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TRANSITION METAL COMPLEXES PRODUCED FROM DIPICOLINIC ACID: SYNTHESIS, STRUCTURAL CHARACTERIZATION, AND ANTI-MICROBIAL INVESTIGATIONS

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ABSTRACT. A novel series of mononuclear complexes of the type, $[M(L)(H_2O)_2]$ [M = Co(II) (**1**), Ni(II) (**2**), Zn(II) (**3**), Cd(II) (**4**), L = dipicolinate), has been investigated using various techniques, including elemental analyses, FT-IR, ^{1}H- and ^{13}C NMR spectroscopy, powder XRD and thermogravimetric analysis. The results indicate that the coordination of the dipicolinic acid to the metal ions involves two carboxylate O atoms, the pyridine N atom, and two water molecules. The pyridine-2,6-dicarboxylic acid and its studied compounds have been screened against microbial species. The findings show that the complexes have higher activity in comparison to the free pyridine-dicarboxylic acid.

KEY WORDS: Dipicolinic acid, Metal complexes, Antimicrobial activity

INTRODUCTION

Pyridine-2,6-dicarboxylic acid has been proven to have a broad range of biological uses in medicine and pharmaceuticals, as well as a significant function in coordination chemistry and catalysis [1-3]. Pyridine-2,6-dicarboxylic acid, also known as dipicolinic acid (DPA), acts as a versatile multidentate ligand and forms stable complexes of a limited steric hindrance with various metals ions via two carboxyl oxygen atoms situated at 120^o angle and pyridine ring nitrogen atom, providing interesting topologies and physical properties, such as the photoluminescence, gas adsorption, catalysis, multifunctional materials and nonlinear optics under the appropriate conditions [1-11]. Furthermore, DPA-based complexes act as electron carriers in various biological systems as specific molecular tools in DNA cleavage and NO scavenging [3, 12]. Therefore, various experimental and theoretical studies have been carried out using pyridine-2,6-dicarboxylic acid due to the importance of intramolecular proton transfer in many chemical and biological reactions [12-15]. Furthermore, DPA ligands are found in a variety of natural compounds, produced from the oxidative degradation of vitamins, coenzymes, and alkaloids [12]. In particular, the pyridine2,6-dicarboxylic acid analog, commonly known as dipicolinic acid, is a useful ligand system to mimic possible pharmaceutically active molecules because of its low toxicity, amphophilic nature, and wide range of biological activity [15-17]. Therefore, taking into account the wide significance of DPA, we are reporting here a series of mononuclear metal complexes derived from DPA with Co(II) (**1**), Ni(II) (**2**), Zn(II) (**3**), and Cd(II) (**4**) ions. The synthesized compounds were investigated using elemental analyses, FT-IR, TGA, and NMR studies. In addition, the free DPA and its complexes with metal ions were also tested for *in vitro* antimicrobial activity. The results show that the metal complexes have significant antimicrobial properties in comparison to free DPA.

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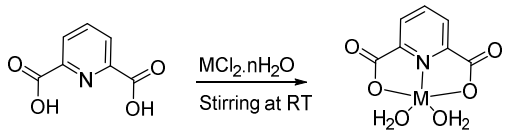
EXPERIMENTAL

Chemicals and methods

All chemicals used in this experiment were of AR grade and used as received. Hydrated metal chlorides, pyridine-2,6-dicarboxylic acid (Aldrich) were used as received. FT-IR spectra recorded at the range 400-4000 cm^{-1} were obtained using the Perkin Elmer 621 spectrophotometer using KBr as a disc pallet. The microanalyses were performed on Elementar Varrio elemental analyzer. The NMR (^{1}H- and -^{13}C) were recorded in Jeol spectrometer at 400 and 100 MHz, respectively in d_6-DMSO. The thermogravimetric analyses were carried out in the inert atmosphere of nitrogen.

General procedure for the synthesis of complexes

$MCl_2.nH_2O$ was added to an alcoholic solution of pyridine-2,6-dicarboxylic acid (50 mg, 3.0 mmol) in an equal molar ratio. The reaction mixture was stirred for 5 h, which led to the formation of a colored precipitate (Scheme 1). The isolated product was washed subsequently with ether and hexane and dissolved in the mixture of deionized water and ethanol to obtain an analytically pure compound.



