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ORIGINAL RESEARCH PAPER

SYNTHESIS, CHARACTERIZATION AND ANTITUMOR ACTIVITY OF A Ca (II) COORDINATION POLYMER BASED ON 3-AMINO-2-PYRAZINECARBOXYLIC ACID

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Abstract: A new Ca(II) coordination polymer has been obtained by reaction of $Ca(ClO_4)_2 \cdot H_2O$ with 3-amino-2-pyrazinecarboxylic acid in CH_3CH_2OH/H_2O. It was characterized by IR, ^{1}HNMR, thermal analysis and X-ray single crystal diffraction analysis. X-ray analysis reveals that each Ca(II) center is seven-coordination with a N_2O_5 distorted pentagonal bipyramidal coordination environment. The Ca(II) ions are linked through the O atoms of 3-amino-2-pyrazinecarboxylic acid ligands to form 1D chain structure. And then a 3D network structure is constructed by hydrogen bonds and π-π stacking. The antitumor activity of 3-amino-2-pyrazinecarboxylic acid ligand and its Ca(II) coordination polymer against human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells line have been investigated.

Keywords: *3-amino-2-pyrazinecarboxylic acid, antitumor activity, Ca(II) coordination polymer, structural characterization*

INTRODUCTION

Metal complex materials have received more research interest because of their excellent properties in luminescent probes, gas absorption, catalysis, antitumor activities, and so on [1 – 7]. Many transition metal complex materials have been reported [8, 9]. In comparison to *d*-block and *f*-block cations, the coordination behavior and potential applications of alkaline earth metal coordination polymers has remained largely an unexplored area [10]. As part of our group to explore the synthesis and property of alkaline earth metals complex, we have been exploring the preparation of metal-organic hybrid materials by combining alkaline earth metal ions and organic ligands [11 – 14]. In this paper, A novel Ca(II) coordination polymer has been obtained and characterized by IR, ^{1}H NMR, thermal analysis and X-ray single crystal diffraction analysis. The antitumor activity of 3-amino-2-pyrazinecarboxylic acid ligand and its Ca(II) coordination polymer against human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells line have been investigated.

EXPERIMENTAL

Materials and methods

The following A. R. grade chemicals were used for the preparation of the studied compound without further purifications: $Ca(ClO_4)_2 \cdot H_2O$, 3-amino-2-pyrazinecarboxylic acid, sodium hydroxide. Infrared spectrum (4000 – 400 cm^{-1}) was recorded with KBr optics on a Nicolet AVATAR 360 FTIR spectrophotometer. ^{1}H NMR were measured with a Bruker-300MHz nuclear magnetic resonance instrument using DMSO-d_6 as solvent and TMS as internal reference. Thermogravimetric analysis was performed on a Shimadzu PT-40 with heating rate programmed at 5 °C min^{-1}. The crystal data was collected on a Bruker smart CCD Area Detector.

Synthesis of the Ca(II) coordination polymer

A solution of 3-amino-2-pyrazinecarboxylic acid (1.0 mmol, 0.139 g) and sodium hydroxide (1.0 mmol, 0.04 g) in 10 mL CH_3CH_2OH/H_2O (v:v = 1:1) was stirred at 60 ºC. Then 0.5 mmol (0.1200 g) of $Ca(ClO_4)_2 \cdot H_2O$ was added to the above solution. The mixture was continuously stirred for 5 h at refluxing temperature. The mixture was cooled at room temperature, and the resulting solution was filtered. The colourless crystals were obtained after the filtrate was kept in air after 20 days. Yield: 56 %. IR ν_{max} (cm^{-1}): $\nu_{as}(COO^-)$: 1687 cm^{-1}, $\nu_s(COO^-)$: 1518 cm^{-1}, $\nu(NH_2)$: 2926 cm^{-1}, $\nu(H_2O)$: 3258 cm^{-1}.

Crystal data and structure refinement

The crystal data were collected on a Bruker Smart Apex CCD diffractometer equipped with a graphite-monochromatic Mo *Kα* radiation at 293 (2) K. A total of 6284

reflections were collected in the range 3.34 - 27.47 °, of which 1543 were unique (R_{int} = 0.0236) and 1447 were observed with $I>2\sigma(I)$. The data were corrected for *Lp* factors. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2. The structure was solved by direct methods using *SHELXS-97* [15] and refined using *SHELXL-97* [16]. All of the non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. Molecular graphics were drawn with the program package *SHELXTL-97* crystallographic software package [17].

Antitumor activity

Human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells were propagated continuously in culture and grown in RPMI 1640 medium with 10 % inactivated fetal calf serum and antibiotics. Cell harvested from exponential phase were seeded equivalently into 96 well plates and incubated for 24 h then compounds studied were added in a concentration gradient. The final concentrations were maintained at $c/(\mu g \cdot mL^{-1})$ 5, 10, 20, 30, 40, 60 respectively. The plates were maintained at 37 °C in a humidified 5 % CO_2 – 90 % N_2 – 5 % O_2 atmosphere and incubated for 48 h, the MTT solution was added, the following procedure referred to [18]. The measurements of absorption of the solution concerned with the number of live cells were performed on spectrophotometer at 570 nm.

