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Synthesis, crystal structure, spectroscopic and biological properties of mixed ligand complexes of zinc(II) valproate with 1,10-phenanthroline and 2-aminomethylpyridine

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ABSTRACT

Mononuclear zinc(II) complexes with mixed ligands formulating $[Zn(valp)_2(1,10\text{-phen})H_2O]$ (**2**), and $[Zn(valp)(2\text{-picam})_2](valp)$ (**3**) (valp = valproate, phen = 1,10-phenanthroline, 2-picam = 2-aminomethylpyridine (2-picolylamine)) have been synthesized and characterized using IR, ^1H NMR, $^{13}C\{^1H\}$ NMR and UV–Vis spectroscopic techniques, as well as single-crystal X-ray diffraction. Zn(II) cation in **2** exhibits a distorted octahedral environment resulting from one bidentate phen ligand, one valproate ligand with asymmetric chelating mode, and another one with monodentate mode and a molecule of water. Complex **3** has two bidentate 2-ampic ligands and two valproate ligands. Only one of the carboxylate ligands was bonded to Zn(II) in a monodentate mode. The second valproate ligand acted as a counter ion and was bonded to the NH_2 groups of 2-picam through hydrogen bonding. The Zn(II) cation in **3** has a distorted trigonal bipyramidal arrangement. The complexes were also evaluated for their anti-bacterial activity using *in vitro* agar diffusion method. Three Gram-positive (*Micrococcus luteus*, *Staphylococcus aureus*, and *Bacillus subtilis*) and three Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*) species of bacteria were used for testing anti-bacterial activities. Complex **2** showed considerable activity against all tested microorganisms. The effect of complexation on the anti-bacterial activity of the parent ligand of **2** was also investigated. The anti-bacterial activity of 1,10-phen against both Gram-positive and Gram-negative bacteria was reduced upon complexation with zinc valproate. Complex **3** showed weak inhibition activity against *S. aureus*, *B. subtilis*, *E. coli* and *K. pneumoniae*.

1. Introduction

Zn(II) is one of the most important metal cations in biological systems as it plays an essential role in the activity of nearly 300 enzymes that catalyze approximately 50 important cellular biochemical reactions [1]. In bacteria, Zinc plays a role in catalysis, protein structure and perhaps as a single molecule [2]. However, at high concentrations Zn(II) shows inhibitory action on the growth of bacteria species like. *Escherichia coli*, *Streptociccus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* [3]. This inhibition might be explained by the combination of Zn(II) with membrane proteins (sulfur groups) resulting in cross-linking and deactivation, which changes cell membrane permeability and disrupts transport of nutrients and wastes across the membrane [3a].

In some cases, the interaction of metal ions (i.e. Zn(II)) with bioactive anti-bacterial organic compounds increases the biological activity of the ligands [4]. The metal oxidation state, the type and number of donor atoms, as well as their relative positions within the ligand are major factors determining the relationship between the structure and activity. In other cases, the interaction of bioactive organic compounds with metals inhibits their activity, e.g. the anti-bacterial activity of cefadroxil is diminished when it binds to Zn(II) complex [5].

Valproic acid (Fig. 1) is a broad spectrum anti-epileptic drug which is effective against all seizure types and that is increasingly used in the treatment of other diseases, including bipolar disorder, migraine, and neuropathic pain [6]. In addition, valproic acid was shown to enhance the effect of chemotherapy on EBV-positive tumors, and to possess a multitude of anti-tumor properties *in vitro* and in clinically relevant animal models [7]. Esiobu and Hoosein [8], examined the effect of sodium valproate on the growth of a wide spectrum of microorganisms and they found that it is selectively potent against yeast strains and *Mycobacterium smegmati.* Synthesis, characterization and biological activity of

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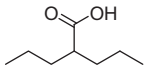

Fig. 1. Structure of valproic acid.

mixed ligands metal complexes of valproate with different nitrogen based ligands have been studied for copper [9], rhodium [10], and platinum [11].

