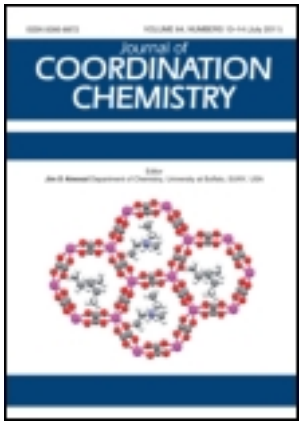

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Synthesis, characterization, and biological evaluation of Cu(II) complexes with the proton transfer salt of 2,6-pyridinedicarboxylic acid and 2-amino-4-methylpyridine

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A proton transfer compound, $(Hamp)^{+}(Hdipic)^{-} \cdot 1.5H_2O$ (**1**), and Cu(II) complexes, $[Cu(dipic)(amp)(H_2O)] \cdot [Cu(dipic)(amp)] \cdot H_2O \cdot CH_3COOH$ (**2**) and $[Cu(dipic)(amp)Cu(dipic)(amp)(H_2O)Cu(dipic)(amp)(H_2O)] \cdot 3H_2O$ (**3**), have been synthesized from 2,6-pyridinedicarboxylic acid (H_2dipic) and 2-amino-4-methylpyridine (amp). They have been characterized by elemental, spectral (^{1}H-NMR, IR, and UV-Vis), and thermal analyses. In addition, magnetic measurements and single crystal X-ray diffraction have been applied to **2** and **3**. The crystal structure of **2** consists of two independent and different cationic sites with Cu^{2+} ions. Cu1 is four-coordinate in a distorted square planar geometry and Cu2 is five-coordinate in a distorted square pyramid. Compound **3** has three independent and different cationic sites of Cu^{2+} ions. Cu1 is four-coordinate in a distorted square planar geometry and Cu2 and Cu3 have five-coordinate, distorted square-pyramidal sites. Inhibitory effects of **1**, **2**, and **3** have been studied and compared with starting compounds (amp and H_2dipic) on bacterial growth of *Staphylococcus aureus* and *Escherichia coli* cultures. Compounds **2** and **3** prevent bacterial growth although **1** has no effect. Compounds **2** and **3** are more effective than amp and H_2dipic, at similar concentrations on preventing bacterial growth for both organisms.

Keywords: Proton transfer; Cu(II) complex; Crystal structure; *Staphylococcus aureus*; *Escherichia coli*; Bacterial growth

1. Introduction

2,6-Pyridinedicarboxylic acid (or dipicolinic acid) (H_2dipic) forms stable chelates with simple metal ions and oxometal cations and can display widely varying coordination, functioning as a multidentate ligand. Dipicolinates (dipic) commonly coordinate to transition metals by either carboxylate bridges between metal centers, to form

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polymeric or dimeric complexes [1–3], or by tridentate (O, N, O′) chelation to one metal [4, 5]. Dipicolinic acid has applications in analytical chemistry [6, 7], corrosion inhibition, decontamination of nuclear reactors [8], and diverse biological activities [9–11]. Dipicolinate complexes have been used as electron carriers in some model biological systems as specific molecular tools in DNA cleavage [12] and as NO scavengers [13]. Dipicolinic acid, along with its 2,4- and 2,5-isomers, is also able to inhibit the enzyme GA 2β-hydroxylase and its mechanistically related enzyme proline 4-hydroxylase [14]. The heat resistance of the spores of several Gram positive eubacteria during sporulation is attributed to the presence of the calcium salt of H_2dipic [15].

2-Aminopyridines also serve as useful chelating ligands in a variety of inorganic and organometallic applications [16, 17]. Aminopyridines and their derivatives are usually monodentate coordinating through the nitrogen of the ring [18–20], although there are several works on 2-aminopyridine complexes in which the amino group participates in coordination [21, 22]. The high incidence of pharmacological activity among heteroaromatic amines has stimulated efforts to prepare compounds of this structural type [23, 24].

The chemistry of Cu(II) carboxylate complexes, especially with N-donor ligands, has been extensively studied [25–27]. The crystal structures of copper complexes of 2-aminopyridine with carboxylate [28, 29] and oxalate [30] are also reported in the literature. Some Cu(II) complexes possess a wide range of biological activity, such as antivirals, fungicides, pesticides, and even tracers, depending on the ligand-binding sites [31–34]. Dipicolinic ligand with Cu(II) commonly has one or two coordination modes. In one, a single planar dipic binds in the equatorial plane of a Cu(II) cation and other ligands, such as H_2O or pyridine, occupy the remaining sites, forming a square planar or square-pyramidal coordination geometry [18, 35]; or two planar dipic molecules coordinate perpendicularly, generating a distorted octahedral coordination geometry [36]. Attention of bioinorganic chemists has been directed toward the synthesis and characterization of new Cu(II) carboxylates with N-donor ligands to model the active sites in metalloenzymes [37].