Scheme 1. Schematic representation of designed complexes.

Antimicrobial studies

Pyridine-2,6-dicarboxylic acid and its metal complexes were tested for *in-vitro* antimicrobial activity against bacterial species, *P. aeroginosa*, *S. sonnei*, *E. coli* and fungal species, *Aspergillus niger*, *A. flavus*, *F. oxysporum*, *Candida albicans* using the Kirby Bauer Disc diffusion method using agar nutrient as the medium [18]. Amoxicillin (30 µg/disc) and Fluconazole (30 µg/disc) were used as the standard antibacterial and antifungal drugs, whereas the DMSO was considered a negative control in the experiment. To perform the Kirby-Bauer disk diffusion assay, the test agar plate swabbed with a standardized concentration of the test organism was developed, and then filter paper with defined antibiotic concentration was immersed into the petri-dish. The titled complexes were dissolved in DMSO (50 µg/mL), and then, a thick filter paper disc was immersed in the solution. The prepared discs with title complexes were again immersed into the petri-dish possessing the test organism and incubated at a standard temperature of 37 °C. After incubating bacterial and fungal species for 24 h and 72 h, respectively, the diameter of the zone of inhibited growth caused by each of the title complexes was measured (Table 1). The MIC for the title complexes was measured by the broth micro-dilution method by means of 96 well microtitration plates against bacterial and fungal species [19-20].

The MIC of each tested title complex against bacterial (10^5 CFU mL^{-1}) and fungal (10^5 CFU mL^{-1}) species was evaluated by inoculating in DMSO in the varying concentration. In brief, the MIC is the lowest concentration of the title complex to restrict the observable growth of bacterial and fungal species at 37°C after the incubation of 24 h and 48 h, respectively. The MIC and zone

of inhibition (IZ) of the tested compounds against the studied bacterial and fungal species at standard temperatures of 37 °C and 24 h and 48 h incubation are given in Table 1.

Table 1. Inhibition zones (mm) and minimum inhibitory concentration (MIC) caused by synthesized compounds against microbial strains.

Microbial test strains		Inhibition zone (mm)/MIC (µg/mL)					Inhibition zone/MIC (µg/mL)	
		L	**1**	**2**	**3**	**4**	Amoxicillin	Fluconazole
P. aeruginosa	Bacteria	8/500	21/61.5	14/120	12/120	11/120	25/11.5	
E. coli		7/500	16/125	13/120	11/120	13/120	28/22	
S. sonnei		8/500	20/61.5	15/120	17/120	15/120	25/120	
A. niger	Fungi	12/500	22/120	21/120	23/120	16/120		25/60.5
A. flavus		11/500	23/120	21/120	22/120	18/120		20/120
F.oxysporum		12/500	16/120	18/120	24/120	13/120		18/120
C. albicans		9/500	18/120	16/120	22/120	15/120		18/120

RESULTS AND DISCUSSION

The FT-IR spectra in all the complexes are characterized by the absence of a band near 3000–3450 cm^{-1}, suggesting the deprotonation of carboxylate groups in the complexes (Figure 1) (Table 2) [21, 22]. Furthermore, the characteristic sharp bands near 1600- 1625 cm^{-1} and 1365-1370 cm^{-1} are accredited to the asymmetric (ν_{as}) and the symmetric (ν_s) stretching vibrations of the COO groups [14, 22-23]. However, the difference in the peak values of asymmetric and symmetric vibrations indicates the monodentate coordination of the carboxylic groups to metal ions [14, 22-23]. In addition, the weak aromatic C-H stretching vibrations appear near 3050 cm^{-1} in all the title complexes [22, 24-25]. In addition, the IR spectra of the complexes reveal the presence of a wide intensity band in the high-frequency area at around 3395-3420 cm^{-1} assigned to the OH stretching vibrations of the coordinated water molecules [22, 24, 26].

