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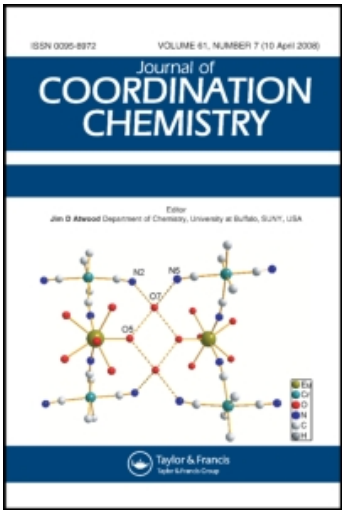

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Synthesis, structural characterization and biological activity of polyoxometallate-containing protonated amantadine as a cation

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SYNTHESIS, STRUCTURAL CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF POLYOXOMETALLATE-CONTAINING PROTONATED AMANTADINE AS A CATION

JUAN LI[a,b], YANFEI QI[a], ENBO WANG[a,*], JING LI[b], HONGFANG WANG[b], YANGGUANG LI[a], YING LU[a], NA HAO[a], LIN XU[a] and CHANGWEN HU[a]

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A novel isopolyoxomolybdate complex $(C_{10}H_{18}N)_4Mo_8O_{26}\cdot 6(CH_3)_2SO$ **1** was synthesized, purified and characterized by means of elemental analysis, IR and ^1H NMR spectra and single-crystal X-ray diffraction. It crystallizes in a triclinic system with $a = 11.5090(6)$, $b = 12.8399(3)$, $c = 14.774(13)$ Å, $\alpha = 105.390(16)$, $\beta = 93.09(4)$, $\gamma = 106.100(10)^\circ$, $V = 2003.1(2)$ Å^3, $Z = 2$, $R1 = 0.0789$, $wR2 = 0.2190$. Complex **1** is constructed from $[Mo_8O_{26}]^{4-}$, $(C_{10}H_{18}N)^+$ and $(CH_3)_2SO$ and extends to form a two-dimensional network via hydrogen bonds and weak interactions in the *ab* plane. Chicken embryo experiments show that Compound **1** has high antiviral activity in vitro.

Keywords: Polyoxometallate; Amantadine; Crystal structure; Antiviral activity

INTRODUCTION

Polyoxometallate (POM) chemistry is representative of inorganic clusters, which form a class of compounds unique in their properties, structures and electronic versatilities [1]. Contemporary interest in these compounds and their derivatives stems from their applications in catalysis, bioanalysis, materials and medicine [2–5]. Considerable attention has been paid to polyoxometallate compounds as drugs against tumors and viruses.

Since Raynaud *et al.* reported the first observation of the anti-retroviral activities of POMs in 1971 [3], various species of polyoxometallates have demonstrated good inhibitory activities with low cytotoxicity in a wide variety of viruses in vitro and in vivo, such as HIV, herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2), human cytomegalovirus (HCMV) and influenza virus [6–9]. However, POMs' marked toxicity make further trials of the drug unacceptable. HPA-23 succeeded in inhibiting human immunodeficiency virus (HIV) in vitro but failed in clinical trials. These problems have so far

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remained unsolved and have prompted several research groups to develop or modify novel potent nontoxic POM remedies. Cocrystallization with small organic molecules to modify the surface of those polyoxometallate clusters may offer a rational way to fine-tune the inhibition properties and bring about novel synergistic effects [10].

Reasons for the biological activities of POMs may include: (1) ionic size and shape; (2) electron-transfer and reservoir properties; and (3) stability at micromolar concentrations and physiological pH [4]. Our attempts to synthesize new polyoxometallate-based drugs [11–15], according to 'electron-transfer and reservoir theory', via bonding organic functional groups to the surface of POMs, led to a novel isopolyoxomolybdate complex $(C_{10}H_{18}N)_4Mo_8O_{26}{\cdot}6(CH_3)_2SO$ **1**. Chicken embryo experiments showed that **1** has high antiviral activity in vitro. Furthermore, the successful synthesis of the new POM derivative has enriched the medicinal chemistry of POMs.

