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New mixed ligand cobalt(II/III) complexes based on the drug sodium valproate and bioactive nitrogen-donor ligands. Synthesis, structure and biological properties

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ABSTRACT

New cobalt valproate complexes with different nitrogen based ligands were synthesized and characterized using various techniques such as IR, UV–Vis, single crystal X-ray diffraction as well as other physical properties. The general formula of the prepared complexes is $[Co_n(valp)_m(L)_z]$, (n = 1, 2 …; m = 1, 2, …; Z = 1, 2 …). The complexes $[Co_2(valp)_4]$ **(1)**, $[Co(valp)_2(2\text{-ampy})_2]$ **(2)** and $[Co_2(valp)_4(quin)_2]$ **(3)** showed different carboxylate coordination modes. The crystal structures of the complexes **2** and **3** were determined using single crystal X-ray diffraction. Kinetic studies of hydrolysis reactions of BNPP [*bis*-(p-nitrophenyl)phosphate] with complexes **2** and **3** were performed. The hydrolysis rate of BNPP was studied at different temperatures, pH and concentrations by UV–Vis spectrophotometric method. The results showed that the hydrolysis rate of BNPP was 7.70×10^2 L mol^{-1} s^{-1} for (**3**) and 2.60×10^{-1} L mol^{-1} s^{-1} for (**2**).

1. Introduction

Co^{3+} ion can be found in different biological systems such as vitamin B12 (cobalamin) which is a cofactor for many enzymes like methyl transferases, and isomerases and it's a key important in biological system in the formation of blood and the normal functioning of the nervous system and brain [1–5].

Cobalt ion has been widely used in therapeutic drugs because it has a variety of geometries, coordination numbers and oxidation states [6]. Moreover, it is less toxic than other metals like platinum [5]. Among the most common ligands which were used to prepare Co complexes as anticancer agents are phenanthroline and tridentate N,O-donor ligands [7].

Nitrogen based ligands can be used in the synthesis and design of compounds in biological, chemotherapy and pharmacological applications such as anti-rheumatics and anti-histamines [8,9]. The ligands 2-amino pyridine and quinoline exhibit anti-tumor, anti-bacterial, anti-viral, anti-malarial and anti-fungal activities [10–12].

Valproic acid (2-propylvaleric or *n*-dipropylacetic or 2-propylpentanoic acid) is a short chain fatty acid which is a carboxylic acid [13–17]. Recently, valproic acid has a wide range clinical uses such as antibiotic drugs for treatment of many diseases such as epilepsy and bipolar disorder [13,15,17]. But it causes many side effects in human organisms such as gastrointestinal disturbances and headache. Valproate complexation with metal may reduce these side effects and enhance the biological activity [15,17,18].

The transition metal with carboxylate complexes are used in biological systems and industrial applications such as dirheniu-m(III) dichlorotetraisobutyrate which inhibits cancer cells while dirhodium(II) tetraacetate which is used as catalyst [19]. There are many examples of metal valproate complexes such as copper, cadmium(II), cobalt(II), zinc(II) and manganese(II) [20–23]. Tabrizi and McArdle have studied cadmium (II), cobalt(II) and manganese(II) valproate with 1,10-phenanthroline and imidazole. These complexes were synthesized and characterized by using various techniques. The complexes were tested for their biological activities such as anti-bacterial activity by using agar diffusion method and anti-cancer cells [23].

The hydrolytic cleavage of phosphatediester bond is very difficult to occur, but the hydrolysis may be enhanced by using an artificial catalyst which may be organic or inorganic compound.

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The temperature, structure of the catalyst and the pH value are factors affecting the hydrolysis of phosphatediester bond [24,25]. The hydrolysis of BNPP is very important in environmental, industrial and biological applications [26,27].

2. Experimental

2.1. Chemicals, materials and biological species

All reagents, chemicals and solvents were purchased from commercial sources and were used without further purification.

2.2. Physical measurements

Melting points were measured by using Electrothermal melting point apparatus. IR spectra of cobalt complexes were taken on a Bruker Tensor II as KBr pellets in the region 200–4000 cm^{-1}. UV–Vis spectra in MeOH solvent in the region 200–800 nm were determined by using Agilent 8453 photodiode array (PDA) spectrophotometer. The magnetic susceptibility measurements of the powder solid complexes were determined by magnetic susceptibility, $HgCo(NSC)_4$ complex (mercury cobalt-thiocyanate) was used as a standard complex.

2.3. Synthesis of cobalt valporate complexes

All cobalt valproate complexes were prepared at room temperature (RT).

2.3.1. Synthesis of cobalt valporate $[Co_2(valp)_4]$ (**1**)

Sodium valproate (2.00 g, 12.1 mmol) in water was slowly added to a stirred aqueous solution of $CoCl_2 \cdot 6H_2O$ (1.42 g, 6.00 mmol), then the formed purple solid was filtered from aqueous solution, washed with cold water and air dried. The complex was characterized by using IR-spectroscopy, UV-spectroscopy.

Yield = 86.50%; m. p = 58 °C; IR (KBr, cm^{-1}): 2959, 2872, 1556, 1450, 1419, 1330, 753, 469; UV–Vis (MeOH, λ (nm) (ε/$Lmol^{-1}cm^{-1}$)): 270 (7576.5), 492 (43.6).