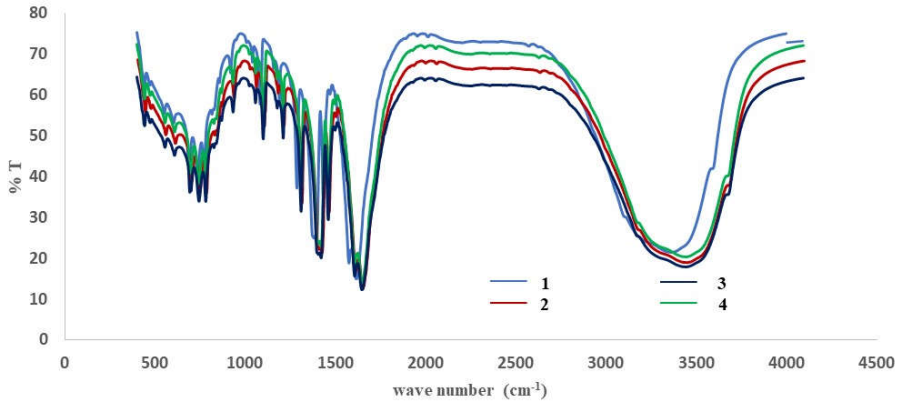


Figure 1. IR spectra of complexes **1**, **2**, **3** and **4**.

Table 2. Physicochemical studies for complexes **1**, **2**, **3** and **4**.

Complexes	FW	Anal Cal (Found) in % C	H	N	IR (KBr, cm^{-1})
Complex **1** $C_7H_7CoNO_7$	260.07	32.33 (32.25)	2.71 (2.68)	5.39 (5.35)	1625, 1370
Complex **2** $C_7H_7NNiO_6$	259.83	32.36 (32.35)	2.72 (2.68)	5.39 (5.35)	1600, 1365
Complex **3** $C_7H_7NO_6Zn$	266.51	31.55 (31.48)	2.65 (2.59)	5.26 (5.19)	1620, 1367
Complex **4** $C_7H_7CdNO_6$	313.15	26.81 (26.76)	2.25 (2.18)	4.47 (4.41)	1623, 1369

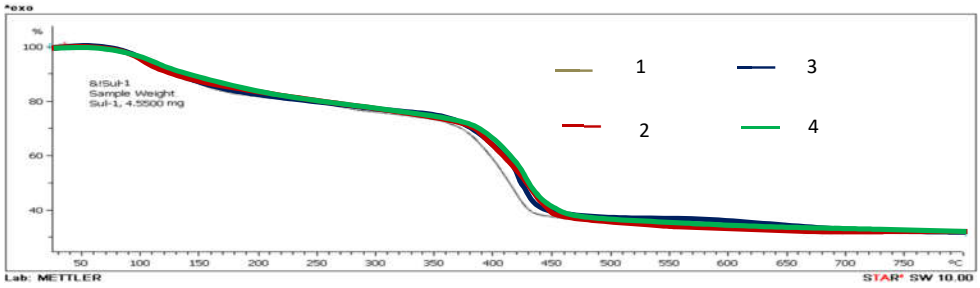


Figure 2. TG spectra of complexes **1**, **2**, **3** and **4**.

The thermogravimetric analysis was investigated to understand the decomposition pattern of the studied mononuclear complexes in the inert atmosphere of nitrogen and revealed a two-step decomposition pattern. The first degradation peak observed at 160 °C was accompanied by the release of two coordinated water molecules, corresponding to a mass loss of ~13.80% of the complex. The second thermolytic step which begins at 390 °C and ends at about 360 °C, brings the expulsion of the whole organic moiety, consistent with ~ 64.37% mass loss of the complex

NMR spectroscopy

The ^{1}H-NMR spectrum reveals multiplet corresponding to aromatic protons at 7.60-7.69 ppm (3H, m, Ar-H). The ^{13}C-NMR spectrum of complex **3** reveals signals due to aromatic carbons at 129.1, 132.0, and 132.2 ppm, whereas the carboxylate carbon signal appears at 167.4 ppm, thus confirming the proposed structure for the complex (Figure 3). Similarly, complex **4** has a carboxylate signal at 165.5 ppm and aromatic carbon signals at 148.1, 128.4 and 126.8 ppm, ascertaining the proposed structures for the complex **4** (Figure 4).

