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The synthesis, characterization and antitumor activities of A C-type arsenomolybdate

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Abstract: A new heteropolyoxometal compound $(\text{NH}_4)_{14}\text{Fe}_{0.5}[\text{As}_2\text{Fe}_6\text{Mo}_{22}\text{O}_{85}(\text{H}_2\text{O})]\cdot 16\text{H}_2\text{O}$ (**1**) has been synthesized and characterized by elemental analysis, thermal analysis and single crystal X-ray diffraction. Crystal data for **1**: Triclinic, $P\bar{1}$, $a = 12.6245(4)$ Å, $b = 16.8421(5)$ Å, $c = 27.1396(8)$ Å, $\alpha = 98.892(2)^\circ$, $\beta = 91.161(2)^\circ$, $\gamma = 104.129(3)^\circ$, $V = 5518.5(3)$ Å³, $Z = 2$. The structural analysis has revealed that **1** represents a rare example of hexa-iron arsenomolybdate. The inhibitory effects of the compound **1** on A549 (human lung cancer) tumour cells were investigated by MTT assay. It is shown that compared with the reference polyoxometalate-based antitumor agent $(\text{NH}_3\text{Pri})_6[\text{Mo}_7\text{O}_{24}]\cdot 3\text{H}_2\text{O}$ (PM-8), **1** present higher antitumor activities.

1. Introduction

Polyoxometalate (POM) is a kind of unique inorganic metal oxygen anion clusters that have significant potential to act as molecular based platforms for different targets [1-3]. Over half of the elements in the periodic table can participate in the formation of the POM compounds, affording a wide range of structural versatility and diverse properties [4-7]. Although POM have been known for almost two centuries, the research interest in this field becomes more and more intense [8-11].

A hotspot of these compounds has focused on their applications in bio-activities [12-14]. The pioneering studies have demonstrated that some POM structures possess exceptional antitumoral activities and can be used as potential anti-tumoral agents [15-17]. The reason for these discoveries lie in the fact that nearly all the molecular properties that can influence the reactivity and recognition of POM with target biological macromolecules can be finely adjusted and controlled, such as polarity, oxidation-reduction potential, surface charge distribution, and so forth [18-21]. For example, in 1970s, Jasmin *et al.* firstly demonstrated sandwich-type heteropolytungstate $[\text{Na}(\text{SbW}_7\text{O}_{24})_3(\text{Sb}_3\text{O}_7)_2]^{18-}$ and $[(\text{AsW}_9\text{O}_{33})_4(\text{WO}_2)_4]^{28-}$ could inhibit various non-retro RNA and DNA viruses both *in vitro* and *in vivo* [22]; after this, Yamase reported the antitumor activities of a series of isopolyoxomolybdates, especially the $(\text{NH}_3\text{Pri})_6[\text{Mo}_7\text{O}_{24}]\cdot 3\text{H}_2\text{O}$ (PM-8) was found has the growth suppression against several tumors [23]; in 2010, Compain showed the activity of tetra- to dodeca-nuclear oxomolybdate complexes with functionalized bisphosphonate ligands in killing tumor cells [24], these discoveries



undoubtedly brought a significant progress for POM compounds in medicine. However, although great success has been gained in classic POM compounds, a close survey of literature suggested that related research made on the novel POM structures remains largely unexplored.

Meanwhile, we notice that the antitumor activities of iron containing complexes have attracted considerable attention recent years. For example, in 2014, Vanco *et al.* reported the high level and broad-spectrum inhibition of six human cancer cell by a series of iron (II/III) salophen complexes [25]; in 2015, Gust *et al.* demonstrated the salen-type iron complexes have growth inhibitory effects against cancer cells, and some of these complexes exhibited tenfold higher activities than cisplatin [26]. However, up to present research about the antitumor effect of iron-based POM compound has not yet been achieved.

