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Synthesis and Crystal Structures of Novel Keggin and Dawson Polyoxometalates Containing Amantadine

Shu Xia LIU*, Chun Mei WANG, Hong Ju ZHAI, De Hui LI, En Bo WANG

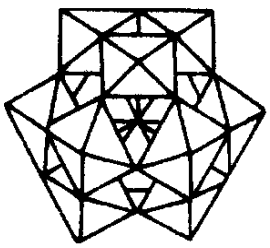
Institute of Polyoxometalate Chemistry, Department of Chemistry, Northeast Normal University, Changchun 130024

Abstract: Two novel polyoxometalates containing pharmaceutical component amantadine, formulated with $(C_{10}H_{18}N)_5PMo_{12}O_{40}Cl_2 \cdot 5H_2O$ (**I**) and $(C_{10}H_{18}N)_6As_2Mo_{18}O_{62} \cdot 6CH_3CN \cdot 6H_2O$ (**II**) were first synthesized and characterized by IR, UV-Vis spectra and X-ray diffraction. Structural analyses of **I** and **II** suggested that polyanions in these compounds were reserved their Keggin or Dawson structures and were linked to amantadine through electrostatic interaction and hydrogen bonding.

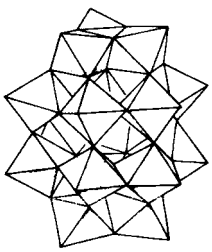
Keywords: Amantadine**,** polyoxometalate, synthesis, crystal structure.

Heteropolyoxometalates are a large family of potent medicines due to their excellent antiviral and antitumor activity [1-4], while their application in clinic meets great difficulties for their toxicity [5]. How to synthesize heteropolyoxometalate medicines possessing high activity and low toxicity has become the focus in heteropolyoxometalate medicine research. Previously reported polyoxometalates showing medical activities are all salts simple Na^+, K^+ or NH_4^+ *etc.* inorganic cations, in which only polyanion creates activity against virus. We consider that if pharmaceutical activity substances are introduced to polyanions, high effective bifunctional medicines will be obtained and the toxicity will be decreased accordingly. Here we report the synthesis and novel crystal structures of a

Figure 1 Polyhedron diagrams of (a) α - Keggin polyanion and (b) α - Dawson polyanion



(a)



(b)

* E-mail: liusx@nenu.edu.cn

α-Keggin type (**Figure 1a**) and a α-Dawson type (**Figure 1b**) heteropolyoxometalates containing pharmaceutical activity component amantadine. Amantadine is considered as a preferred anti-flu viral medicine in clinic [6-7], and it also generates inhibitory activity in tumor cells [8]. Recently the medicine research of amantadine has achieved new progress, amantadine is found effective to chronic hepatitis C and Parkinson disease [9-10]. Analyses of complex **I** and **II** showed that polyanions and amantadine preserve their original cage structures, which predicates that their medical activities will be reserved. Cooperation of amantadine and polyanion doubtless will greatly improve the medical activities of these new heteropolyoxometalates. We anticipate our work and will make new breakthrough in polyoxometalate medicine chemistry fields.

Amantadine acidated by diluted hydrochloride is added into $H_3PMo_{12}O_{40}$ [11] aqueous solution with stirring, produced yellow deposit was isolated by filteration. Yield: 65%. Elemental Analysis for **I**. Found, N, 2.42; C, 21.37; H, 3.31; P, 0.98; Mo, 40.86. Calcd, N, 2.55; C, 21.86; H, 3.64; P, 1.13; Mo, 41.97. **II** was synthesized in similar process of **I**, only without preacidification with diluted hydrochloride. Yield: 70%. Elemental analysis. Found, N, 3.98; C, 18.97; H, 3.33; As, 3.55; Mo, 40.13. Calcd, N, 4.03; C, 20.72; H, 3.43; As,3.59; Mo, 41.39. Crystal suited for X-ray single crystal diffraction was obtained from recrystallization in the mixture of acetonitrile and water.

Figure 2 Molecular structure of **I**

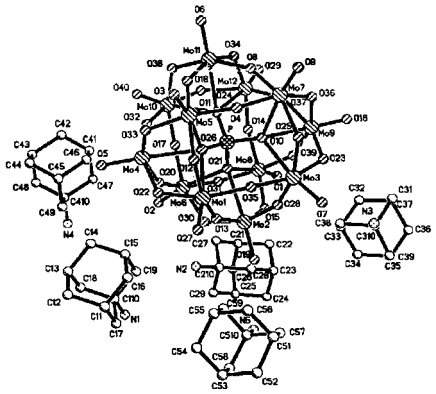
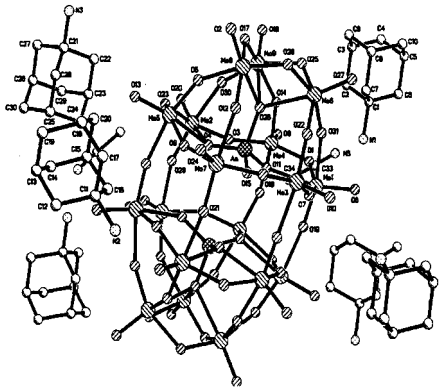