EXPERIMENTAL

General Considerations

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All the chemicals were of reagent grade and used without further purification. Influenza A freeze-dried virus strains A/Beijing/34/96 and 10-day-old healthy embryo eggs were obtained from Changchun Institute of Biological Products (CCIBP). The elemental analyses (C, H and N) were performed on a Perkin-Elmer 2400 CHN instrument. The Mo was determined with a Leaman inductively coupled plasma (ICP) spectrometer. The IR spectrum of **1** was recorded in the range 4000–400 cm^{-1}on an Alpha Centauri FT/IR spectrophotometer as KBr pellets. The ^1H NMR spectrum was obtained on a Bruker Am-500 spectrometer operated at 500 MHz with DMSO as the solvent.

Preparation of $(C_{10}H_{18}N)_4Mo_8O_{26}{\cdot}6(CH_3)_2SO$

A solution of 5.00 g (20.7 mmol) sodium molybdate dihydrate ($Na_2MoO_4{\cdot}H_2O$) in 12 cm^3 water was acidified with 5.17 cm^3 of 6.0 M aqueous HCl (31.0 mmol) in a 50 cm^3 Erlenmeyer flask with vigorous stirring over a period of 1 to 2 min at room temperature. A solution of 0.30 g amantadine in 5 cm^3 water (pH = 7) was then added to the sodium molybdate solution with vigorous stirring, causing the immediate formation of a white precipitate. The resulting slurry was stirred for 10 min. During this period the white precipitate slowly changed to primrose yellow. The precipitate was collected on a medium-porosity filter and washed successively with 20 cm^3 water, 20 cm^3 ethanol and 20 cm^3 diethyl ether. (Yield: 4.1 g, 82% based on $Na_2MoO_4{\cdot}H_2O$). Some of the crude product was dissolved in 5 cm^3 of mixed solvent of dimethylsulfoxide (DMSO) and acetone for one month. Colorless crystals of **1** grew from the yellow solution. Anal. Calcd. for $(C_{10}H_{18}N)_4Mo_8O_{26}{\cdot}6(CH_3)_2SO$(%): C, 27.62; H, 4.78; N, 2.48; Mo, 33.97. Found: C, 27.28; H, 4.99; N, 2.66; Mo, 33.69.

Anti-influenza-virus Activity and Toxicity Assays of 1

Toxicity to the chicken embryo

A quantity of **1** was dissolved in a sterile equal volume mixture of dimethylsulfoxide and saline solvent (DMSO-PS), diluted to obtain five different concentrations in

duplicate, then 0.2 cm^3 of each solution was injected into each of the allantois cavities of the 10-day-old chicken embryos, which were these incubated at 33°C. The number of dead chicken embryos was recorded and the 50% lethal dose (LD_{50}) was calculated using Karber's method.

Anti-influenza-virus activity

The virus (200×10^{-3} cm^3, about 103 to 104 PFU) was injected into each of the allantois cavities of the 10-day-old chicken embryos. The experimental dose was divided into five various concentration groups and three control groups, including the group of the virus control, the DMSO-PS control and the amantadine control. After 72 h, the chicken embryos were chilled at 4°C in a refrigerator overnight. The allantoic fluid was collected the next day for hemagglutination testing. The 50% effective concentration (EC_{50}) was calculated using Reed–Muench's method. The therapeutic index (TI) was calculated for **1** ($TI = LD_{50}/EC_{50}$).

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X-ray Crystallography

The selected crystal was mounted on a glass fiber and placed in a stream of cold nitrogen on a Rigaku R-AXIS RAPID IP diffractometer equipped with a Mo anode. Data processing was accomplished with the RAXWISH processing program. An empirical absorption correction was applied. The structure was solved by the direct method and refined by full-matrix least squares on F^2 using the SHELXL 97 software [16]. The hydrogen atoms were placed in idealized positions. A total of 12 018 reflections were measured in the range $2.42° < \theta < 27.48°$. Structure solution and refinement based on 8299 independent reflections with $I > 2\sigma(I)$ and 468 parameters gave $R1 = 0.0789$ $[wR2 = 0.2190]$ $\{R1 = \Sigma\|F_0| - |F_c\|/\Sigma|F_0|;$ $wR2 = \Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]^{1/2}\}$. A summary of the crystal data and structure refinement for **1** is provided in Table I.

Detailed crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication CCDC 210252.

