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Study of the first antibacterial agent pipemidic acid modifying Keggin polyoxometalate

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ABSTRACT

A new compound based on polyoxometalates (POMs) and the quinolone antibacterial pipemidic acid (HPPA), $\{[Co(PPA)_2]H_2[SiW_{12}O_{40}]\}\cdot HPPA\cdot 3H_2O$ (**1**), has been prepared and characterized by elemental analyses, IR and singe crystal X-ray diffraction. The title compound represents the first example of POMs modified by the quinolone antibacterial HPPA, in which the POMs are modified by $[Co(HPPA)_2]$ subunits. Its antitumor activity on MCF-7 cells was investigated by the. The results show that the title compound exhibits higher antitumor activity than its parent, which indicates that introduction of M-PPA into the POM surface can increase their antitumor activity and make the compounds to penetrate into the cells easily.

Polyoxometalates (POMs), as a class of well-defined oxo nanoclusters, has become a large growing and appealing area in inorganic chemistry [1–4]. Researchers have found versatile structures [5–10] and numerous potential applications in catalysis, materials science, magnetism and medicine [11–15]. Recently, a large number of POMs have been reported in the literatures, and formed a comprehensive review of their physical, chemical and others properties. Parallel to the rapid progress of POMs, ongoing interests are driven mainly by the introduction of abundant organic compounds or their coordination polymers into the POM surface. Because they may adopt several roles: (1) as charge-compensating subunits, (2) as covalently bound subunits of the POMs, (3) as bridging inorganic ligands linking others into infinite extended framework. The introduction of organic compounds or their coordination polymers can not only enrich the structures of POMs, but also ameliorate their polar, electricity, acid and redox properties [16–20]. Hill has also pointed out that the versatility of the POMs and the bounding with organic compounds or their coordination groups onto the POM surface can significantly increase their catalytic or medical applications [15,21], particularly the introduction of some medicine molecules into the POM surface [22].

On the other hand, POMs, as anti-tumor, -viral, and -bacterial inorganic medical agents, are rendered attractive for applications in medicine. Unfortunately, the only mechanism for the antitumoral activity of POMs, that proposed by Yamase, is that POM revolves around a single electron reduction/oxidation cycle in isopolymolybdates [23], and POMs are also too toxic to be effective in clinical trial [24,25], which leads to its applications to medicine being in its infancy.

On the basis of the aforementioned points, we try to modify the surface of POMs with medicine molecules to ameliorate their properties. Pipemidic acid (HPPA), a 4-quinolone product, captures our attention based on the following reasons: Firstly, it is an antibacterial agent [26] and severely damages DNA in the absence of an exogenous metabolizing system [27]. Secondly, the HPPA may act as a multidentate ligand to coordinate with metal ions and POMs. Finally, the reported literature about the complexes of HPPA molecules suggest that metal ion coordination might be involved in the antibacterial activity of HPPA [28]. Thus, in the work, we explored the synthesis and properties of HPPA medicine molecules modifying POMs based compound, expecting to combine two interesting moieties to construct novel compounds. Herein, we report a new compound, $\{[Co(PPA)_2]H_2[SiW_{12}O_{40}]\}\cdot HPPA\cdot 3H_2O$ (**1**), which was prepared under hydrothermal conditions from a mixture of $H_4[SiW_{12}O_{40}]\times H_2O$, $Co(CH_3COO)_2\cdot 4H_2O$, HPPA, HAc and H_2O at 150 °C for 6 days [29]. Single crystal X-ray structural analysis [30] reveals that compound **1** is constructed from $[SiW_{12}O_{40}]^{4-}$ (abbreviated to SiW_{12}) polyoxoanions, binuclear cobalt $[Co(PPA)_2]^{2+}$ cations, isolated HPPA and water molecules, as shown in Fig. 1. The parent SiW_{12} is a classical α-Keggin type anion, except for one terminal O atom coordinated by a $[Co(PPA)_2]^{2+}$ subunit. And the full oxidized SiW_{12} contains four W_3O_{13} units and one ordered $[SiO_4]^{4-}$ in the center with Si–O bonds ranging from 1.624(8) to 1.646(9) Å, and the distances of W–O bonds are divided in three groups: 1.683(8)–1.722(8) Å for W–O_t, 1.880(8)–1.944(10) Å for W–$O_{b/c}$, and 2.334 (9)–2.368(8) Å for W–Oa, respectively. The valence sum calculations [31] show that all W atoms are in the +VI oxidation states and Co atoms are in the +II oxidation.