In this study a proton transfer compound (**1**) [38] and Cu(II) complexes (**2** and **3**) have been synthesized and characterized by elemental, spectral (^{1}H-NMR, IR, and UV-Vis), and thermal analyses. Magnetic measurements and single crystal X-ray analyses of **2** and **3** are also reported. The complexes are (2-amino-4-methylpyridine) (2,6-pyridinedicarboxylate) copper(II) (2-amino-4-methylpyridine) (2,6-pyridinedicarboxylate) aqua copper(II) monohydrate monoaceticacid ([Cu(dipic)(amp)(H_2O)] · [Cu(dipic)(amp)] · H_2O · CH_3COOH) and (2-amino-4-methyl pyridine) (2,6-pyridinedicarboxylate) copper(II) (2-amino-4-methylpyridine) (2,6-pyridine dicarboxylate) aqua copper(II) (2-amino-4-methylpyridine) (2,6-pyridinedicarboxylate) aqua copper(II) trihydrate ([Cu(dipic)(amp)Cu(dipic)(amp)(H_2O)Cu(dipic)(amp)(H_2O)] · $3H_2O$). We have studied activities of **1**, **2**, **3**, amp, and H_2dipic on growth of *Staphylococcus aureus* and *Escherichia coli* cultures.

2. Experimental

2.1. *General methods and materials*

All chemicals used were of analytical reagents purchased from Aldrich. $Cu(CH_3COO)_2 \cdot H_2O$, 2-amino-4-methylpyridine and 2,6-pyridinedicarboxylic acid

were used as received. Elemental analyses for C, H, N, and S were performed on an Elementar Vario III EL and Cu was detected with a Perkin Elmer Optima 4300 DV ICP-OES. ^{1}H-NMR spectra were recorded with a Bruker DPX FT NMR (500 MHz) spectrometer ($SiMe_4$ as internal standard and 85% H_3PO_4 as an external standard). FT-IR spectra were recorded from 4000 to 400 cm^{-1} with a Bruker Optics, Vertex 70 FT-IR spectrometer using ATR techniques. Thermal analyses were performed on an SII Exstar 6000 TG/DTA 6300 model using platinum crucible with 10 mg sample. Measurements were taken in static air from 30 to 700°C. UV-Vis spectra were obtained for aqueous solutions of the compounds (10^{-3} molL^{-1}) with a SHIMADZU UV-2550 spectrometer from 900 to 200 nm. Magnetic susceptibility measurements at room temperature were performed on a Sherwood Scientific Magway MSB MK1 model magnetic balance by the Gouy method using $Hg[Co(SCN)_4]$ as calibrant. Molar conductances of the compounds were determined in DMSO (10^{-3} molL^{-1}) at room temperature using a WTW Cond 315i/SET Model conductivity meter.

2.2. *Synthesis of $(Hamp)^+(Hdipic)^- \cdot 1.5H_2O$ (1), $[Cu(dipic)(amp)(H_2O)] \cdot [Cu(dipic)(amp)] \cdot H_2O \cdot CH_3COOH$ (2), and $[Cu_3(dipic)_3(amp)_3(H_2O)_2] \cdot 3H_2O$ (3)*

A solution of amp (0.541 g, 5 mmol) in ethanol (10 mL) was added to a solution of H_2dipic (0.825 g, 5 mmol) in ethanol (10 mL). The mixture was refluxed for 4 h and then cooled to room temperature. The reaction mixture was kept at room temperature for 3 h to give white solid of **1** (1.323 g, 85% yield).

A solution of $Cu(CH_3COO)_2 \cdot H_2O$ (0.199 g, 1 mmol) in water (10 mL) was added dropwise to a solution of **1** (0.311 g, 1 mmol) in water (10 mL) with stirring at room temperature for 2 h. The reaction mixture was kept at room temperature for 1 week to give green crystalline solid (0.385 g, 35% yield) as **2**. Compound **3** was obtained from the mother liquor of **2** after 2 weeks as blue crystalline solid (0.248 g, 35% yield). Green crystals of **2** and blue crystals of **3** suitable for X-ray diffraction separated and were washed with water.

Anal. Calcd for **1** ($C_{13}H_{17}N_3O_6$) (%): C, 50.18; H, 5.51; N, 13.53. Found (%): C, 50.16; H, 5.50; N, 13.50; for **2** ($C_{28}H_{30}N_6O_{12}Cu_2$): C, 43.70; H, 3.90; N, 10.91; Cu, 16.50. Found (%): C, 43.69; H, 3.93; N, 10.92; Cu, 16.51; for **3** ($C_{39}H_{43}N_9O_{17}Cu_3$) (%): C, 42.55; H, 3.92; N, 11.45; Cu, 18.70. Found (%): C, 42.57; H, 3.94; N, 11.46; Cu, 17.32.