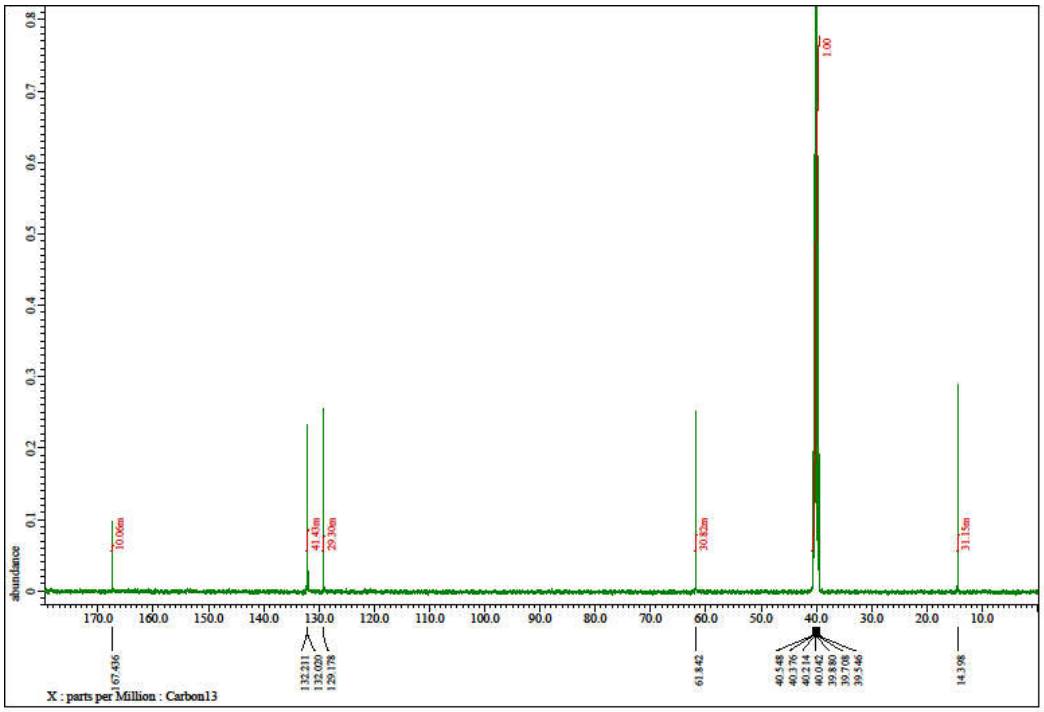


Figure 3. ^{13}C NMR spectrum of complex **3**.

PXRD

The powder XRD patterns were used to investigate the crystalline structures of complex 2 on a Bruker D2 Phaser X-ray diffractometer with CuKα radiation (λ = 1.5418), accelerating voltage and current of 30 kV and 10 mA, respectively, (Bruker, Berlin, Germany) at a wavelength of 1.5406 Å and 2θ range of 0°-90°. The findings revealed that the complexes under investigation showed well-defined sharp crystalline peaks, indicating high crystallinity. We only show the diffractogram of complex **2** (Figure 5) because all of the complexes have a similar structure. Bragg's equation n λ = 2dsin θ was used to calculate the maximum reflection at 2θ = 29.74 and inter-planar distance at d = 3.00 Å. The average crystallite size for the complexes was measured using Scherrer's formula [26], and it ranged between 31.0 - 51.0 nm.