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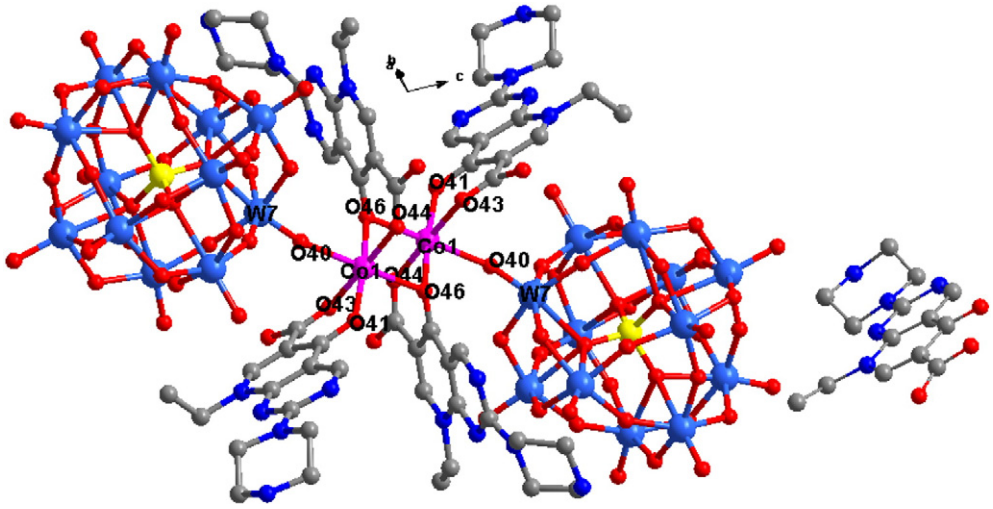

Fig. 1. Stick/ball view of the unit of compound **1**. The hydrogen atoms and crystalloid water molecules are omitted for clarity.

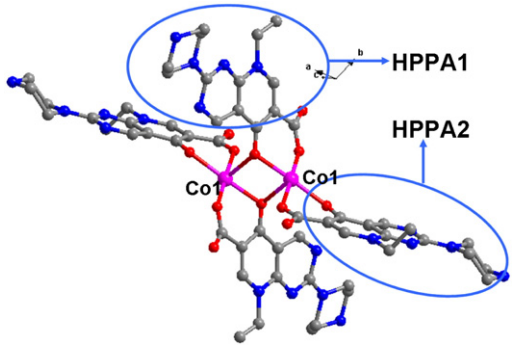

Fig. 2. Stick/ball view of binuclear cobalt cluster.

In compound **1**, there is a crystallographically independent cobalt ion (Co1), and it is six-coordinated by five O atoms from three HPPA ligands and one O atom from one SiW_{12} anion in an octahedral coordination mode. The bond distances around the Co1 are 1.983(11) and 2.237(13) Å for Co–O. Note that there are three crystallographically unique HPPA drug molecules (HPPA-1, HPPA-2, HPPA-3), in which two HPPA molecules (HPPA-1, HPPA-2) covalently link to the same cobalt ions to form binuclear cobalt clusters (shown in Fig. 2) and HPPA-3 as isolated subunit stabilize the whole structure *via* short interactions. In the binuclear cobalt clusters, HPPA-1 as bridging and chelate bi-dentate organic ligands and HPPA-2 as chelate bi-dentate organic ligands coordinate to cobalt ions.

In the solid state structure of the title compound, short interactions play an important role in stabilizing the whole structure. A notable feature in the structure of compound **1** is that there contains two different kinds of chains: i) Inorganic–organic hybrid Keggin-Metal-Organic chains. These adjacent subunits, $\{[Co(HPPA)_2]H_2[SiW_{12}O_{40}]\}$, link with each other through short interactions (N10 ⋯ O27 = 3.060 Å, C29 ⋯ O27 = 3.240 Å, N15 ⋯ O14 = 2.849 Å, N15 ⋯ O15 = 3.069 Å) (shown in Fig.S1). ii) Medicine molecules organic chains formed *via* short interaction of N1 ⋯ O49 = 2.868 Å (shown in Fig.S2). And both constitute two building blocks of compound **1**, and form 2D layers *via* C1 ⋯ O2 = 3.199 Å and C4⋯ O2 = 3.190 Å (shown in Fig. 3 left). Furthermore, the 2D layers are fused together to 3D framework shown in Fig. 3 right.