2.3. *X-ray data collection and structure refinement*

The crystal and instrumental parameters used in the unit cell determinations and data collections are summarized in table 1 for **2** and **3**. Diffraction measurements were performed on a Stoe IPDSII image plate detector using Mo-Kα radiation ($\lambda = 0.71073$ Å) at 296(2) K. Empirical absorption corrections were applied by the integration method *via* X-RED software [39]. Both structures were solved by direct methods using SHELXS-97 and anisotropic displacement parameters were applied to non-hydrogen atoms in full-matrix least-squares refinement on F^2 with SHELXL-97 [40]. In **2**, the unit cell has an accessible solvent volume of 207.00 Å^3 occupied by a severely disordered acetic acid and a water molecule, but, unfortunately, it was not

Table 1. Crystal data and structure refinement details for **2** and **3**.

	2	**3**
Empirical formula	$C_{26}H_{24}N_6O_{10}Cu_2$	$C_{39}H_{43}N_9O_{17}Cu_3$
Formula weight	707.61	1100.47
Temperature (K)	296(2)	296(2)
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Unit cell dimensions (Å, °)		
a	8.0490(4)	10.4525(3)
b	12.0933(5)	14.1834(4)
c	18.0366(8)	17.3689(5)
α	103.992(3)	110.788(2)
β	100.721(4)	92.348(3)
γ	107.224(4)	107.683(2)
Volume (Å^3), Z	1563.05(14), 2	2261.38(12), 2
Absorption coefficient (mm^{-1})	1.422	1.481
Calculated density (Mg m^{-3})	1.503	1.616
F(000)	720	1126
θ range (°)	1.86–26.50	1.63–26.50
Crystal size (mm^3)	$0.580 \times 0.323 \times 0.04$	$0.480 \times 0.343 \times 0.100$
Max. and min. transmission	0.945 and 0.582	0.862 and 0.549
Absorption correction	Integration	Integration
Limiting indices	$-10 \le h \le 10$; $-15 \le k \le 15$; $-22 \le l \le 22$	$-13 \le h \le 13$; $-17 \le k \le 17$; $-21 \le l \le 21$
Reflections collected/unique	14,458/6474 [$R_{(int)} = 0.0517$]	23,230/93,590 [$R_{(int)} = 0.0450$]
Reflections observed [$I \ge 2\sigma(I)$]	4665	7800
Number of parameters	405	682
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0423$, $wR_2 = 0.1011$	$R_1 = 0.0395$, $wR_2 = 0.1095$
R indices (all data)	$R_1 = 0.0630$, $wR_2 = 0.1083$	$R_1 = 0.0500$, $wR_2 = 0.1114$
Goodness of fit on F^2	0.953	1.051
Largest difference peak and hole (eÅ^{-3})	0.552, −0.387	0.561, −0.483

possible to find hydrogen atom of this O2w of water. Therefore, the acetic acid was eliminated from the refinement of the structure leaving the O2w atom by means of the SQUEEZE subroutine of PLATON [41] and the ($h\,k\,l$) intensities were modified accordingly. Hydrogen atoms of other water molecules in both structures were located in difference Fourier syntheses, with distances of O–H = 0.817(16)–0.85(10) Å. The remaining hydrogen atoms were placed geometrically at distances of 0.86–0.96 Å from their parent atoms for N–H and C–H bonds. ORTEP drawings [42] of **2** and **3** with 40% probability displacement thermal ellipsoids and atom-labeling schemes are shown in figures 1 and 2, respectively. Intra- and intermolecular hydrogen bonds are also shown in these figures.

2.4. *Bioassays*

2.4.1. Antimicrobial assay. The minimum inhibitory concentrations (MICs) of H_2dipic, amp, **1**, **2**, and **3** against bacterial strains were determined. MIC was defined as the lowest concentration of antimicrobial agent showing complete inhibition of growth. The MIC of reference drugs amoxicillin and ampicillin were compared with

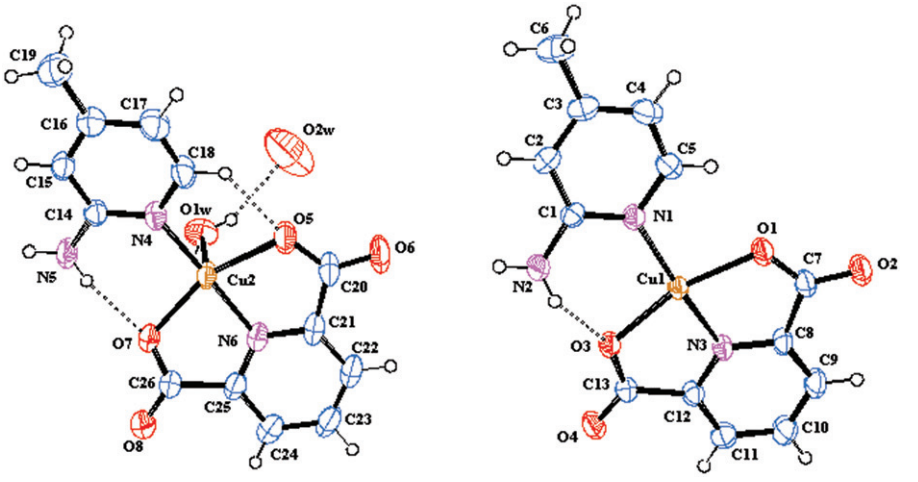


Figure 1. An ORTEP drawing of asymmetric unit of **2** with the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