Based on the aforementioned consideration, a motivation to explore new iron-containing POM class compound as well study their antitumor activities has been put forward. Herein, a new POM analog $(\text{NH}_4)_{14}\text{Fe}_{0.5}[\text{As}_2\text{Fe}_6\text{Mo}_{22}\text{O}_{85}(\text{H}_2\text{O})]\cdot 16\text{H}_2\text{O}$ (**1**) was prepared and structurally characterized. Structural analysis shows that compound **1** represents a rare example of hexa-iron arsenomolybdate. The antitumor activities research results indicate that compared with PM-8, compound **1** exhibits higher antitumor activities against A549 cells.

2. Experimental Section

All chemicals were purchased and used without further purification. Mo, Fe and As were analyzed on a PLASMA-SPEC (I) ICP atomic emission spectrometer. $[\text{NH}_3\text{Pri}]_6[\text{Mo}_7\text{O}_{24}]\cdot 3\text{H}_2\text{O}$ (PM-8) was synthesized according to the previous literature [27]. The UV-vis absorption spectrum was obtained using a 752 PC UV-vis spectrophotometer. TG analyses were performed on a Perkin–Elmer TGA7 instrument in flowing N_2 with a heating rate of $10\text{ }^\circ\text{C}\cdot\text{min}^{-1}$. The magnetic susceptibility measurements were carried out with the use of a Quantum Design SQUID magnetometer MPMS-XL. Measurements were performed on a polycrystalline sample of 32.25 mg.

Human lung cancer cell cancer cells, A549 cells, were purchased from the Shanghai Institute for Biological Science, Chinese Academy of Science (Shanghai, China) and were supplemented with 1 mM glutamine and 10 % (v/v) FCS (fetal calf serum). Cell cultures were grown to confluence and maintained in a humidified atmosphere at $37\text{ }^\circ\text{C}$ and 5 % CO_2 . All cell lines were placed into 96-well plates at a density of 1×10^4 cells per well and incubated with fetal bovine serum-free medium for 24 h prior to the experiments with the POM compounds (compound **1** and PM8). The compounds were added to a final concentration in the range of 1–100 μM . The antitumor activity of compound **1** and PM8 on A549 cells was tested by the MTT assay (MTT = 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazoliumbromide).

3. X-ray crystallography

The crystallographic data were collected at 296(2) K on a Super Nova diffractometer using ω scan technique with CuK_α radiation ($\lambda = 1.54178\text{ \AA}$). Suitable crystals were mounted in a thin-glass tube and transferred to the goniostat. Data integration was performed using SAINT. Routine Lorentz and polarization corrections were applied. Multi-scan absorption correction was applied. Molybdenum, iron and arsenic atoms were located by Direct Methods, and successive Fourier syntheses revealed the remaining atoms. Refinements were achieved by the full-matrix method on F^2 using the Shelxtl-97 crystallographic software package [28-30]. The NH_4^+ cations could not be precisely found from the difference Fourier maps and were taken care of with the SQUEEZE program. The elemental analysis and the charge balance confirmed their presence. The highest residual peak and the deepest hole are 2.90 and -2.54 e \AA^{-3} , respectively. The detailed crystal data and structure refinement for **1** are given in Table 1. The drawings were made with Diamond 3.2i.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number

CCDC-1422677(1) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

4. Synthesis of 1.

(NH₄)₆Mo₇O₂₄·4H₂O (0.5 g, 0.4 mmol) and As₂O₃(0.04g, 0.2mmol) was dissolved in 20 mL distilled water and stirred for 10 min. Then, 10 mL H₂O containing 10 mmol hydrochloric acid and 0.6 mmol FeCl₃·6H₂O (0.17g) was added dropwise within 10 min to above solution. The mixture was kept stirring for 1 h at room temperature. The resulting reaction mixture was further refluxed for 3 h, cooled to room temperature and filtered. Sealed with a parafilm with a few of tiny pores. After 2 weeks, yellow block crystals were obtained. (yield 36% based on Mo). Anal. for **1**: Calcd. N 4.31, Mo 46.47; Fe 7.99; As 3.30, found N 4.20, Mo 46.26; Fe 8.21; As 3.13%. TG analysis indicates that there are about 16 lattice water molecules in the compound.