The IR spectrum of compound **1** is shown in Fig. S3. In the spectrum, characteristic band at 923 cm^{-1} is attributed to ν(Si–O), 978 cm^{-1} is attributed to $\nu(W–O_d)$, 888 cm^{-1} is attributed to $\nu(W–O_b–W)$, and

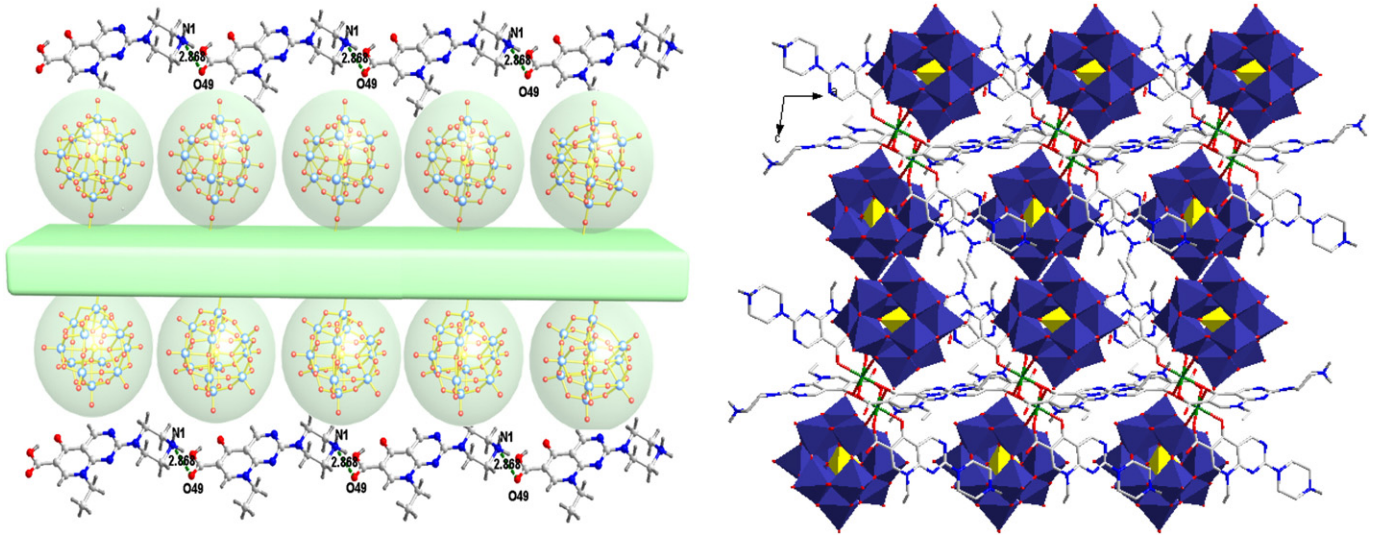

Fig. 3. The 2D (left) and 3D (right) of the compound **1**.

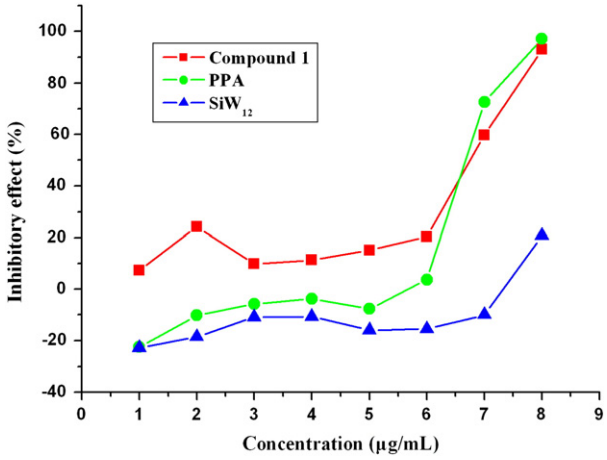

Fig. 4. The anti-tumor activity against MCF-7 about compound **1** and the parent compounds.

792 cm^{-1} is attributed to ν(W–O_c–W), respectively. The absorption bands at 1621 and 1270 cm^{-1} are assigned to the stretching vibrations for HPPA ligand (shown in Fig. S4).

A comparison of the antitumor activity on MCF-7 cells for compound **1** and their parent compound was made [32]. The inhibitory effect against MCF-7 cells lines (shown in Fig. 4) shows that the compound **1** and medicine molecules HPPA all exhibit high antitumor activity to MCF-7, however parent molecules SiW_{12} exhibit no antitumor activity to MCF-7. The inhibitory effective cell 50% lethal concentration (IC_{50}) against MCF-7 cells (see Table 1) shows that the values of IC_{50} about the compound **1** and HPPA are 0.092 to 0.217 mg/ml, respectively. These results indicate the introduction of metal complexes of HPPA into the POM surface can change the properties of POM, such as polar, electricity, acid and redox, and help the compounds to penetrate into the cells easily, which result in the higher antitumor activity. Additionally, in the title compound, POMs are surrounded by HPPA drug molecules shown in Fig. 3 right, which increase the interactions among POMs and HPPAs, and result in the bigger changes of properties of POMs. So the title compound exhibits the higher antitumor activity than that of SiW_{12}, and the antitumor activity comes from the synergism of POMs and Co-PPA.

Table 1
Inhibitory effect of compound**1** on tumor cells in vitro.