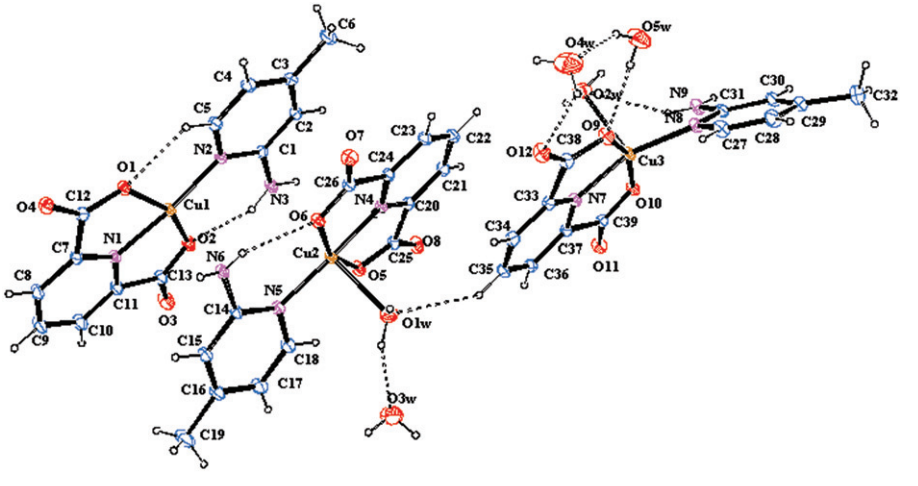


Figure 2. An ORTEP drawing of asymmetric unit of **3** with the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

the complexes. Due to the fact that the MIC values depend on the compound–strain combination, we used the geometric mean MIC values for comparison.

3. Results and discussion

3.1. *FT-IR measurements*

The significant frequencies in the IR spectra of free ligands, amp, and H_2dipic are given together with **1**, **2**, and **3** (table 2). Weak bands between 3113 and 3069 cm^{-1} and between 3054 and 2852 cm^{-1} are attributed to ν(C–H) of aromatic and methylene

Table 2. IR spectral data (cm^{-1}).

Assignment	amp	H_2dipic	1	2	3
$\nu(OH)_{water}$	–	–	3425(br)	3480(br)	3485(br)
$\nu(OH)_{COOH}$	–	2900(br)	–	2935(br)	–
$\nu(NH_2)$	3317(m)	–	3345(m)	3312(m)	3346(m)
	3175(m)		3171(m)	3201(m)	3225(m)
$\nu(^+NH)_{py}$	–	–	2508(w)	–	–
$\nu(C–H)_{aromatic}$	3072(w)	3069(w)	3113(m)	3084(m)	3093(m)
$\nu(C–H)_{alifatic}$	2971(w)	–	2957(w)	3054(w)	3053(w)
	2855(w)		2852(w)	3008(w)	3027(w)
ν(COO)	–	1701(s)	1681(s)	1748(m)	1670(s)
		1456(s)	1486(s)	1635(s)	1498(s)
				1470(s)	
$\nu(C=N) + \nu(C=C)$	1580(s)	1574(s)	1656(s)	1599(s)	1633(s)
	1460(s)	1415(s)	1621(s)	1561(s)	1594(s)
	1445(s)		1581(s)	1500(s)	1576(s)
			1570(s)	1453(s)	1562(s)
			1530(s)	1432(s)	1472(s)
ν(C–O)	–	1333(s)	1375(s)	1374(s)	1376(s)
		1299(s)	1298(s)	1275(s)	1272(s)
		1080(s)	1073(s)	1080(s)	1076(s)
γ(py)	768(s)	782(s)	785(s)	765(s)	771(s)
	701(s)	702(s)	697(s)	679(s)	682(s)
Cu–N	–	–	–	593(m)	593(m)
Cu–O	–	–	–	446(m)	444(m)

w: weak, br: broad, m: medium, s: strong.

groups, respectively. There is a broad absorption at 3425 cm^{-1} attributed to ν(OH) of water in **1**. There is a broad absorption at 2900 cm^{-1} attributed to ν(OH) of H_2dipic. There are also broad absorptions at 3480 and 3485 cm^{-1} attributed to ν(OH) of water in **2** and **3**, respectively. The broad peak at 1748 cm^{-1} can be attributed to acetic acid in the crystal structure of **2**. The relatively weak and broad band at 2508 cm^{-1} is attributed to $\nu(N–H)_{pyridinium}$ vibration of **1** due to proton transfer to pyridine nitrogen [43]. Absorptions at 3317 and 3175 cm^{-1} of NH_2 of amp are slightly shifted from those found in **1** (3345 and 3171 cm^{-1}), **2** (3312 and 3201 cm^{-1}), and **3** (3346 and 3225 cm^{-1}) due to weak intermolecular interactions. The carboxylates exhibit strong carbonyl bands at 1700–1570 cm^{-1}; an asymmetric C=O peak (2935 cm^{-1}) is also observed for acetic acid in **2**. The ν(C–O) vibrations were observed at 1333, 1299, and 1080 cm^{-1} for H_2dipic, 1375, 1298, and 1073 cm^{-1} for **1**; 1374, 1275, and 1080 cm^{-1} for **2**; and 1376, 1272, and 1076 cm^{-1} for **3**, consistent with a previous report [44]. Strong absorptions at 1656–1426 cm^{-1} are attributed to the ν(C=N) and ν(C=C) in amp, H_2dipic, **1**, **2**, and **3** [45]. The ring wagging vibrations of pyridines are observed at 768 and 701 cm^{-1} for amp, 782 and 702 cm^{-1} for H_2dipic, 785 and 697 cm^{-1} for **1**, 765 and 679 cm^{-1} for **2**, and 771 and 682 cm^{-1} for **3**. Weak bands at 593 and 446 cm^{-1} and 593 and 444 cm^{-1} are attributed to Cu–N and Cu–O vibrations of **2** and **3**, respectively.