RESULTS AND DISCUSSION

The crystal structure of **1** consists of the discrete clusters $[Mo_8O_{26}]^{4-}$ and $(C_{10}H_{18}N)^+$, and DMSO solvent molecules, as shown in Fig. 1. Six isomers of the octamolybdate cluster, namely, α, β, γ, δ, εand ζ forms, have been described, whose structures differ in number, type and fusion made of the molybdenum polyhedron [17–22]. The $[Mo_8O_{26}]^{4-}$ unit in **1** is composed of eight edge-sharing $\{MoO_6\}$ octahedra and two Mo_4O_{13} subunits are stacked together by a relatively long Mo–O bond, which displays the characteristic β-octamolybdate arrangement. The Mo–O (terminal) bond and the Mo–O (bridge) bond lengths are in the range of 1.699–1.711(4) and 1.761(4)–2.500(4) Å, respectively. The selected bond distances (Å) for $[Mo_8O_{26}]^{4-}$ in **1** are given in Table II.

The β-octamolybdate subunit $[Mo_8O_{26}]^{4-}$ is linked to four protonated $(C_{10}H_{18}N)^+$ units via hydrogen bonds. Two $(C_{10}H_{18}N)^+$ units are linked by hydrogen bonds to

TABLE I Crystal data and structure refinement for **1**

Empirical formula	$C_{26}H_{54}Mo_4N_2O_{16}S_3$
Formula weight	1103.44
Temperature (K)	93
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions (Å,°)	$a = 11.5090(6)$ $\alpha = 105.390(16)$ $b = 12.8399(3)$ $\beta = 93.09(4)$ $c = 14.7740(13)$ $\gamma = 106.100(10)$
Volume (Å^3)	2003.1(2)
Z	2
D_c (Mg m^{-3})	1.829
Absorption coefficient (mm^{-1})	1.445
$F(000)$	1082
Crystal size (mm^3)	$0.767 \times 0.661 \times 0.654$
θ range for data collection (°)	2.42–27.48
Limiting indices	$-14 \le h \le 14$, $-16 \le k \le 16$, $-19 \le l \le 19$
Reflections collected	12 018
Independent reflections	8299 [$R_{int} = 0.0937$]
Completeness to θ = 27.48	90.5%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	8299/0/468
Goodness-of-fit on F^2	0.992
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0789$, $wR2 = 0.2190$
R indices (all data)	$R1 = 0.0823$, $wR2 = 0.2239$
Largest diff. peak and hole (e Å^{-3})	2.363 and −2.741

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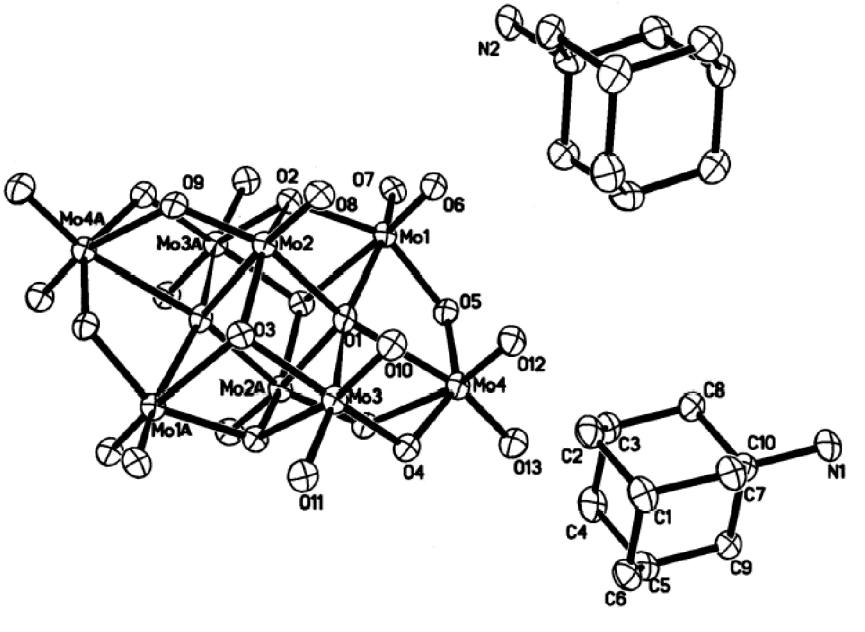

FIGURE 1 ORTEP diagram of Compound **1** with the atom labeling scheme and 50% thermal ellipsoids. H atoms are omitted for clarity.