Zinc carboxylate compounds with nitrogen donor organic ligands have attracted an increasing interest because of their potential biological activity. Therefore, zinc complexes of aliphatic carboxylate such as formate, acetate, propionate and butyrate with nitrogen based ligands have been synthesized and screened against microbial species [12]. In the present work, we describe the structure and biological activity of mixed ligand zinc valproate complexes with two nitrogen based ligands. The crystal structure, spectroscopic properties and anti-bacterial activity of: [Zn(valproate)$_2$(1,10-phenanthroline)H_2O] (**2**), and [Zn(valproate)(2-aminomethylpyridine)$_2$](valproate) (**3**) is reported.

2. Experimental

2.1. Chemicals, materials and biological species

Zinc(II) chloride was purchased from Merck, sodium valproate was purchased from Sigma, 1,10-phenanthroline and 2-aminomethylpyridine were purchased from Aldrich. All solvents used were of analytical reagent grade and purchased from commercial sources. *Micrococcus luteus*, *S. aureus*, *Bacillus subtilis*, *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* were kindly obtained from the Biology and Biochemistry Department at Birzeit University.

2.2. Physical measurements

Infrared (IR) spectra were recorded in the 200–4000 cm^{-1} region (KBr) on a Varian 600 FT-IR Spectrometer. UV–Vis spectra were recorded using Hewlett Packard 8453 photo diode array spectrophotometer in the 200–800 nm region using DMSO as solvent. NMR spectra were recorded on a Varian Unity Spectrometer operating at 300 MHz for ^{1}H measurements and 75 MHz for the $^{13}C\{^1H\}$ measurements ($CDCl_3$). Melting points were determined in capillary tubes with EZ-Melt apparatus without any correction.

2.3. Synthesis of Zn(II) complexes

Synthesis of all zinc(II) complexes was conducted at room temperature in ambient conditions.

2.3.1. Synthesis of the precursor [Zn(valproate) complex] (*1*)

Water solution of sodium valproate was gradually added to a stirred aqueous solution of zinc chloride in 2:1 M ratio and a white solid was formed immediately. The solid was filtered off, washed with cold water and allowed to stand for air drying.

*[Zn(valproate) complex] (**1**): ~88 %* yield, m.p. (>250) °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.87 (t, 6H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 1.24–1.44 (m, 6H, CH_2), 1.56 (m, 2H, CH_2), 2.39 (m, 1H, CH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (ppm) 14.16 (CH_3), 20.64 (CH_2), 35.05 (CH_2), 47.72 (CH), 186.03 (C=O). IR (KBr, cm^{-1}): 2956 s, 2930 s, 2870 m, 1594 vs 1450 s, 1426 vs 1328 s, 1229 s, 1120 s, 1067 w, 984 w, 940 w, 874 m, 757 m, 685 m, 663 m, 596 w, 524 m, 475 w, 425 w, 410 w.

2.3.2. Synthesis of [Zn(valp)$_2$(1,10-phen)(H_2O)] (*2*)

1,10-Phen (0.58 g, 3.2 mmol) was dissolved in methanol and gradually added to stirred methanol solution of [Zn_2(valp)$_4$] (**1**) (1.04 g, 1.5 mmol). The solution was stirred for several hours then evaporated to get a solid residue. The solid product was then washed with ether and allowed to dry in air. Suitable crystals for X-ray structural analysis were obtained by crystallization from methanol. The compound is soluble in methanol, ethanol, dichloromethane and chloroform.

*[Zn(valp)$_2$(1,10-phen)(H_2O)] (**2**): 53%* (0.85 g) yield; m.p. (197–203) °C; ^{1}H NMR ($CDCl_3$): $\underline{\delta}$ (ppm) 0.81 (t, 12H, CH_3, $^3J_{H-H}$ = 6.9 Hz), 1.20–1.43 (m, 12H, CH_2), 1.56 (m, 4H, CH_2), 2.39 (m, 2H, $CH_{(valp)}$), 7.89 (d, d, 2H, CH, $^3J_{H-H}$ = 6.2 Hz), 7.97 (ds, 2H, CH, $^4J_{H-H}$ = 0.9 Hz), 8.52 (dd, 2H, CH, $^3J_{H-H}$ = 8.1 Hz, $^4J_{H-H}$ = 1.5 Hz), 9.31 (d, 2H, CH, $^3J_{H-H}$ = 4.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (ppm) 14.44 (CH_3), 21.10 (CH_2), 35.78 (CH_2); 46.38 ($CH_{(valp)}$), 125.42 (C), 126.97 (CH), 128.89 (CH), 139.15 (CH), 150.45 (C), 184.10 (C=O). IR (KBr, cm^{-1}): 3070 vw, 2959 s, 2930 s, 2870 m, 1594 vs 1515 m, 1450 m, 1407 s, 1365 w, 1347 m, 1318 m, 1300 w, 1222 m, 1140 w, 1113 m, 860 m, 848 s, 780 w, 758 m, 728 s, 639 m, 555 w, 494 w, 423 w; UV–Vis (DMSO, λ (nm)): 268, 297 (sh), 326 (sh); *Anal.* Calc. for $C_{28}H_{40}N_2O_5Zn$: C, 61.15; H, 7.33; N, 5.09. Found: C, 61.25; H, 7.38; N, 5.15%.