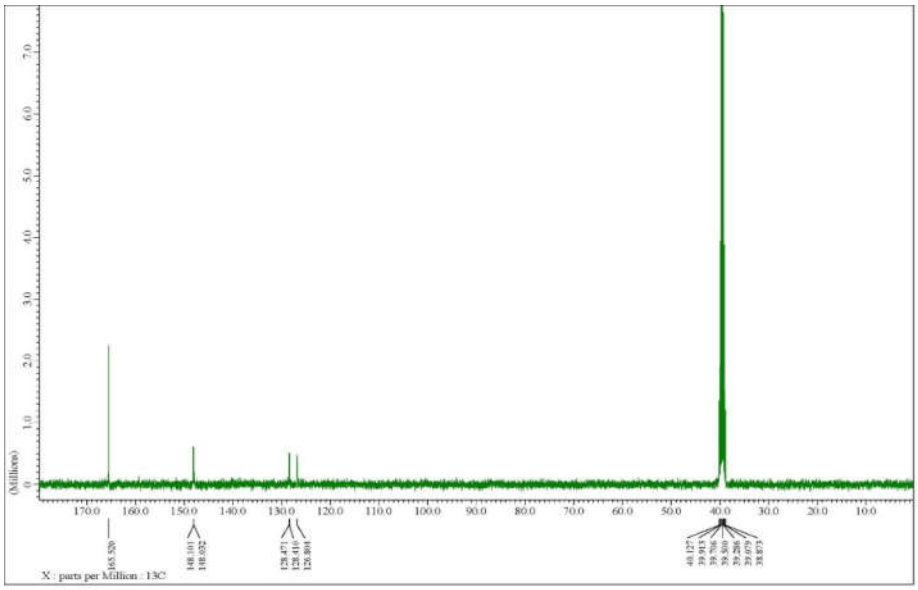


Figure 4. ^{13}C NMR spectrum of complex **4**.

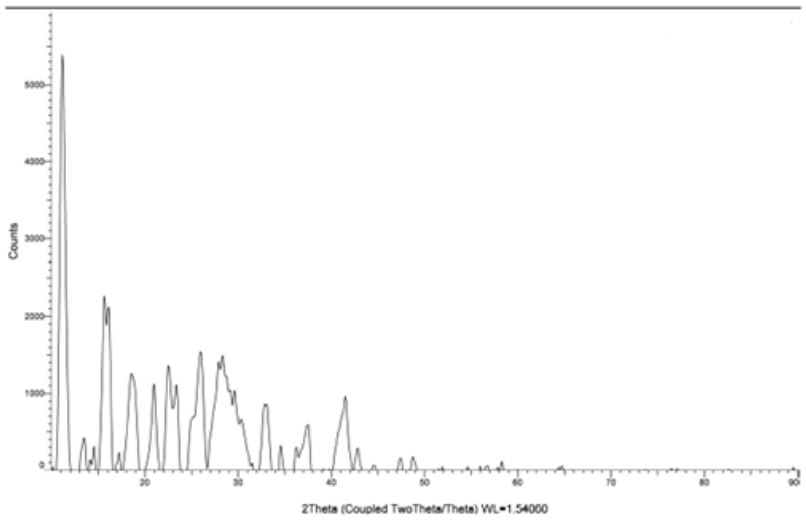


Figure 5. Diffractogram of complex **2**.

Antibacterial and antifungal activity analysis

The antimicrobial data given in Table 1 suggests py-2,6-DCA to be less antimicrobial agent in comparison to its synthesized complexes **1-4** against the tested microbial species. However, this can be better explained by the Tweedy's chelation theory, which reveals that the binding of the ligand to metal ion decrease the polarity of the metal ion within the chelate ring system, thus causing the increase in the lipophilicity of the complexes, which later favors the permeation into the lipid layers of the bacterial cell membrane [28, 29].

To calculate the antimicrobial activity, the diameters of zone of inhibition around ligand and its complexes was measured. Antimicrobial results in comparison to the reference drug are illustrated in Table 1, and suggest the different zone of inhibition for various studied complexes against tested microbial species. The studied complex **1** and **4** show moderate antibacterial activity against *S. sonnei*, *B. subtillis* and *P. aeruginosa* pathogens with inhibition zone/MIC 20 mm/61.5 µg/mL), 28 mm/12.5 µg/mL and 21/61.5 µg/mL on comparing with standard drug Amoxicillin (Table 1). However, the complex **1** and **3** bring retardation in the growth of fungal species *A. flavus*, *A. niger*, and *P. notatatum* and expand the zone of inhibition 23 mm (120 µg/mL), 23 mm (120 µg/mL) and 2 mm (120 µg/mL), respectively, and suggest the significant antifungal activity with reference to the standard drug Fluconazole.

CONCLUSION

We successfully investigated a novel series of complexes derived from pyridine-2,6-dicarboxylic acid using elemental analyses and various spectroscopic studies. Studies reveal that the coordination of py-2,6-dicarboxylate ion to the metal ion occurs via two carboxylate oxygen atoms, one pyridine N atom and two water molecules. All the investigated complexes, including py-2,6-dicarboxylic acid, were tested *in-vitro* for antimicrobial activity. In comparison to the free py-2,6-dicarboxylic acid, the complexes show to be effective antimicrobial agent.

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