3.2. *Crystal structures of $[Cu(amp)(dipic)(H_2O)]\cdot[Cu(amp)(dipic)]\cdot H_2O\cdot CH_3COOH$ (2) and $[Cu_3(dipic)_3(amp)_3(H_2O)_2]\cdot 3H_2O$ (3)*

The structure of $[Cu(amp)(dipic)(H_2O)]\cdot[Cu(amp)(dipic)]\cdot H_2O\cdot CH_3COOH$ (**2**) consists of two independent and different Cu^{2+} sites (figure 1). Cu1 is four-coordinate in a

distorted square-planar geometry, doubly chelated by one dipic anion, sharing one pyridine nitrogen atom and two oxygen atoms provided by two α-located carboxylate functions. The copper ion is bonded to the pyridine nitrogen atoms [Cu1–N1 = 1.977(2) and Cu1–N3 = 1.909(2) Å], as well as to one oxygen atom of each carboxylate [Cu1–O1 = 1.991(2) and Cu1–O3 = 2.036(2) Å], which is *trans* to the nitrogen atom of dipicolinic acid in a distorted square plane. The bond distances were similar to those found in other dipicolinate copper complexes with 2-aminopyridine, 2-amino-4-methylpyrimidine, N,N-dimethylpyridin-4-amine and N-methyl-imidazole [18, 46]. Cu2 in **2** is a distorted square pyramid from two nitrogen atoms, one from dipic (N6) and one from amp (N4), two carboxylate oxygen atoms from dipic (O5 and O7) and one coordinated water molecule (O1w). The value of structural index τ (0.12) indicates a distorted square-pyramid geometry around Cu2 [47]. Two nitrogen atoms from dipic and amp occupy equatorial positions with Cu–N distances of 1.975(2) and 1.926(2) Å from Cu2–N4 and Cu2–N6, respectively, similar to the other related copper complexes [18, 44, 48]. The Cu2–O5 and Cu2–O7 bond distances are 2.041(2) and 2.032(2) Å from carboxylate coordination to copper, consistent with those observed [48] (table 3).

The crystal structure of $[Cu_3(dipic)_3(amp)_3(H_2O)_2]\cdot 3H_2O$ (**3**) consists of three independent and different Cu^{2+} sites (figure 2). Cu1 is a distorted square plane with copper bonded to the pyridine nitrogen atoms [Cu1–N1 = 1.916(2) and Cu1–N2 = 1.976(2) Å], as well as to one oxygen atom of each carboxylate [Cu1–O1 = 2.0160(18) and Cu1–O2 = 2.0368(19) Å]. Bond distances were similar to those found in other dipicolinate copper complexes [18, 44, 46, 48]. Cu2 is coordinated in a distorted square pyramid, in which structural index τ is 0.30, two nitrogen atoms, one from dipic (N4) and one from amp (N5), two carboxylate oxygen atoms from dipic (O5 and O6), and a terminal water molecule (O1w) form the coordination sphere. Two nitrogen atoms from dipic and amp are equatorial with Cu–N distances of 1.916(2) and 1.982(2) Å from Cu2–N4 and Cu2–N5, respectively, similar to the other related copper complexes [18, 44, 46, 48]. The average Cu-O (carboxylate) bond distances (2.0377(19) Å) are also similar to those found in square-pyramidal, carboxylate-bridged Cu(II) complexes [18, 44, 46]. Cu3 is five-coordinate in a distorted square pyramid, with structural index τ of 0.014, from two nitrogen atoms, one from dipic (N7) and one from amp (N8), two carboxylate oxygen atoms from dipic (O10 and O9) and a water molecule (O2w). The equatorial bonds, formed by two nitrogen atoms and two oxygen atoms, have normal Cu–O and Cu–N bond distances. The average Cu–N and Cu–O (carboxylate) bond distances [1.934(2) Å; 2.0173(19) Å] are similar to related copper complexes [18, 44, 46, 48, 49] (table 3).