2.3.2. Synthesis of cobalt valporate 2-aminopyridine complex $[Co(valp)_2(2\text{-}ampy)_2]$ (**2**)

2-ampy (0.96 g, 10.2 mmol) in MeOH was slowly added to a stirred MeOH solution of complex **1** (0.93 g, 2.6 mmol), the solution was then stirred for 3.5 h, the solvent was evaporated and a pink precipitate was obtained. The complex was characterized by using IR-spectroscopy, UV-spectroscopy, magnetic moment and single crystal X-ray diffraction. Recrystallization from methanol produced suitable crystals for X-ray structure determination.

Yield = 79.85%; m. p = 121–125 °C; IR (KBr, cm^{-1}): 3413, 3331, 3080, 3070, 2959, 2930, 2870, 1651, 1565, 1495, 1448, 1329, 1270, 1226, 1156, 1113, 1066, 1003, 864, 769, 740, 657, 518, 451; UV–Vis (MeOH, λ (nm) (ε/$Lmol^{-1}cm^{-1}$)): 235 (20072), 295 (8022.1), 520 (20.2); μ_{eff} = 4.83 BM.

2.3.3. Synthesis of cobalt valporate quinoline $[Co_2(valp)_4(quin)_2]$ (**3**)

Quin (0.91 ml, 0.98 g, 7.6 mmol) was slowly added to a stirred MeOH solution of complex **1** (1.4 g, 3.8 mmol), then the solution was stirred for 5 h, the solvent was evaporated and a green precipitate was obtained. The complex was characterized by using IR-spectroscopy, UV-spectroscopy, magnetic moment and single crystal X-ray diffraction. Recrystallization from methanol produced suitable crystals for X-ray structure determination.

Yield = 26.23%; m. p = 110–111 °C; IR (KBr, cm^{-1}): 3100, 3050, 2956, 2930, 2870, 1613, 1560, 1510, 1450, 1417, 1241, 1145, 1110, 1050, 803, 782, 735, 520, 467; UV–Vis (MeOH, λ (nm) (ε/$Lmol^{-1}cm^{-1}$)): 213 (49030), 276 (9119), 366 (3.6), 520 (2.6).

2.4. X-ray crystallography

Single crystal X-ray analysis of complexes **2** and **3** were carried out by attaching single crystal to a glass fibber with epoxy glue, and then it transferred to X-ray diffractometer system (Bruker SMART APEX CCD) which is controlled by using Pentium-based PC running the SMART software package [28–30]. The diffracted graphite-monochromated (Kα radiation λ = 0.71073 Å) was detected on a phosphor screen at −44 °C and it held at 6.0 cm from the crystal. A detector array of 512 × 512 pixels (a pixel size 120 μm) was used to collect data [28]. Crystal data and structure refinements are summarized in Table 1.

2.5. Kinetic measurements of BNPP hydrolysis

The kinetic experiments were performed at different temperatures (25 °C, 37 °C and 40 °C), different pH values (7.04, 7.48 and 7.91) and different catalytic concentrations from 1×10^{-3} to 1×10^{-6} M.

HEPES buffer, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) was used to maintain a constant pH value. The buffer solutions were prepared by dissolving 50 μM of HEPES buffer in minimum amount of deionized water then the pH of the solution was adjusted with HCl or NaOH after that BNPP was dissolved in buffer solution and the volume of the solution was adjusted to 100 ml in the volumetric flask [31,32].

Different concentrations of the cobalt complexes were prepared in MeOH solution in order to use them as catalysis in the BNPP hydrolysis process. The rate of p-nitrophenol formation was measured using UV–vis spectrophotometer at λ = 400 nm (ε = 13400 L mol^{-1} cm^{-1}) [32–34].

The kinetic experiments were carried in triplicates by adding 1.5 ml of the cobalt complex into 1.5 ml of BNPP solution in a quartz cell at constant temp, then the solution was immediately mixed and the kinetic measurement was performed [32,33]. The initial rate (V_o) was calculated from the slope of the linear plot of p-nitrophenol concentration against time; $[(rate)_0 = (dc/dt)_0 = (dA/dt)_0/\varepsilon]$ [26].

3. Results and discussion

3.1. Synthesis of cobalt complexes

Cobalt valproate complex $[Co_2(valp)_4]$ (**1**) was prepared by adding 2 equivalents of sodium valproate to 1 equivalent of $CoCl_2$ as shown in Scheme 1. The purple solid product was obtained in 86.50% yield.

Cobalt valproate complexes **2** and **3** with different molar ratios of the N-donor ligands were synthesized as shown in Scheme 2. The physical properties of complexes **2** and **3** are listed in Table 2.

3.2. Crystallographic study

3.2.1. Crystal structure of complex 2 $[Co(valp)_2(2\text{-}ampy)_2]$

The crystal structure of complex **2** is shown in Fig. 1. The mononuclear $[Co(valp)_2(2\text{-}ampy)_2]$ complex crystallizes in triclinic crystal system and P-1 space group. For the four molecules per unit cell, the asymmetric unit (one molecule) consists of one Co(III) cation, two bidentate chelating valp groups and two monodentate 2-ampy ligands forming distorted octahedral geometry; (O(2)–Co(1)–O(1) = 59.5(2)°, O(1)–Co(1)–O(3) = 95.6(3)°, O(4)–Co(1)–O(3) = 103.5(3)°, O(4)–Co(1)–N(3) = 103.5(3)°, N(1)–Co(1)