Figure 3 Molecular structure of **II**



As shown in **Figure 2**, molecule of **I** consists of five amantadine cations, a 12-molybophosphate anion, two chloride ions and five water molecules. 12-molybophosphate anion remains the Keggin structure: A central PO_4 tetrahedron are surrounded by 12 MoO_6 octahedra arranged in four Mo_3O_{13} groups. Each Mo_3O_{13} group is composed of three edge-shared MoO_6 octahedra with each other. Four Mo_3O_{13} groups corner-shared to the PO_4 tetrahedron. Mo-O distances are 1.658-1.682Å for terminal oxygen (Mo-Ot), 1.853-1.970 Å for bridge oxygen in a Mo_3O_{13} group (Mo-Oc), 1.845-1.953 Å for bridge oxygen between different Mo_3O_{13} groups (Mo-Ob), 2.142-2.456 Å for corner-shared oxygen to PO_4 tetrahedron. P-O distances vary from 1.509-1.534 Å. Amantadines also preserve their basic cage structures: C-C distances range from 1.410-1.610 Å, and C-N distances range from1.470-1.516 Å. Non-bonding distances of N atoms in amantadines and O atoms in polyanion are in the range of Van der Waals

distance, it is considered that hydrogen bonds are formed in molecule **I**: N2-H…O30, 2.981 Å; N4-H…O24, 2.930 Å; N5-H…O19, 3.044 Å. Cl^- ions play a role of balancing over positive charges of protonated amantadine in **I**. While analysis of **I** shows that faint hydrogen- bonding also exists among Cl^- ions and N atoms in amantadines: N5-H…Cl2, 3.289 Å; N2-H…Cl2, 3.2 Å; N1-H…Cl1, 3.07 Å; N2-H…Cl1, 3.27 Å; N3-H…Cl1, 3.253 Å. Water molecules in **I** also be hydrogen boned to each other, to N atoms in amantadine or O atoms in polyanion: N4-H…Ow1, 2.753 Å; Ow7-H…Ow1 Å, 2.853 Å; Ow9-H…O40, 2.898 Å; N3-H…Ow9, 2.804 Å. In short, molecule **I** is constructed based on electrostatic interaction and hydrogen-bonding.

As shown in **Figure 3**, **II** consists of six amantadine cations, a 18-molybo-2-arsenic polyoxoanion and solvent molecules (six acetonitrile and six water molecules). 18 - molybo - 2 - arsenic polyoxoanion remains the Dawson structure composed of two α - $AsMo_9O_{31}^{3-}$ units (each derived from the well known α - $AsMo_{12}O_{40}^{3-}$ anion by removal of a set of three corner-sharing with MoO_6 octahedra) which are linked through corner-sharing with the elimination of six oxygen atoms. The anion contains only two structurally distinct types of Mo atoms: six 'cap' atoms vertical mirror planes and grouped in two sets of three, and 12 'belt' atoms that do not lie on mirror planes but are grouped in two sets of six. Mo-O distances are 1.676-1.705 Å for terminal oxygen (Mo-Ot), 2.272-2.364 Å for AsO_4 oxygen (Mo-Oa). As-O distances are in the ranges of 1.665-1.704 Å. Amantadine preserves its basic tricycle structure: C-C distances vary from 1.417-1.65 Å; C-N distances vary from 1.494 -1.520Å. Polyanion and amantadines in **II** are linked together with hydrogen bonds: N1-H…O1, 2.941 Å; N2-H…O10, 2.877 Å; N3-H…O17, 2.953 Å.

Figure 4 IR spectrum of **I**

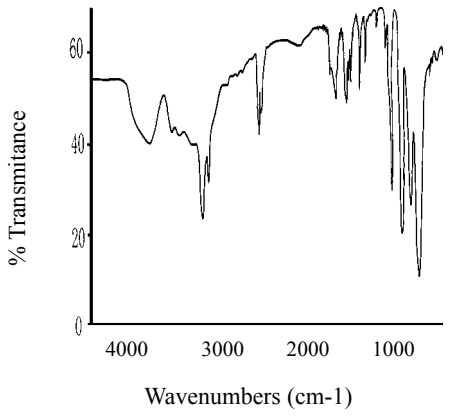
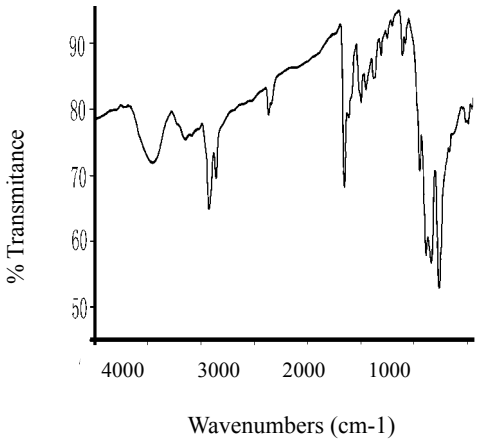


Figure 5 IR spectrum of **II**



As shown in **Figure 4** and **Figure 5**, there are similar features in IR spectra of **I** and **II**: Four peaks in rang of 700-1100cm^{-1} are attributed to characteristic absorptions (Oa-Mo, Ot-Mo, Mo-Ob-Mo, Mo-Oc-Mo) of Keggin or Dawson polyanions. We can conclude that polyanions in these organic derivatives of heteropolyoxometalates preserve their original Keggin or Dawson structures. Two peaks at approximate 2853 and 2920

cm^{-1} are attributed to ν_s (N-H) and ν_{as} (N-H) in amantadine, respectively. Strong absorption at 3460 cm^{-1} is attributed to ν_s (O-H) in water molecule.

The UV spectrum of **I** in water have two peaks at 208 and 260 nm which are attributed to Ot→Mo and Ob/c→Mo charge shift transmittances, respectively. These two absorption peaks are characteristic absorption of Keggin anion. It demonstrates Keggin structure is remained in I in aqueous solution.

In summary, two novel Keggin and Dawson heteropolyoxometalates containing amantadine are first synthesized and structurally characterized. In these complexes, amantadine and polyanion are reserved their original structure and are linked together through electrostatic forces and hydrogen bonds.

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