In both complexes, the Cu–Ow bond distances [Cu2–O1w = 2.224(3) Å for **2**; Cu2–O1w = 2.350(3), Cu3–O2w = 2.275(3) Å for **3**] are much longer than Cu–O (carboxylate) bond distances. All corresponding Cu–N bonds and Cu–O bonds in both structures are nearly equal to each other (table 3). Intramolecular hydrogen bonds between carboxylate groups and N–H and C–H and intermolecular ones between coordinated and uncoordinated water molecules play important roles in stabilizing the crystal structure for both structures. The ranges of D–H$\cdots$A angles and those of the H$\cdots$A and D$\cdots$A distances indicate the presence of strong and weak hydrogen bonds (figures 1 and 2, and table 4).

Table 3. Selected bond distances (Å) and angles (°) for **2** and **3**.

2			
Cu1–N1	1.977(2)	Cu2–N4	1.975(2)
Cu1–N3	1.909(2)	Cu2–N6	1.926(3)
Cu1–O1	1.991(2)	Cu2–O5	2.041(2)
Cu1–O3	2.036(2)	Cu2–O7	2.032(2)
		Cu2–O1w	2.224(3)
N1–Cu1–N3	174.69(10)	N4–Cu2–O5	97.88(10)
N1–Cu1–O1	96.31(9)	N4–Cu2–O7	101.54(9)
N1–Cu1–O3	103.41(9)	N4–Cu2–O1w	94.10(11
N3–Cu1–O1	80.46(9)	N6–Cu2–N4	165.43(12)
N3–Cu1–O3	79.68(9)	N6–Cu2–O5	79.60(11)
O1–Cu1–O3	160.11(8)	N6–Cu2–O7	79.09(10)
		O7–Cu2–O5	158.15(10)
		O7–Cu2–O1w	95.74(11)
		O5–Cu2–O1w	92.76(12)
3			
Cu1–N1	1.916(2)	Cu2–O6	2.0334(18)
Cu1–N2	1.976(2)	Cu2–O1w	2.350(3)
Cu1–O1	2.0160(18)	Cu3–N7	1.903(2)
Cu1–O2	2.0368(19)	Cu3–N8	1.965(2)
Cu2–N4	1.916(2)	Cu3–O9	2.0201(19)
Cu2–N5	1.982(2)	Cu3–O10	2.0145(18)
Cu2–O5	2.0420(19)	Cu3–O2w	2.275(3)
N1–Cu1–N2	174.94(9)	O6–Cu2–O5	159.30(8)
N1–Cu1–O1	79.83(8)	N4–Cu2–O1w	90.58(9)
N1–Cu1–O2	79.51(9)	O6–Cu2–O1w	93.48(9)
N2–Cu1–O1	96.50(8)	N7–Cu3–N8	160.03(10)
N2–Cu1–O2	103.76(8)	N7–Cu3–O9	80.47(8)
O1–Cu1–O2	158.64(8)	N7–Cu3–O10	80.74(8)
N4–Cu2–N5	177.65(9)	N8–Cu3–O9	97.89(9)
N4–Cu2–O5	79.97(8)	N8–Cu3–O10	98.53(8)
N4–Cu2–O6	79.84(8)	O10–Cu3–O9	160.87(8)
N5–Cu2–O5	98.35(8)	N7–Cu3–O2w	96.81(11)
N5–Cu2–O6	101.69(8)	O10–Cu3–O2w	95.94(9)

3.3. *^{1}H NMR studies of (Hamp)$^+$(Hdipic)$^-$•1.5H$_2$O (1)*

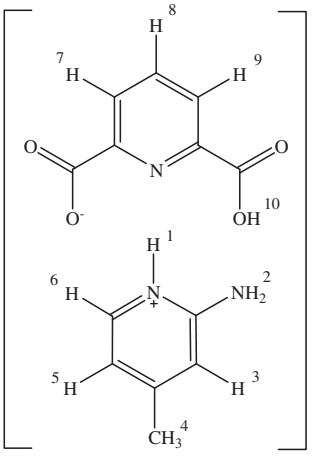
The ^{1}H NMR spectrum of **1** was obtained in DMSO-d$_6$ with and without D$_2$O at room temperature using TMS as internal standard; ^{1}H NMR assignments, listed in table 5, were made on the basis of chemical shifts, multiplicities, intensity of the signals, and coupling constants. In figure S1a, the CH$_3$ protons (H-4) are easily distinguishable as a singlet at 2.21 ppm. H-5 and H-6 protons of the Hamp$^+$ are doublets integrating as one hydrogen atom at 6.47 ppm ($^3J_{H5–H6} = 5.90$ Hz) and 7.83 ppm ($^3J_{H6–H5} = 5.65$ Hz), respectively. In addition, H-8 of (Hdipic)$^-$ is a triplet (one H) at 8.12 ppm ($^3J_{H8–H7,9} = 6.92$ Hz). H-7 and H-9 are symmetric, observed at 8.19 ppm as a doublet with $^3J_{H7,9–H8} = 7.95$ Hz (two H). The broad singlet at 7.05 ppm is assigned to H-1, the transferred proton, together with water molecules (H-11, four H) (figure S1a). These protons could not be observed in the ^{1}H NMR spectrum obtained in DMSO-d$_6$ with D$_2$O due to deuterium exchange (figure S1b). Hydrogen atoms on –NH$_2$ (H-2) and COOH (H-10) have not been observed in the ^{1}H NMR spectra for **1**. The room temperature ^{1}H NMR spectra, 500 MHz, for **1** (figure S1)

Table 4. Hydrogen-bonding geometry of **2** and **3** (Å, °).