RESULTS AND DISCUSSION

Properties of the Ca(II) coordination polymer

The molar conductance value of the Ca(II) coordination polymer measured in methanol solution (10^{-3} mol·L^{-1}) is 9.3 S·cm^2·mol^{-1}, indicating that it is non-electrolyte [19].

Infrared spectra

In the infrared spectra, the ν_{as}(COOH) and ν_s(COOH) vibrations of the free ligand are at 1745 and 1605 cm^{-1}, respectively. For the complex, the vibration observed at 1708 cm^{-1} was assigned as ν_{as}(COO$^-$) and that at 1498 cm^{-1} as ν_s(COO$^-$). It can be explained that the carboxylate oxygen atoms of 3-amino-2-pyrazinecarboxylic acid ligand take part in the coordination with Ca(II) atom [20]. The difference between the ν_{as}(COO$^-$) and ν_s(COO$^-$) band is 210 cm^{-1}, indicating an bidentate carboxylate moiety. The ν(C=N) vibration of the free ligand is at 1560 cm^{-1}, and it shifts to 1547 cm^{-1} in the complex, indicating that the nitrogen atoms of the ligand take part in the coordination with Ca(II) atom. The band of the NH_2 groups at 2926 cm^{-1} show that there are uncoordinated atoms of the groups, because compared with the free ligand the strong absorption bands are not shifted. In addition, the band at 3258 cm^{-1} shows that the complex contains water molecules.

^{1}H NMR spectra

The ^{1}H NMR spectra of the 3-amino-2-pyrazinecarboxylic acid and the Ca(II) coordination polymer were recorded in DMSO-d_6. The spectrum of 3-amino-2-pyrazinecarboxylic acid exhibits proton signals at 10.98 (s, 1H, COOH), 8.25 (s, 1H, CH), 7.89 (s, 1H, CH) and 7.32 (s, 2H, NH_2) ppm, respectively. Upon coordination, the Ca(II) coordination polymer exhibits proton signals at 8.36 (s, 1H, CH), 8.12 (s, 1H, CH) and 7.60 (s, 2H, NH_2). Meanwhile, the proton signal of COOH disappears in the Ca(II) coordination polymer. The differences between the 3-amino-2-pyrazinecarboxylic acid ligand and the Ca(II) coordination polymer show that the ligand has coordinated with Ca(II) ion.

Structural characterization

The crystal structure of the Ca(II) coordination polymer is revealed in Figure 1. As shown in Figure 1, in the crystal structure, each Ca(II) ion is seven-coordination by four oxygen atoms (O2b, O2c, O3, O3a) from the COO^- of 3-amino-2-pyrazinecarboxylic acid ligand, one oxygen atoms (O1) from the coordinated water molecule and two nitrogen atoms (N3b, N3c) from the 3-amino-2-pyrazinecarboxylic acid ligand, forming up a distorted pentagonal bipyramidal coordination environment. There are strong π-π stacking in the crystal structure (Figure 2).

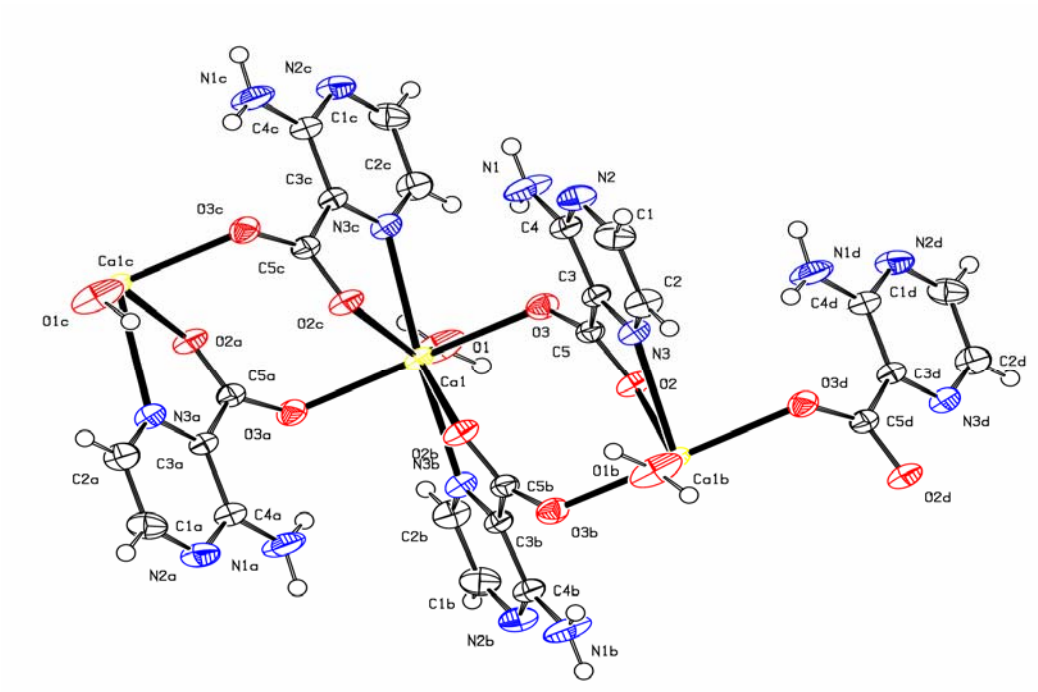

Figure 1. *Molecular structure of the title compound, where the thermal ellipsoids were drawn at 30 % possibility*