Material	Dose (μg/mL)	Inhibitory effect (%)	IC_{50}[a](mg/mL)
Compound 1	500	93.0	0.092
	100	59.8	
	20	20.4	
	4	15.1	
	0.8	11.2	
	0.16	9.7	
	0.032	24.1	
	0.0064	7.4	
	500	97.1	
	100	72.6	
	20	3.7	
PPA	4	−7.7	0.217
	0.8	−3.7	
	0.16	−5.8	
	0.032	−10.2	
	0.0064	−22.5	
	500	20.7	
	100	−9.9	
	20	−15.5	
SiW_{12}	4	−15.9	–
	0.8	−10.7	
	0.16	−10.8	
	0.032	−18.5	
	0.0064	−22.8	

[a] The 50% inhibitory concentration (IC_{50}) is the concentration that suppresses tumor cells by 50%.

In the summary, a new compound based on SiW_{12}-HPPA-Co was synthesized, characterized and studied about antitumor activity in this paper. The title compound represents the first example of POMs modified by the quinolone antibacterial pipemidic acid, which, to some extent, provides a good example of reasonable design and controllable assembly of drug molecule-based POMs compounds. The MTT investigations found that the title compound possessed higher antitumor activity than the parent compound due to the changes of the properties and the synergism of POMs and Co-PPA. This work implies that the introduction of M-PPA/HPPA into the polyoxoanion surface could increase their antitumor activity and make the compounds to penetrate into the cells easily. Thus more work need to be done about the M-drugs-POMs reaction system so as to explore the possible effect of drug molecules modifying POM clusters.

Acknowledgements

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Appendix A. Supplementary material

CCDC 808599 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2011.03.075.

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[29] Compound **1** was prepared under hydrothermal condition. The mixture of $H_4[SiW_{12}O_{40}]\cdot xH_2O$(300 mg), $Co(CH_3COO)_2\cdot 4H_2O$(49 mg), HPPA(60 mg) was dissolved in 10 mL of distilled water at room temperature. When the pH value of the mixture was adjusted to about 4 with 1.0 $mol\cdot L^{-1}$ HAc, the suspension was put into a Teflon-lined autoclave and kept under autogenous pressure at 150 °C for 6 days. After slow cooling to room temperature, kermesinus block crystals were filtered and washed with distilled water. Anal. Calcd for $SiW_{12}O_{52}CoC_{42}N_{15}H_{57}$ (M = 3897): Calcd. C 12.93, H 1.46, N 5.39, Co 1.51%; Found. C 12.91, H 1.61, N 5.40, Co 1.54%.
[30] Crystal data for compound **1**: $SiW_{12}O_{52}CoC_{42}N_{15}H_{57}$, FW = 3897, Triclinic, space group P 1, $a=12.815(5)$ Å, $b=17.154(5)$ Å, $c=19.417(5)$ Å, $\alpha=103.829(5)^o$, $\beta=92.497(5)^o$, $\gamma=109.984(5)^o$, $V=3858(3)$ $Å^3$, $Z=2$, $D_{cal\ c}=3.350$ mg/m^3, $\lambda=0.71069$ Å, $T=293(2)$K, R_1 (wR_2) = 0.0530 (0.1250) [I>2sigma(I)] ,and 0.0816 (0.1440) [all data], Bruker Smart Apex-II CCD area detector, Mo K_α radiation. The structure was solved by direct methods and refined on F2 by full-matrix least squares methods using SHELXTL 97. CCDC reference number 808599.
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[32] The antitumor activity of compounds **1** and their parent on MCF-7 cells was tested by the MTT experiment, respectively. MTT, 3-[4,5-dimethylthiazol-2-yl] -2.5-diphenyl-tetrazolium bromide, also known as thiazolyl blue, is a dye which can accept a hydrogen atom. Surviving tumor cells are able to reduce the yellow MTT to an insoluble blue formazan in water whereas dead tumor cells do not possess this capability. The formazan product is dissolved in DMSO and then determined colorimetrically with a Microplate Reader (490 nm). Subcultured MCF-7 cells were suspended in 0.25% trypsin, respectively. The cell suspension (*ca.* 10^5–10^6 cells mL) was added to a 96 well plate (100 μL per well) and incubated at 37 °C in a 5 % CO_2 incubator for 24 h. 100 μL samples containing the compounds were then added. After 48 h, 20μL MTT solution (5 mg mL^{-1} in 0.01 M PBS (phosphate buffer solution)) was added, and the mixture allowed to incubate for 4 h. The supernatant was removed and DMSO (150 μL) added. The resulting mixture was shaken for 10 min at room temperature, and colorimetric analysis was used to examine the cell survival rate. These samples containing the title compound and parent compound were obtained by dissolving the title compounds in DMSO, autoclaving and diluting by a RPMI 1640 medium to a final concentration of 500, 100, 20, 4, 0.8, 0.16, 0.032 and 0.0064 μg mL^{-1}.