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	∠D–H···A
2				
N2–H2A···O3	0.86	2.04	2.816(3	150.4
N2–H2B···O8^{i}	0.86	2.25	3.046(4)	153.6
O1w–H1A···O2^{ii}	0.82(5)	1.97(5)	2.768(3)	164(5)
O1w–H1B···O2w	0.80(5)	2.15(3)	2.881(6)	153(5)
N5–H5A···O7	0.86	1.96	2.758(3)	153.0
N5–H5B···O4^{i}	0.86	2.21	3.018(3)	157.6
3				
N3–H3A···O2	0.86	1.97	2.777(3)	155.2
N6–H6A′···O6	0.72(4)	2.14(4)	2.823(3)	159(4)
N9–H9A···O10	0.86	2.37	2.931(3)	123.4
O1w–H15A···O3w	0.832(18)	2.15(3)	2.872(4)	146(4)
O4w–H16A···O12	0.82(9)	2.18(9)	2.831(4)	136(4)
O5w–H17A···O4w	0.83(9)	2.10(6)	2.846(6)	151(11)
O5w–H17B···O9	0.82(6)	2.00(7)	2.798(4)	162(6)
O3w–H14A···O5w^{i}	0.84(10)	1.98(10)	2.816(6)	173(11)
O1w–H15B···O4^{iii}	0.83(9)	2.10(6)	2.846(6)	151(11)

Symmetry codes: (^{i}) $-x+1, -y+1, -z+1$; (^{ii}) $x-1, y, z-1$; (^{iii}) $x-1, -y, -z$.

Table 5. ^{1}H-NMR chemical shifts (ppm) with coupling constants and assignments for **1**.



H^4	2.21 (3H, s)
H^3	6.46 (1H, d) [$^{3}J_{H5–H6} = 5.90$ Hz]
H^5	6.47 (1H, d) [$^{3}J_{H5–H6} = 5.90$ Hz]
H^6	7.83 (1H, d) [$^{3}J_{H6–H5} = 5.65$ Hz]
H^8	8.12 (1H, t) [$^{3}J_{H8–H7,9} = 6.92$ Hz]
H^7 and H^9	8.19 (2H, d) [$^{3}J_{H7,9–H8} = 7.95$ Hz]
H^1 and H^{11}	7.05 (4H, s)

clearly indicate formation of the proton transfer compound with 1 : 1 ratio of amp and H_2dipic.

3.4. *Thermal analyses of 1, 2, and 3*

Figures S2, S3, and S4 show the TG-DTG and DTA curves of **1**, **2**, and **3**, respectively. For **1**, the first stage between 30°C and 203°C, an endothermic peak

Table 6. Optical properties of **1**, **2**, **3**, free amp, and H_2dipic in water and DMSO.

	λ_{max} (ε)				
	Amp	H_2dipic	**1**	**2**	**3**
Water	289 (26850)		289 (26760)	290 (27110)	289 (31450)
		286 (19860)	305 (31640)	305 (32490)	304 (39430)
	300 (31840)		310 (31740)	310 (31790)	311 (39760)
				775 (670)	766 (510)
				785 (680)	786 (500)
DMSO	309 (33120)		310 (33400)	305 (36580)	309 (32160)
		297 (36160)	305 (32990)	301 (36410)	305 (32440)
	290 (26310)	290 (27690)	289 (26780)	290 (30680)	290 (26820)
				768 (710)	761 (430)
				785 (690)	779 (450)

($DTG_{max} = 199°C$), corresponds to loss of 1.5 moles of water (found 8.90, Calcd 8.94%). The endothermic second stage ($DTG_{max} = 220°C$), between 203°C and 232°C, corresponds to loss of $(Hamp)^+$ together with $C_6H_4O_4$ of $(Hdipic)^-$ of **1** (found 82.50, Calcd 82.45%). In the last stage, an endothermic peak ($DTG_{max} = 249°C$ and 305°C) between 232°C and 315°C is consistent with loss of CN residue (found 8.60, Calcd 8.61%).

For **2**, the first stage (endothermic, $DTG_{max} = 118°C$) between 30°C and 135°C corresponds to loss of water and acetic acid (found 10.0, Calcd 12.4%). The endothermic second stage ($DTG_{max} = 290°C$) between 135°C and 310°C is consistent with loss of amp and CO_2 from dipic (found 50.0, Calcd 50.9%). In the third stage, decomposition of two moles of C_6H_3N of dipic in **2** is observed between 310°C and 360°C with DTG_{max} at 344°C (found 19.0, Calcd 20.0%). The final decomposition product was CuO identified by IR spectroscopy (found 21.0%, Calcd 20.7%).