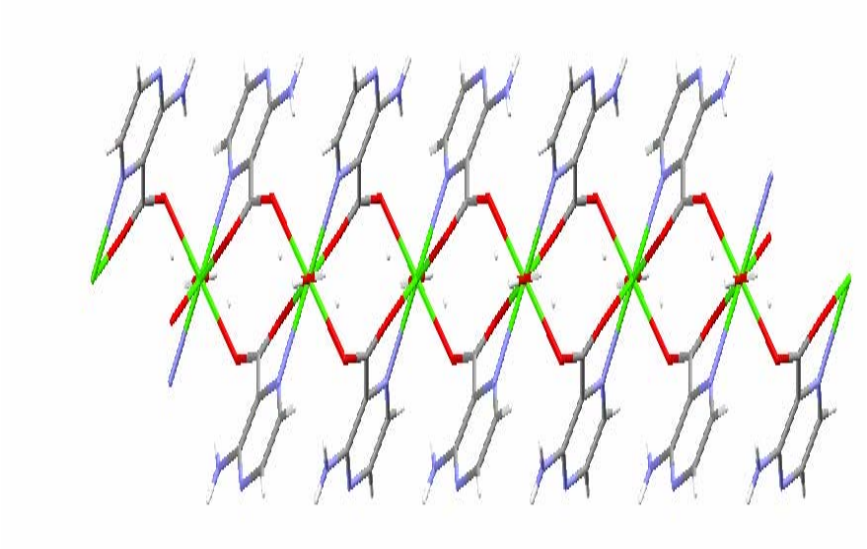

Figure 2. *One-dimensional chained structure of the title compound*

Thermogravimetric analysis

The thermal analysis of the Ca(II) coordination polymer has been studied in air atmosphere using Al_2O_3 as reference. The Ca(II) coordination polymer is stable until 180 °C, which shows that the complex does not contain uncoordinated water molecules. The coordinated water molecules were removed *ca.* 195 °C, the mass loss is 5.38 % in the range 190 - 200 °C corresponds to the loss of one water molecules. On further heating, the TG curve shows a continuous mass loss up to 700 °C due to the decomposition of 3-amino-2-pyrazinecarboxylic acid ligand.

Antitumor activity

The data of antitumor activities of Ca(II) coordination polymer and 3-amino-2-pyrazinecarboxylic acid are given in Table 1. The concentration of DMSO was controlled under 1 % to assure not to affect the results. It can be seen that both Ca(II) coordination polymer and 3-amino-2-pyrazinecarboxylic acid exerted cytotoxic effect against human lung adenocarcinoma *A549* cells, and the antitumor effect of Ca(II) coordination polymer is better than that of 3-amino-2-pyrazinecarboxylic acid. Ca(II) coordination polymer has stronger cytotoxicity against human intestinal adenocarcinoma *HCT-8* cells with lower IC_{50} (19 ± 0.5 μg·mL^{-1}), however, 3-amino-2-pyrazinecarboxylic acid does not have effect.

Table 1. *Antitumor activities of Ca(II) coordination polymer and 3-amino-2-pyrazinecarboxylic acid*

Compound	**IC_{50} [μg·mL^{-1}]**		
	HCT-8	***HCT-116***	***A549***
3-amino-2-pyrazinecarboxylic	----	31 ± 2.9	27 ± 2.3
Ca(II) complex	19 ± 0.5	----	23 ± 1.2

-----: no antitumor activity

CONCLUSIONS

In summary, a novel Ca(II) coordination polymer has been obtained and characterized by IR and X-ray single crystal diffraction analysis. The results show that each Ca(II) center is seven-coordination with a N_2O_5 distorted pentagonal bipyramidal coordination environment. The Ca(II) ions are linked through the O atoms of 3-amino-2-pyrazinecarboxylic acid ligands to form 1D chain structure. And then a 3D network structure is constructed by hydrogen bonds and π-π stacking. The antitumor activity of 3-amino-2-pyrazinecarboxylic acid ligand and its Ca(II) coordination polymer against human intestinal adenocarcinoma *HCT-8* cells, lung adenocarcinoma *HCT-116* cells and human lung adenocarcinoma *A549* cells line have been investigated.

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SUPPORTING INFORMATION

Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1008951. Copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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