2)	2.855(2)	169.7(3)
O(6)—H(1W)···O(3)^{II}	0.88(3)	2.21(3)	3.034(3)	156.7(3)
N(2)—H(2N)···O(3)^{III}	0.82(4)	2.28(4)	3.088(3)	167.9(3)
O(6)—H(2W)···O(3)^{IV}	0.83(2)	1.96(2)	2.778(2)	169.7(3)
O(7)—H(3W)···O(6)^{V}	0.84(4)	2.28(4)	3.086(3)	159.84(3)
O(7)—H(4W)···O(1)^{I}	0.79(4)	2.12(4)	2.896(2)	165.9(4)
O(5)—H(5O)···O(7)^{IV}	0.82(2)	1.81(2)	2.618(3)	167.3(2)

Symmetry codes: (I) −x+1, −y+2, −z; (II) −x+1, −y+1, −z; (III) x, +y+1, +z; (IV) x, y, z; (V) x, +y, +z−1.

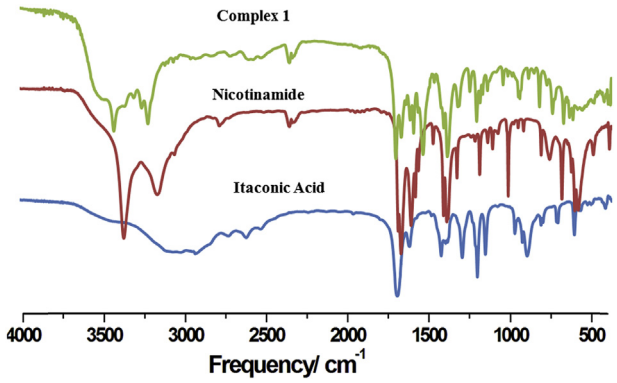


Fig. 3. FT-IR spectra of Itaconic acid, Nicotinamide and **1**.

characteristic frequencies and appearance of some new frequencies. In the itaconic acid, two carboxylate groups are present. The two are deprotonated and are involved in coordination with copper ion. Itaconic acid is a dicarboxylic acid having coordination sites at only the carboxylic acid functional groups while nicotinamide is an amide having three potential donor atoms: nitrogen of pyridine as well as oxygen and nitrogen of amide. Nicotinamide can either be monodentate or bidentate bridging ligands. In the complex, nicotinamide acts as a monodentate ligand and binds through the pyridine N1 with metal ions. This mode of binding is in good agreement with the previous work carried out by Sadikov et al. [49].

The IR spectrum of the compound shows characteristic bands of itaconate (ITA) and nicotinamide (NIC). The appearance of the broad band at 3524 cm^{-1} in the spectra of complex is due to the stretching vibration of the associated water molecules [50]. The ν(NH) absorption bands of the amide group in free nicotinamide appear at 3367 and 3165 cm^{-1}. These NH bands in the complex have shifted to a higher wave number compared to the bands in free nicotinamide and appear at 3449 and 3360 cm^{-1}, this is indicative of hydrogen bonding. The groups of bands at 2952–3058 cm^{-1} correspond to aromatic and aliphatic ν(CH) stretching vibrations. The band at 1593 cm^{-1} in the nicotinamide ligand corresponding to ν(C═N) shifted to 1558 cm^{-1} upon complexation. The coordination of the metal ion to the nicotinamide occurs through the pyridine nitrogen atom [49].The very strong band centered at 1712 cm^{-1} is characteristic of the ν(C═O) stretch of the COOH group [51] and the strong absorptions at 1548 and 1400 cm^{-1} arise from the asymmetric (ν_{as}) and symmetric (ν_{s}) vibrations of the carboxylate group. An additional strong absorption band at 1626 cm^{-1} is attributed to NH_2 scissoring mode of nicotinamide. The broad absorption band at 3068 cm^{-1} assigned to the O—H stretching in the free itaconic acid disappeared in the complex, this is indicative of the deprotonation and coordination through the O—H group. The bands at 1421 and 1201 cm^{-1} are assigned to the C—O stretching and O—H bending vibrations of the Itaconic acid. New bands at 515 and 405 cm^{-1} in the complex gives inference about ν(M—O) and ν(M—N) bonding [52].

3.3. Solution stability studies

Stability studies were performed in aqueous media through UV-visible absorption studies as shown in (Fig. 4). Absorbance spectra measurements of the diluted solution of the complex with 1.50×10^{-3} M concentration taken during a time period of 12 h.There were no changes neither in shape nor position of the peak ($\lambda_{max} = 370$). This shows that the complex is stable in aqueous solution.

3.4. Antibacterial results

For comparison purpose of antibacterial activities, copper(II) nicotinamide **2** and Copper(II) itaconate **3** were synthesized using literature procedure [28and29]. The FT-IR and solid state UV-Visible spectra of the complexes are shown in (Figs. S2–S5).

The ligands and their complexes **1**,**2** and **3** were tested for their inhibitory effect on the growth of *E. coli*, *S. aureus* and *P. aeruginosa.*

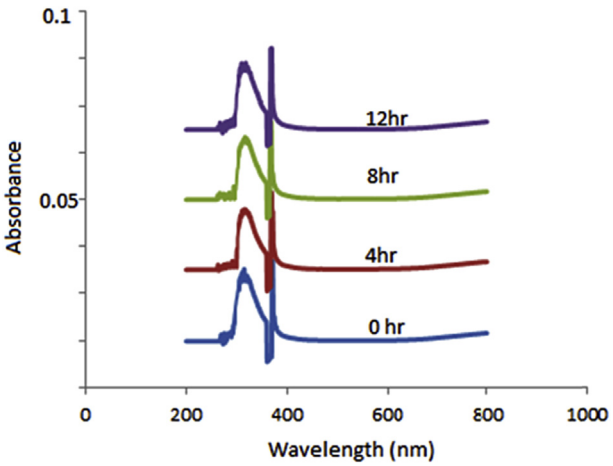


Fig. 4. UV-visible for **1** in aqueous solution during 12 h.

