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Two new $\text{Mg}_3(\text{II})$ -cluster-based coordination polymers: their synthesis, crystal structures and inhibiting activity on the human spinal tumor cells

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Abstract: In this study, two new Mg_3 -cluster-based coordination polymers are obtained via a one-pot solvothermal reaction of $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ with two C_3 -symmetrical N-rich polycarboxylic acid organic ligands with different ligand flexibilities, which show interesting structural diversity. The complex **1** with the formula of $[\text{Mg}_3(\text{tatb})_2(\text{MeOH})_2(\text{DMA})_2](\text{DMA})_2$ ($\text{H}_3\text{tatb} = 4,4',4''\text{-s-triazine-2,4,6-triyl-tribenzoic acid}$, $\text{DMA} = \text{N,N-dimethylacetamide}$) is constructed from the linear Mg_3 cluster, which is further extended via the rigid tatb^{3-} ligand to afford a 2D layered framework. In comparison, the complex **2** with the formula of $[\text{Mg}_3(\text{tatab})_2(\text{H}_2\text{O})_6](\text{DMA})_2$ ($\text{H}_3\text{tatab} = 4,4',4''\text{-s-triazine-1,3,5-triyltri-p-aminobenzoic acid}$) is built from the similar Mg_3 cluster but shows a 3D framework due to the flexibility of the tatab^{3-} ligand. Furthermore, the *in vitro* anticancer activity is evaluated against human spinal tumor lines U-266 via the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay.

Keywords: coordination polymer; lung cancer cell; N-rich ligand.

Introduction

Cancer is one of the major diseases that seriously harm human health globally every year (Du et al., 2017). According to the development trend of cancer disclosed by the World Health Organization, it is expected that cancer-related deaths in developed and developing countries will reach 5 million and 6 million people by 2020, respectively (Wang et al., 2016; Sun et al., 2017). Hence, it has been

estimated that 11 million people will die in that year. In relation to cancer, chemotherapy is still the most important treatment method. Metal-organic compounds, such as cisplatin and carboplatin, are widely used as anticancer drugs in chemotherapy (Reedijk, 1992). The search for new coordination complexes for cancer therapy remains a hot topic in the fields of chemistry and medicine.

The last few decades have witnessed the rapid development of a new kind of metal-organic crystalline materials called coordination polymers, which are composed of organic connection ligands and inorganic metal ions or clusters (Bedwani et al., 2008; Dong et al., 2016). Due to the endless possibility in the selection of inorganic and organic building units and their highly ordered crystalline nature, coordination polymers have demonstrated many unique properties, including high surface areas, clearly defined crystal structures, special confined nanopore microenvironments and uniform pore structures (Umbach et al., 2012; Bebensee et al., 2014). According to recent studies, coordination polymers great promise in the biomedical fields. For instance, Wang and co-workers have used the coordination polymers for cancer theranostic applications (Liu et al., 2015). In general, the properties of coordination polymers are largely dependent on the organic ligands used. The organic polycarboxylic acid ligands have been widely used in the construction of coordination polymers, which show structural and functional diversity based on the ligand flexibility and the metal cluster generated in suit (Li and Li, 2018). Furthermore, the organic ligand could be gifted many polar atom sites, which can be useful in binding the guests (Li et al., 2017). In the present study, two new Mg_3 -cluster-based coordination polymers have been obtained via the one-pot solvothermal reaction of $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ with two C_3 -symmetrical N-rich polycarboxylic acid organic ligands (Figure 1) with different ligand flexibilities. The complex **1** with the formula of $[\text{Mg}_3(\text{tatb})_2(\text{MeOH})_2(\text{DMA})_2](\text{DMA})_2$ is constructed from the linear Mg_3 cluster, which is further extended via the tatb ligand to afford a 2D layered framework. In comparison, the complex **2** with the formula of $[\text{Mg}_3(\text{tatab})_2(\text{H}_2\text{O})_6](\text{DMA})_2$ is built from the similar Mg_3 cluster but shows a 3D framework due to the flexibility of the tatab^{3-} ligand. According to the literature, most of the

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Figure 1: The chemical structures of H_3tatb = 4,4',4''-s-triazine-2,4,6-triyl-tribenzoic acid and H_3tatab = 4,4',4''-s-triazine-1,3,5-triyltri-p-aminobenzoic acid used in this study.

reported Mg -MOFs are based on the linear organic carboxylic acid linkers, whereas those based on the C_3 -symmetrical N-rich polycarboxylic acid organic ligands have been scarcely reported so far (Senkovska and Kaskel, 2006; Yang et al., 2012; Zhai et al., 2016). In the current study, the *vitro* anticancer activity of the polymers are evaluated against human spinal tumor cell lines U-266 via the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