5. Results and discussion

5.1. Descriptions of Crystal Structures

Single-crystal XRD analysis reveals that the polyoxoanion of **1** exhibits an usual C-type structure in which a central-placed FeMo₇O₂₈ (*abbr.* {FeMo₇}) unit and two external-wrapped AsMo₇O₂₇¹¹⁻ (*abbr.* {AsMo₇}) units group bridged together via two trimeric Fe₂MoO(μ₂-O)₂⁶⁺ (*abbr.* {Fe₂Mo}) and Fe₃⁹⁺ (*abbr.* {Fe₃}) cluster (see Figure 1(a)). Hence, the overall polyoxoanion can be formulated as {[AsMo₇][Fe₂][FeMo₇][Fe₃][AsMo₇]}¹⁵⁻. The basic structural feature of {FeMo₇} and {AsMo₇} units are similar to those reported previously [31], which can be deduced from hexalacunary mono-{MoO₆} capped β-Keggin FeMo₁₂O₄₀⁵⁻ and α-Keggin AsMo₁₂O₄₀³⁻, respectively. In the polyoxoanion, all the six Fe atoms exhibit two different coordination geometries: five 'side' Fe atoms are octahedron, which are coordinated with three O atoms from the {AsMo₇} and the other three O atoms from the central {FeMo₇}; the central sited Fe atoms shows tetrahedron geometry, four coordination sites are complete by two O atoms from bridging oxygens of the central {FeMo₇} and the remaining two oxygen atoms from the {Fe₃} and {Fe₂Mo}, respectively. The Fe-O bond lengths and O-Fe-O bond angles are in the range of 1.886(13) ~ 2.337(11) Å and 77.3(5) ~ 174.3(5) °, respectively. Bond valence sum (BVS) calculations indicate that all of these iron centers exhibit a 3+ oxidation state.

Regardless of {Fe₃} cluster linked {AsMo₇} unit (Fe₃-{AsMo₇}), the symmetry of {[AsMo₇][Fe₂][FeMo₇]} moiety is C_{2v}, however, Fe₃-{AsMo₇} unit rotate 90 ° with symmetry plane of {[AsMo₇][Fe₂][FeMo₇]} moiety (see Figure 1(b)), ascribing to such unprecedented asymmetric coordination mode, the original symmetry was reduced and finally leading the polyoxoanion {[AsMo₇][Fe₂][FeMo₇][Fe₃][AsMo₇]}¹⁵⁻ shows C₁ symmetry. However, **1** crystallizes in the centrosymmetric space group *P*-1, that is to say, two enantiomeric forms Λ and Δ exist as a racemic pair equally cocrystallized in the unit cell (See Figure 2).

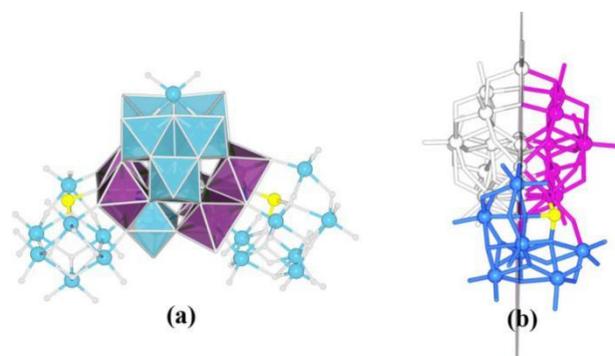


Figure 1. Combined polyhedral and ball-and-stick representation of the polyoxoanion of **1**, (a) side view of **1**: {FeMo₇}, {Fe₂Mo} and {Fe₃} polyhedron (Mo, blue octahedra; Fe, green octahedra); {AsMo₇} ball-and-stick (Mo, blue; As, yellow, O red); (b) front view of the polyoxoanion of **1**: two sides of {[AsMo₇][Fe₂][FeMo₇]} white and purple; symmetry plane grey; Fe₃-{AsMo₇} blue, As, yellow.

Table 1. Crystal data and structure refinements for **1**.