TABLE II Interatomic distance (Å) and angles (°) in crystal of **1**

Hydrogen bonds				
D–H···A	D–H	H···A	D···A	∠D–H···A
N(1)–H(1)A···O(15)	0.890	1.898	2.781	142.87
N(1)–H(1)B...O(6)	0.889	2.003	2.827	153.69
N(1)–H(1)C···O(12)	0.890	2.294	2.972	132.92
N(2)–H(2)A···O(14)	0.890	1.910	2.772	162.60
N(2)–H(2)B···O(4)	0.890	2.034	2.910	168.21
N(2)–H(2)C···O(16)	0.890	1.947	2.797	159.09
Other contacts				
C(21)···O(7)	3.344			
S(1)···O(7)	3.253			
S(1)···S(3)	3.619			
Selected distances for $[Mo_8O_{26}]^{4-}$				
Mo(1)–O(6)	1.709(4)		Mo(3)–O(11)	1.701(4)
Mo(1)–O(7)	1.700(4)		Mo(3)–O(10)	1.710(4)
Mo(1)–O(5)	1.903(4)		Mo(3)–O(4)	1.919(4)
Mo(1)–O(2)	2.004(4)		Mo(3)–O(3)	2.003(4)
Mo(1)–O(3)#1	2.309(4)		Mo(3)–O(1)	2.307(4)
Mo(1)–O(1)	2.316(4)		Mo(3)–O(2)#1	2.343(4)
Mo(2)–O(8)	1.700(4)		Mo(4)–O(12)	1.707(4)
Mo(2)–O(9)	1.761(4)		Mo(4)–O(13)	1.711(4)
Mo(2)–O(2)	1.936(3)		Mo(4)–O(5)	1.921(4)
Mo(2)–O(3)	1.947(4)		Mo(4)–O(4)	1.930(4)
Mo(2)–O(1)	2.133(4)		Mo(4)–O(9)#1	2.248(4)
Mo(2)–O(1)#1	2.380(4)		Mo(4)–O(1)	2.500(4)

Symmetry transformations used to generate equivalent atoms #1: $-x+1, -y+2, -z+1$.

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the octamolybdate core via a double-bridging oxygen atom ligand coordinated to two adjacent molybdenum centers [N(2)···O(4) 2.910 Å]. The other two $(C_{10}H_{18}N)^+$ units are bound to the octamolybdate core via two terminal oxygen atoms [N(1)···O(6) 2.827 Å, N(1)···O(12) 2.972 Å]. Hydrogen bonds also occur between the six solvent molecules and amantadine. Interatomic distances (Å) and bond angles (°) partly involving hydrogen-bond and short-contact atoms are listed in Table II.

Two $[Mo_8O_{26}]^{4-}$ clusters, two $(C_{10}H_{18}N)^+$ cations and four DMSO solvent molecules are joined together to form a ring by N(2)A(B)–H···O(4)A(B), N2–H···O(16)A(B) hydrogen bonds (O···N range 2.771–2.911 Å) and weak interactions between S(1)A(B)···S(3)A(B) (S···S 3.619 Å), C(21)A(B)···O(7)A(B) (C···O 3.344Å). The other two $(C_{10}H_{18}N)^+$ cations attaching to O(6)A(B) fill in the ring, as shown in Fig. 2a. The extended ringed systems generate a two-dimensional infinite network in the *ab* plane, illustrated in Fig. 2b. The two-dimensional layers are further extended into a three-dimensional supramolecular framework.

The IR spectrum of **1** is similar to that observed for a basal $[Mo_8O_{26}]^{4-}$ structure: peaks at 943 and 841 cm^{-1} are assigned to Mo–O_t stretching vibrations; strong bands at 907, 704 and 661 cm^{-1} are due to Mo–O_μ stretching vibrations. $(C_{10}H_{18}N)^+$ cations and DMSO molecules are shown in the IR spectrum of **1** between 3600 and 1000 cm^{-1}.

The ^1H NMR spectrum of **1** in DMSO shows the following signals: the resonance at 7.669 ppm is assigned to $-NH_3^+$ and resonances at 2.539 and 1.561–1.758 ppm are assigned to $-CH_2-$ and =C–CH of amantadine respectively; the resonance at 3.312 ppm is attributed to H_2O in DMSO; the resonances at 2.495–2.504 ppm are due to DMSO; the resonance at 2.087 ppm is assigned to residual acetone.