Results and discussion

Crystal structure description

Yellow prism crystals for **1** with the formula of $[\text{Mg}_3(\text{tatb})(\text{MeOH})(\text{DMA})](\text{DMA})_2$ could be obtained by a solvothermal reaction of H_3tatb and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ in a mixed solvent of DMA and MeOH. It should be noted that the addition of HNO_3 could promote the crystallization of complex **1**, whereas no crystalline products could be formed without the addition of HNO_3 . An X-ray single structural determination demonstrates that **1** is located in the monoclinic crystal system, space group $P2_1/n$ and reveals a 2D layered network structure. The building unit of **1** is formed by two independent Mg^{2+} ions (one with full occupancy and the other with half occupancy), one tatb^{3-} linker, one coordinated DMA and one coordinated MeOH molecule. As described in Figure 2A, six carboxylic O atoms from six different tatb^{3-} ligands form the $[\text{MgO}_6]$ tetrahedral coordination geometry of the Mg_1 ion. Meanwhile, the coordination surrounding of Mg_2 is shaped by four O atoms from three different tatb^{3-} ligands, with the leaving sites completed by two O atoms on the coordinated MeOH and DMA molecules. The observed Mg -O bond distances are in the range of 2.030(2)–2.185(2) Å, which are comparable with

those observed in the Mg -based coordination polymers. The three Mg^{2+} ions are held together by the six carboxylic groups via the *sys*-bridging modes to afford the linear Mg_3 cluster-based secondary building unit with the Mg - Mg distance of 3.615 Å. In **1**, each tatb^{3-} ligand connects with six Mg^{2+} ions by using three deprotonated carboxylate groups, with each showing a $\mu^2\text{-}\eta_1\text{:}\eta_1$, $\mu^2\text{-}\eta_1\text{:}\eta_1$ and $\mu^2\text{-}\eta_2\text{:}\eta_1$ bridging/chelating mode (Figure 2B). Each Mg_3 cluster is connected with six different tatb^{2-} ligands in the *ab* plane to afford the 2D layered structure, with the coordinated MeOH and DMA molecules pointing toward the outside of the plane (Figure 2C). These 2D layers are further stacked along the *c* axis to afford the porous 3D supermolecular network with two different types of 1D channels running along the *b* axis and the *c* axis (Figure 2D). The effective solvent accessible free volume is 44.8% within the consideration of the coordinated MeOH and DMA molecules, as calculated via the software PLATON. A 3,6-connected **kfd**-type topology could be used to express the network of **1**.

The solvothermal reaction of $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ with the H_3tatab ligand using a mixed solvent of DMA and water leads to the formation of compound **2**. A structural determination via the X-ray single-crystal diffraction crystallography technique shows that the complex **2** is situated in the cubic crystal system, $Pa\bar{3}$ space group with $a = 20.2869$ Å. Its molecular building unit consists of one third tatab ligand, two Mg^{2+} ions (one with a third occupancy and the other with a sixth occupancy) and one coordinated water molecule. Figure 3A shows the coordination surrounds of the six-coordinated Mg_1 and Mg_2 ions with disordered octahedral $[\text{MgO}_6]$ geometries, which are shaped by six O atoms from six different carboxylic groups and three carboxylic O atoms with three coordinated water molecules, respectively. The O- Mg bond lengths range from 2.082(3) to 2.727(2) Å, which are comparable with the observed values in the Mg -base coordinated polymers. The three Mg^{2+} ions are held together by the six carboxylic groups

Figure 2: The crystal structure for compound 1.

(A) The Mg_3 cluster in 1 (symmetric code: $A\ 1-x, 1-y, -z$); (B) the binding pattern of the tatb^{3-} ligand; (C) the 2D layered network of 1; (D) View for the 1D channels of the stacking supermolecular structure.

Figure 3: The crystal structure for compound 2.

(A) The Mg_3 cluster in 2 (symmetric code: $A\ 1-x, 2-y, 1-z$); (B) the binding pattern of the tatb^{3-} ligand; (C) the 3D network of 2; (D) pyr/ pyrite -type (3,6)-connected net for 2.

Figure 4: The PXRD patterns for 1 and 2.

via the sys-bridging modes to afford the linear Mg_3 cluster-based secondary building unit with the Mg-Mg distance of 3.34 Å. As for the tatab^{3-} ligand, it binds with six Mg^{2+} ions via the three carboxylic arms in a $\mu^2\text{-}\eta_2$ pattern (Figure 3B).