Empirical formula	$N_{14}H_{90}As_2Fe_{6.5}Mo_{22}O_{102}$
Formula weight	4542.3
Temperature / K	293(2)
Wavelength / Å	1.54178
Crystal system	Triclinic
space group	$P\bar{1}$
a / Å	12.6245(4) Å
b / Å	16.8421(5) Å
c / Å	27.1396(8) Å
α / deg	98.892(2)°
β / deg	91.161(2)°
γ / deg	104.129(3)°
Volume / Å ³	5518.5(3) Å ³
Z	2
Calculated density	2.708 g / cm ³
Absorption coefficient	27.687 mm ⁻¹
F(000)	4196
Theta range for data collection	2.74 to 66.59°
Limiting indices	-15 ≤ h ≤ 14, -16 ≤ k ≤ 20, -32 ≤ l ≤ 32
Reflections collected / unique	43924 / 19168 [R(int) = 0.1065]
Completeness to theta = 25.00	98.4 %
Refinement method	Semi-empirical from equivalents
Data / restraints / parameters	19168 / 0 / 1307
Goodness-of-fit on F ²	0.876
Final R indices [I > 2σ(I)]	R1 = 0.0892, wR2 = 0.2323
R indices (all data)	R1 = 0.1099, wR2 = 0.2513
Largest diff. peak and hole	2.901 and -2.542 e.Å ⁻³
$^a R_1 = \sum F_0 - F_c / \sum F_0 $; $^b wR_2 = \sqrt{\sum [w(F_0^2 - F_c^2)^2] / \sum [w(F_0^2)^2]}^{1/2}$	

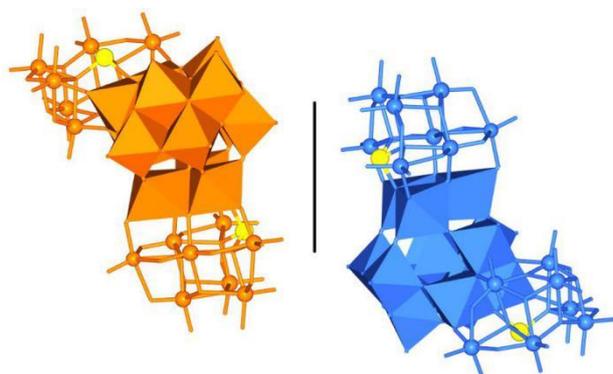


Figure 2. Λ and Δ isomers in the unit cell of **1**, Λ and Δ isomers are in different color.

5.2. IR spectra

The IR spectrum of compound **1** is shown in Figure 3, a broad band centered in the range $3200\text{--}3400\text{cm}^{-1}$ and a strong peak at 1629cm^{-1} caused by the stretching vibration of O-H indicate the presence of lattice and coordinated water molecules. Peaks at 3139 and 1402cm^{-1} corresponds to the vibration of the N-H bonds. The characteristic peaks at 887 , 757 are attribute to the vibrations of $\nu(\text{Mo-O}_i)$ and $\nu(\text{Mo-O}_b)$, and the peak at 688 cm^{-1} to the $\nu(\text{Mo-O-Fe})$. The peak at 557 cm^{-1} is regarded as the characteristic vibrations of transition-metal-oxo (Fe-O) bonds. These results are consistent with the structural analysis.

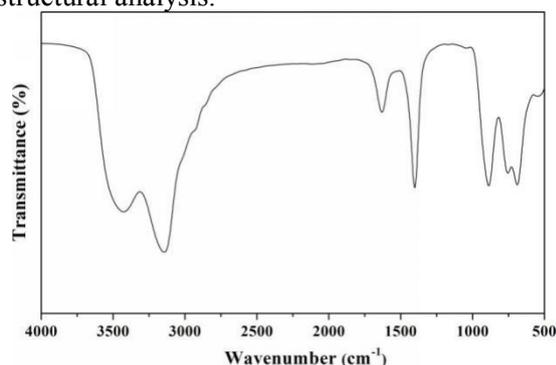


Figure 3. IR absorption spectrum for the compound **1**.

5.3. UV spectra

In order to check the solution-state stability of compound **1**, we redissolved **1** in water and monitored via UV-vis spectrum with a concentration of 1.0×10^{-4} mol/L. As Figure 4 shows, in 2 days time, there is no new peak or peak shift was detected indicating that compound **1** could keep the structural integrity for a long time in solution-state.