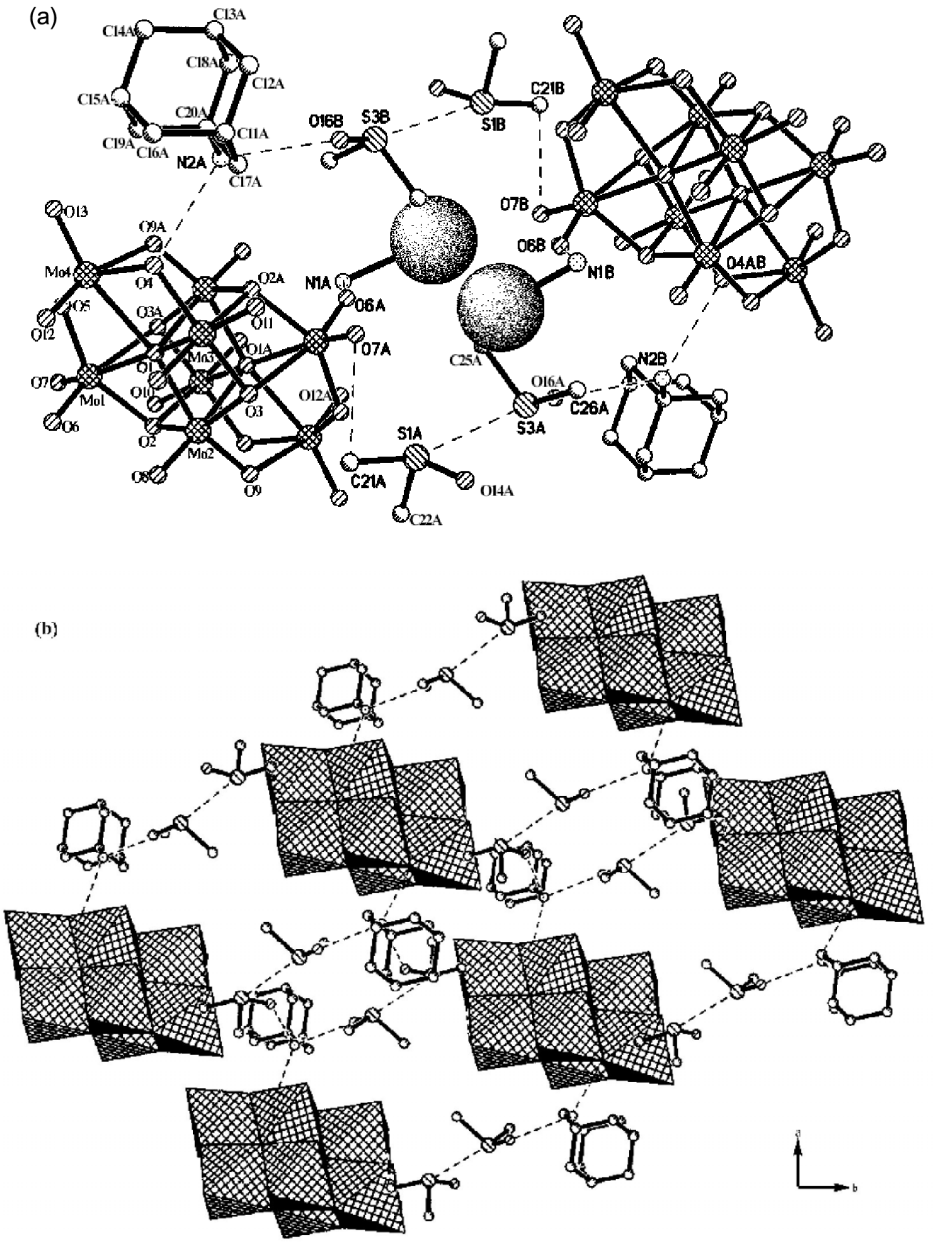

FIGURE 2 (a) Solid-state arrangement of **1** leading to a ring structure dominated by hydrogen-bond interaction. Black pellet represents $C_{10}H_{15}$. (b) A view of the two-dimensional layer result from the hydrogen bonding of β-$[Mo_8O_{26}]^{4-}$ clusters, $(C_{10}H_{18}N)^+$ cations and DMSO solvent molecules along the *c* axis in **1**. Polyhedra represent the polyoxoanions. H atoms are omitted for clarity.

The anti-influenza-virus activity and toxicity of Compound **1** can be obtained from chicken embryo experiments. The 50% effective concentration (EC_{50}) and the 50% lethal dose (LD_{50}) against influenza virus for **1** are $0.1\,mg\,cm^{-3}$ and $9.36\,mg\,cm^{-3}$, respectively. The therapeutic index (TI) is 85.6. Compound **1** has strong antiviral activity *in vitro*.

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