2.3.3. Synthesis of [Zn(valp)(2-picam)$_2$](valp) (*3*)

2-Picam (0.82 ml, 0.86 g, 8.0 mmol) was added to a stirred solution of [Zn_2(valp)$_4$] **(1)** (1.40 g, 2.0 mmol) in methanol. The solution was then stirred for several hours and evaporated to get a solid residue. The oily product was washed with petroleum ether to give a solid which was allowed to air-dry. Suitable crystals for X-ray structural analysis were obtained by crystallization from dichloromethane. The compound was soluble in methanol, ethanol, dichloromethane and chloroform.

*[Zn(valp)(2-picam)$_2$](valp) (**3**): 48%* (1.09 g) yield; m.p. (131–135) °C; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.74 (t, 6H, CH_3, $^3J_{H-H}$ = 6.0 Hz), 1.05–1.23 (m, 6H, CH_2), 1.35 (m, 2H, CH_2), 2.04 (m, 2H, CH(valp)), 3.51 (s, 2H, NH_2), 3.97 (s, 2H, C**H**$_2$–NH_2), 7.38 (t, 1H, CH, $^3J_{H-H}$ = 6.3 Hz), 7.46 (d, 1H, CH, $^3J_{H-H}$ = 7.8 Hz), 7.88 (dt, 1H, CH, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 1.2 Hz), 8.50 (d, 1H, CH, $^3J_{H-H}$ = 4.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (ppm) 14.87 (CH_3), 21.062 (CH_2), 36.04 (CH_2), 45.27 (CH_2–NH_2), 46.95 (CH(valp)), 122.70 (CH), 123.34 (CH), 138.92 (CH), 148.48 (CH), 160.15 (C), 182.21 (C=O); IR (KBr, cm^{-1}): 3250 br, 3057 vw, 2954 s, 2928 s, 2869 m, 1601 s, 1553 vs 1439 s, 1399 s, 1350 w, 1297 s, 1221 w, 1154 m, 1110 m, 1039 s, 1016 m, 953 m, 861 w, 840 w, 765 s,750 w, 730 w, 686 w, 639 s, 544 w, 478 w, 451 m, 415 m; UV–Vis (DMSO, λ (nm)): 263; *Anal.* Calc. for $C_{28}H_{46}N_4O_4Zn$: C, 59.20; H, 8.16; N, 9. 86. Found: C, 59.26; H, 8.21; N, 9.89%.

2.4. X-ray crystallography

X-ray intensities data of complexes **2** and **3** were carried out at room temperature on a Bruker SMART APEX CCD X-ray diffractometer system (graphite–monochromated Mo Kα radiation λ = 0.71073 Å) by using the SMART software package [13a]. The data were reduced and integrated by the SAINT program package [13b]. The structure was solved and refined by the SHELXTL software package [13c]. H atoms were located geometrically and treated with a riding model. Crystal data and details of the data collection and refinement are summarized in Table 1.

2.5. Anti-bacterial activity

Three Gram-positive bacteria (*M. luteus*, *S. aureus*, and *B. subtilis*) and three Gram-negative bacteria (*E. coli*, *K. pneumoniae* and *P. mirabilis*), were used to test the compounds anti-bacterial activity. The tests were carried out using the agar-well diffusion method [14]. Single bacterial colonies were dissolved in sterile saline until the suspended cells reached the turbidity of McFarland 0.5 Standard. The bacterial inocula were spread on the surface of the nutrient agar with the help of a sterile cotton swab and wells (6 mm in diameter),