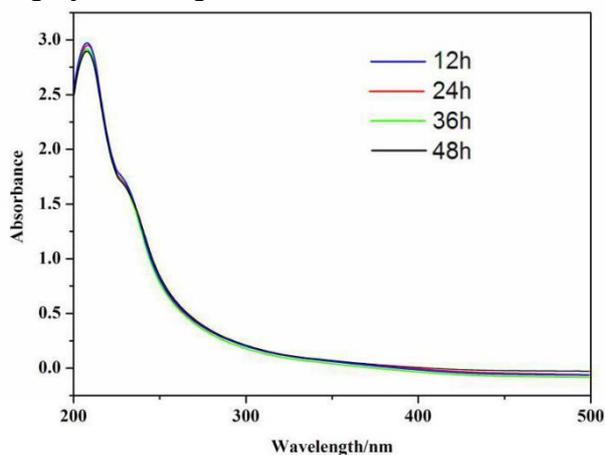


Figure 4. UV-visible spectrum for the compound **1**.

5.4. Antitumor properties

The growth of the A549 cell in the presence of various concentrations of compound **1** and the reference polyoxometalate-based antitumor agent PM-8 was investigated. The inhibit effect shown in Figure 5, both compound **1** and PM-8 exhibit antitumor activities for A549 cells lines at 24h in a dose dependent manner with the concentrations of 1 – 1500 μM . Lethal concentration 50% (IC_{50}) calculated results turn out the IC_{50} value at 24h for **1** is about 221.18 $\mu\text{M}/\text{ml}$, while the value of PM-8 is 313.06 $\mu\text{M}/\text{ml}$, indicating that iron containing arsenomolybdate possesses higher anti-proliferative effects and maybe used as a new class of selective anticancer agents. Meanwhile, this result also confirms that synergetic effect on the cytotoxicity can occurs between POM building block and transition metal ions [32, 33].

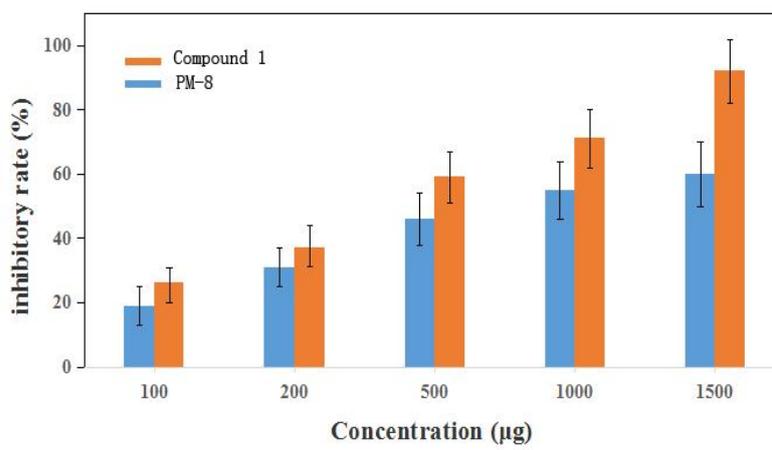


Figure 5. The effect of compound **1** and PM-8 treatment on A549 cell at 24h. Results represent the mean \pm SD from three independent experiments.

6. Conclusions

In conclusion, a rare example of hexa-iron arsenomolybdate $(\text{NH}_4)_{14}\text{Fe}_{0.5}[\text{As}_2\text{Fe}_6\text{Mo}_{22}\text{O}_{85}(\text{H}_2\text{O})]\cdot 16\text{H}_2\text{O}$ (**1**) has been isolated in aqueous solution. In vitro biological studies indicated that **1** possesses preferable inhibitory effects for human lung cancer A549 cells, moreover, the activity of **1** is comparable to that of PM-8. These results indicated that iron-containing arsenomolybdate may represent a novel group of selective anticancer agents. Since the diversity of structures of iron clusters and POM building blocks, further work is now in progress to construct new type iron-based POM complexes.

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