Each Mg_3 cluster binds with the six tatab^{3-} ligands and each tatab^{3-} ligand connects with six different Mg_3 clusters. This generates a 3D framework with a large solvent accessible void of 44.7%, as calculated via the software PLATON (Figure 3C). The framework of 1 could be judged as a **pyr/pyrite**-type (3,6)-connected net with the point symbol of $\{6^{\wedge}12.8^{\wedge}3\}\{6^{\wedge}3\}_2$ (Figure 3D).

To check the purities of the as-synthesized samples, the room temperature PXRD patterns were collected to compare them with the simulated ones from the crystal data. As shown in Figure 4, the collected curves reveal a considerable match between the ones from the crystal data, thus showing the high phase purity of the as-prepared two complexes.

Anticancer activity

In order to explore the low cytotoxicity of complexes 1 and 2 *in vitro*, oral epidermal cells (normal cells) were chosen to incubate with complexes 1 and 2 under different concentrations. As shown in Figure 5A, the cell viabilities all remained above 90% even at a concentration

Figure 5: *In vitro* cell viabilities after incubation for 24 h with different complexes under different concentrations.

(A) Oral epidermal cell viability for 1 and 2; (B) the cancer cell viability for 1, 2, organic ligands and the $\text{Mg}(\text{NO}_3)_2$; (C) the cancer cell viability for the mixture of the $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and the organic ligand; (D) a comparison of the cancer cell viability for 2 and cisplatin.

of 100 µg/mL of complexes **1** and **2**. Thus, both complexes showed low cytotoxicity in the oral epidermal cells. The *in vitro* antitumor activities of the as-prepared two metal-organic complexes as well as the two organic ligands and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ have been evaluated against the human spinal tumor cell lines U-266 via the standard MTT assay under different concentrations (0–100 µg/mL) for 24 h. As shown in Figure 5B, the cell viabilities are all above 90% even at the concentration of 80 µg/mL of the ligands and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, thus indicating that they are unable to kill the cancer cells. In comparison, both complexes show obvious cancer cell growth inhibition, with 44% and 55% U-266 cells killed, respectively, at the concentration of 80 µg/mL. Moreover, increasing the concentration of these two complexes could lead to more cancer cell death, indicating the anticancer activities of these two complexes are dose-dependent. Notably, the mixture of $\text{Mg}(\text{NO}_3)_2$ and the organic ligand in an equal molar ratio do not show obvious anticancer activity, revealing that the observed anticancer activity of compounds **1** and **2** could not be achieved by simply mixing the metal ions with the organic ligands (Figure 5C). These results further indicate that the anticancer activities of both complexes are better than their organic and inorganic compositions, and that the anticancer activity of both complexes comes from the coordination of the metal ions with the organic ligands. In addition, the complex **2** shows a better anticancer activity than complex **1**, indicating that the N sites that are free have a positive effect on the anticancer activity. This finding is similar to a result reported in the literature (Liu et al., 1999). To gain a better insight on the anticancer activities of both complexes, the cytotoxicity of cisplatin against the title cancer cell has also been recorded. The results reveal that the complex **2** shows a comparable anticancer activity compared with that of cisplatin, thus suggesting its promising anticancer activity (Figure 5D).

Conclusion

In summary, we have prepared two new Mg(II)-based coordination polymers using two C₃-symmetrical N-rich polycarboxylic acid organic ligands with different ligand flexibilities, which lead to the observed structural diversity. Both polymers are built from similar Mg₃ cluster-based secondary building units and reveal a similar (3,6)-connected network. Due to the different flexibilities of the organic ligand, the complex **1** reveals a 2D layered network, but complex **2** demonstrates a 3D framework structure. In addition, the MTT assay results show that

these coordination polymers could be potentially used as anticancer drugs.

Experimental

Instruments and chemicals

The Rigaku D/MAX 2500V diffractometer (Rigaku, Tokyo, Japan) was used to collect the Powder X-ray diffraction (PXRD) curves. An Oxford Xcalibur E diffractometer (Oxford, UK) was employed to collect the single crystal XRD data. The Perkin Elmer Model 240C instrument (PerkinElmer, MA, USA) was employed to obtain the element analyses (C, H and N) results. All the chemicals in this study were commercially available and purchased from the Bai Ling Wei Company (Beijing, China).