For **3**, the first stage, an endothermic peak ($DTG_{max} = 119°C$) between 30°C and 127°C, corresponds to loss of five water molecules (found 9.0, Calcd 8.2%). The endothermic second stage ($DTG_{max} = 270°C$) between 127°C and 283°C is consistent with loss of the three moles of amp in **3** (found 28.0, Calcd 29.5%). In the third stage, decomposition of six CO_2 from dipic is observed between 283°C and 310°C with DTG_{max} at 295°C (found 23.0, Calcd 24.0%). The fourth stage, an endothermic peak ($DTG_{max} = 346°C$) between 310°C and 500°C, agrees to loss of three C_6H_3N from dipic residue (found 18.0%, Calcd 16.6%). The final decomposition product was CuO identified by IR spectroscopy (found 22.0%, Calcd 21.7%).

3.5. *UV-Vis spectra, magnetic susceptibility, and conductivity*

Electronic spectra of **1**, **2**, **3**, amp, and H_2dipic were recorded in water and DMSO solutions at 1×10^{-3} molL^{-1} at room temperature (table 6). Characteristic π–π^* transitions are observed in spectra of **1** (289, 305, and 310 nm), **2** (290, 305, and 310 nm), and **3** (289, 304, and 311 nm) in water with the same profiles as observed for free H_2dipic (289 nm) and amp (289 and 300 nm). Two π–π^* transitions were observed for all compounds in DMSO, located at 289 and 310 nm. Bands for d–d transitions present

Table 7. MICs of the compounds ($\mu g\,mL^{-1}$).

Microorganism	Source	H_2dipic	amp	**1**	**2**	**3**	Std
S. aureus	ATCC25923	5	5	–	0.16	0.04	0.31[a]
E. coli	ATCC25922	10	20	–	2.5	5	2.5[b]

[a]Amoxicillin for bacteria as antibacterial standard.
[b]Ampicillin for bacteria as antibacterial standard.

a similar pattern in water (775, 785 and 766, 786 nm) and in DMSO (768, 785 and 761, 779 nm) for **2** and **3** [50].

All the data which we obtained from the electronic spectra of the free ligands do not show any marked differences from those of either proton transfer compound or Cu(II) complexes in both solutions.

The room temperature magnetic moment of the Cu(II) complexes are 1.58 and 1.60 BM per Cu(II) ion in **2** and **3**, respectively, indicating the presence of one unpaired electron (d^9). These results are lower than the spin-only value (1.73 BM), indicating magnetic exchange interaction between metal ions in complex units [51, 52]. The conductivity data in DMSO and in water are 0.7 and $10.5\,\Omega^{-1}\,cm^2\,mol^{-1}$ for **2**, and 2.1 and $12.4\,\Omega^{-1}cm^2\,mol^{-1}$ for **3**, respectively, indicating that **2** and **3** are non-electrolytes [53].

3.6. *Biological activity*

Table 7 shows the MICs of H_2dipic, amp, **1**, **2**, **3**, and of standard compounds (ampicillin and amoxicillin) against *E. coli* and *S. aureus*. Compounds **2** and **3** have more activity on bacterial growth of *S. aureus* culture than amoxicillin. Complex **3** shows poor activity while **2** exhibits the same antibacterial activity as with ampicillin against *E. coli*. However, in both cases, they have better antibacterial activities than amp and H_2dipic since they have Cu(II) ions in their structures. The enhanced bactericidal activity on complexation with copper(II) may be explained by chelation theory [54, 55]. Under the same conditions, **1** does not show any preventing effect on bacterial growth of *S. aureus* and *E. coli* cultures.

Some Cu(II) complexes are known for their antiviral, fungicide, and pesticide properties [31–34]. **2** and **3** have also been compared to simple Cu(II) complexes in the literature and found that they have greater antibacterial activities against *S. aureus* and *E. coli* [56].

4. Conclusion

In this study, a proton transfer compound (**1**) has been synthesized from amp and H_2dipic, and then **2** and **3** have been obtained from the same solution prepared by Cu(II) salt and **1**. Crystal structure of **2** consists of two independent and similar cationic sites by Cu^{2+} and **3** has three independent and similar cationic sites of Cu^{2+} ions. All Cu(II) ions are four- or five-coordinate comprising nitrogen atoms from dipic and amp,

oxygen atoms from two carboxylates of dipic and water. Intermolecular N–H···O and O–H···O hydrogen bonds and π–π stacking interactions are effective in the stabilization of the crystal structure. Elemental analyses and all measurements show good agreement with the structures. Compounds **2** and **3** possess significant antibacterial effects on growth of *E. coli* and *S. aureus* cultures, suggesting that these complexes might be good candidates for antibacterial drugs.

Supplementary material

Crystallographic data (excluding structure factors) for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 765884 for **2** and CCDC No. 765885 for **3**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-(0)1223-336033 or E-mail: deposit@ccdc.cam.ac.uk).

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