Table 4
Antibacterial activities of Nicotinamide, Itaconic acid and Complexes **1, 2** and **3** at different concentrations on test organisms.

Concentration (gL^{-1})	Zones of inhibition (mm)		
	E. coli	*S. aureus*	*P. aeruginosa*
Nicotinamide			
0.0001	0.0	0.0	0.0
0.001	0.0	0.0	0.0
0.01	0.5	0.4	0.3
0.1	1.4	1.3	1.1
1.0	1.7	1.8	1.4
Itaconic acid			
0.0001	0.0	0.0	0.0
0.001	0.0	0.0	0.0
0.01	0.0	0.0	0.0
0.1	1.2	1.0	1.2
1.0	1.8	1.2	1.4
Complex **1**			
0.0001	0.0	1.2	0.0
0.001	1.2	1.4	1.1
0.01	1.6	2	1.4
0.1	2	3.2	1.8
1.0	3.2	4.2	2.8
Complex **2**			
0.0001	0.0	0.0	0.0
0.001	0.5	1.0	0.7
0.01	1.0	0.8	0.9
0.1	1.6	1.9	1.3
1.0	2.5	3.0	2.0
Complex **3**			
0.0001	0.0	0.0	0.0
0.001	0.6	1.1	0.54
0.01	0.8	0.7	1.5
0.1	1.8	2.1	1.1
1.0	2.1	2.0	1.7

It can be observed in Table 4 that **1**, **2** and **3** show appreciable activities compared to the ligands when challenged with test organisms at varying concentrations [53]. The three complexes **1**, **2** and **3** were able to decrease the population of the bacterial species more than the ligands. They were effective at virtually all the concentrations used except against *E. coli*, *S. aureus* and *P. aeruginosa* at 0.0001 g/L^{-1}. Highest susceptibility to the copper complex was recorded by *S. aureus* with clearance zone of 4.2 mm, 3.0 mm and 2.0 mm at 1.0 gL^{-1} for **1, 2** and **3** respectively. The results showed that the complexes possess a measure of antibacterial activity against all the test organisms. The chelating property of the complexes increases the lipophilic nature of the compound which subsequently favours the permeation through the lipid layer of the cell membrane of the organisms [54]. It can be observed from the present results that the antibacterial potency is usually concentration dependent in agreement with our earlier report [55] that antibacterial potency is usually concentration dependent. It can be seen from Tables 5–7 that the activity of the itaconic acid and nicotinamide ligands was bacteriostatic against all the test organisms, while the activity of **1** was bacteriostatic against *E. coli* and *P. aeruginosa* but bactericidal against *S. aureus* at 0.0001 g/L concentration. In comparison, complex **1** showed higher antibacterial activity against all the organisms than complexes **2** and **3**. The increase in antibacterial activity of **1** may be due to the itaconate ion which serves as another donor atom thereby effect the normal cell process as a result of possible pi-delocalization within the entire chelate system that is formed during coordination.

Table 5
Antibacterial activity of different antibiotics used as control on *S. aureus* and *P. aeruginosa*.

Antibiotic	*S. aureus*	*P. aeruginosa*
	Zone of inhibition (mm)	
Ciprofloxacin	17.5 ± 0.6	22 ± 0.4
Gentamycin	0.00	0.00
Pefloxacin	0.03	18.4 ± 0.7

Table 6
Antibacterial activity of different antibiotics used as control on *E. coli*.

Antibiotic	Zone of inhibition (mm)
Erythromycin	15.0 ± 0.6
Gentamycin	23.0 ± 0.8
Augumentin	9.7 ± 1.0
Chloramphenicol	27.0 ± 0.8
Cotrimoxazole	15.0 ± 1.0
Streptomycin	15.4 ± 0.7
Ciprofloxacin	12.6 ± 1.0

Table 7
Minimum Inhibitory Concentration of the Nicotinamide and Complexes **1, 2** and **3** against test organisms.

Test organisms	Minimum inhibitory concentration (g/L)			
	Ligand (Nic)	Complex **1**	Complex **2**	Complex **3**
Escherichia coli	0.03	0.0004	0.007	0.0056
Staphylococcus aureus	0.06	0.00006	0.00008	0.000073
Pseudomonas aeruginosa	0.12	0.0016	0.0020	0.00040

3.5. Conclusion

In summary, we have synthesized and characterized the first Cu(II) complex containing itaconate and nicotinamide as ligands and formulated as $[Cu(C_5H_4O_4)_2(C_6H_6N_2O)_2(H_2O)_2\cdot 2(H_2O)]$ **(1)**. Spectroscopic and X-ray studies revealed that the complex contains copper(II) ion which coordinated through the two nitrogen atoms of nicotinamide, two oxygen atoms of the itaconate and two oxygen atoms of water molecules to form octahedral geometry. The ligands and their complexes **1**, **2** and **3** were tested for bacterial activity against *E. coli, S. aureus* and *P. aeruginosa* and the complexes showed enhanced activity as compared to their ligands. It is evident that the overall potency of the ligand was enhanced on coordination. Complex **1** showed appreciable *E. coli, S. aureus* and *P. aeruginosa* inhibition action comparable to complexes **2** and **3**. These studies may lead to the discovery of new chemotherapeutic agents that are metal-based.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2016.07.016.

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