Preparation and characterization of [Mg₃(tatb)(MeOH)₂(DMA)₂](DMA)₂ (**1**) and [Mg₃(tatab)₂(H₂O)₆](DMA)₂ (**2**)

Into a 50 mL beaker, H₃tatb (0.11 mmol, 48 mg) and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.2 mmol, 52 mg) were added, followed by DMA (4 mL) and MeOH (2 mL) with vigorous stirring for 1 h at room temperature. After the addition of 1 drop of HNO₃ (1 M, aq), the solution was transferred into a vial, kept at 105°C for 72 h and then cooled to room temperature with a cooling rate of 5°C/h. The light yellow prism crystals of **1** were obtained after cooling the reaction system to room temperature, washed with MeOH and air-dried. Yield: 36.4% based on the H₃tatb linker. Elemental analysis Calcd (%) for **1** (C₆₁H₅₅Mg₃N₉O₁₆): H, 4.46; C, 58.94; N, 10.14. Found: H, 4.59; C, 59.02; N, 10.36. The compound **1** could not be dissolved in water and DMF but can be well dispersed in the DMSO solution.

Into a 50 mL beaker, H₃tatab (0.11 mmol, 53 mg) and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.2 mmol, 52 mg) was added, followed by DMA (4 mL) and distilled water (2 mL) with vigorous stirring for 1 h at room temperature. After the addition of 1 drop of HNO₃ (1 M, aq), the solution was transferred into a vial, kept at 80°C for 72 h and then cooled to room temperature with a cooling rate of 5°C/h. The light yellow cubic crystals of **2** were obtained after cooling the reaction system to room temperature, washed with water and air-dried. Yield: 39.6% based on the H₃tatab linker. Elemental analysis Calcd (%) for **2** (C₅₆H₆₀Mg₃N₁₄O₂₀): H, 4.57; C, 50.88; N, 14.83. Found: H, 4.29; C, 51.02; N, 14.36. The compound **2** could not be dissolved in water and DMF but can be well dispersed in the DMSO solution.

Structural determination via X-ray diffraction

An Oxford Xcalibur E diffractometer with graphite monochromatized Mo radiation (0.71073 Å) was used to collect the reflection data of **1** and **2** at 298 K. The direct method in the XS program was used to obtain the initial structural modes, and the least-squares method in XL program (Sheldrick, 2015) was used to refine the structural models. All the H atoms were poisoned at their ideal locations and refined using the AFIX commands according to their C atoms attached. All

Table 1: The crystal data and structure refinements for compounds **1** and **2**.

	1	2
Formula	C ₅₈ H ₄₈ Mg ₃ N ₈ O ₁₆	C ₁₆ H ₁₄ MgN ₄ O ₆
Mr	1185.97	382.62
Crystal system	Monoclinic	Cubic
Space group	P2 ₁ /n	Pa3
a/Å	12.5643 (4)	20.2869 (5)
b/Å	25.6322 (10)	20.2869 (5)
c/Å	13.8231 (4)	20.2869 (5)
α/°	90	90
β/°	99.762 (3)	90
γ/°	90	90
V/Å ³	4387.3 (3)	8349.2 (6)
Z	2	2
D _{calc} /g · cm ⁻³	0.898	0.913
μ(Mo Kα)/mm ⁻¹	0.085	0.091
θ range/°	3.094–24.999	3.012–26.371
Reflections collected	20 255	8021
No. unique data [R(int)]	7698 [0.0286]	2847 [0.0362]
No. data with I ≥ 2σ(I)	5725	1921
R ₁	0.0662	0.0736
ωR ₂ (all data)	0.2217	0.2953
CCDC	1841992	1841993

the non-hydrogen atoms in the two structures were treated anisotropically. Table 1 shows the crystal data and the structural refinements.

Antitumor activity

The antitumor activities of the as-prepared two metal-organic complexes (**1** and **2**) were studied on the human spinal tumor cell lines U-266 by using the MTT assay. In this work, the targeted cells were seeded in the Dulbecco's Modified Eagle's Medium (DMEM), which was supplemented with 10% fetal calf serum (FCS) and 1% penicillin/streptomycin (P/S, Boster), and then cultured in a humidified incubator overnight. The conditions of the incubator were set to 5% CO₂ atmosphere and 37°C. Subsequently, a 96-well plate was used to house the two complexes with various concentrations, respectively, and the incubation time was set to 24 h. Then 10 mL of MTT (3.0 mg/mL) solution was added to each well and then incubated for 4 h. Then, the supernatant was replaced with 150 μL of dimethyl sulfoxide (DMSO) for each well to dissolve the MTT formazan crystals. The absorbances at 490 nm were used to calculate the cell viability.

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