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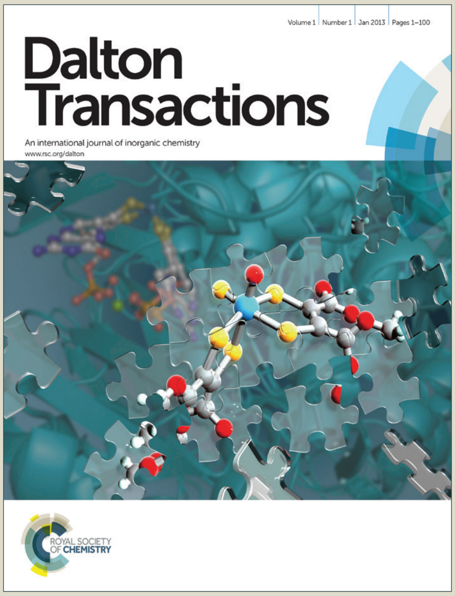

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The Ti_7-Containing, Tetrahedral 36-Tungsto-4-Arsenate(III) $[Ti_6(TiO_6)(AsW_9O_{33})_4]^{20-}$

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We have prepared the Ti_7-containing, tetrahedral 36-tungsto-4-arsenate(III) $[Ti_6(TiO_6)(AsW_9O_{33})_4]^{20-}$ (1) in a simple, one pot procedure. Polyanion 1 contains a novel Ti_7-core, comprising a central TiO_6 octahedron surrounded by six TiO_5 square-pyramids, capped by four $\{As^{III}W_9\}$ trilacunary fragments. The title polyanion is solution-stable, as shown by ^{183}W NMR and mass spectrometry, and exhibits interesting biological properties.

Polyoxometalates (POMs) are a well-known class of discrete, molecular metal oxides comprising early transition metal ions in high oxidation states. POMs are of great fundamental importance and technological relevance.[1] Lacunary heteropolytungstates can act as inorganic ligands allowing to incorporate p-, d-, and f-block metal ions, resulting in products with large structural and compositional versatility and a manifold of properties applicable to catalysis, magnetism, medicine, and material sciences.[2]

The area of Ti^{4+}-containing POMs is well-established nowadays, and many compounds have been isolated. The ionic radius of Ti^{4+} (0.75 Å) is very similar to that of W^{6+} (0.74 Å), and hence Ti^{4+} fits well into the lacunary site of Keggin or Wells-Dawson type POMs, and usually adopts octahedral coordination geometry. In terms of Keggin-derivatives, much progress has been made for mono-, di- and tri-Ti^{4+}-substituted POMs,[3] ranging from monomers to oligomers, comprising Ti-O-Ti' bonds between neighbouring Keggin units, such as dimers, trimers, as well as tetramers. Besides, some work was also carried out on the Ti^{4+}-containing Keggin-type heteropolytungstates with diverse host/guest features.[4]

A milestone in recent years was the discovery of the di-Ti^{4+}-containing $[Ti_2(OH)_2As_2W_{19}O_{67}(H_2O)]^{8-}$, exhibiting rare five-coordinated Ti^{4+} ions.[5] The two square-pyramidal $\{TiO_4(OH)\}$ groups are apparently vital for the unique catalytic properties of this polyanion.[6]

Herein, we report on the synthesis and structure of the novel Ti_7-containing, tetrahedral 36-tungsto-4-arsenate(III) $[Ti_6(TiO_6)(AsW_9O_{33})_4]^{20-}$ (**1**, see Figure 1).

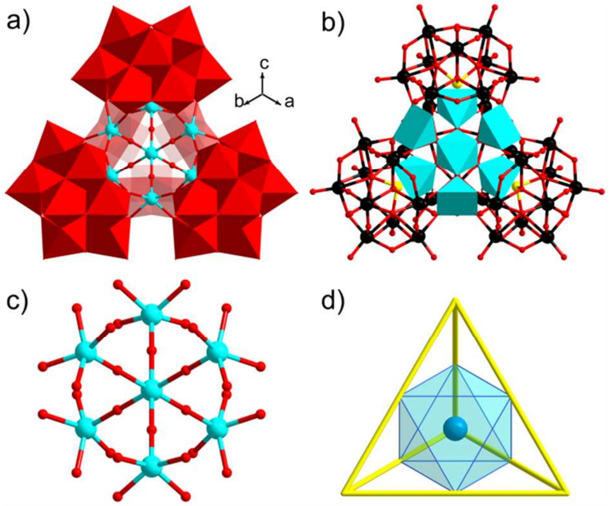

Figure 1. (a) and (b) Combined polyhedral/ball-and-stick representations of polyanion **1**. (c) Ball-and-stick representation of the Ti_7 core in **1**. (d) Topological skeleton representation of **1**, reflecting the high symmetry as shown by a Ti_6 octahedron and a As_4 tetrahedron. Colour code: WO_6 octahedra (red), TiO_5 square-pyramids and TiO_6 octahedron (light blue), W (black), Ti (light blue), As (yellow), O (red).

Polyanion **1** was prepared as the hydrated sodium salt $Na_{20}[Ti_6(TiO_6)(AsW_9O_{33})_4]\cdot 63H_2O$ (**Na-1**), by reaction of $TiOSO_4$ and $Na_9[B\text{-}\alpha\text{-}AsW_9O_{33}]\cdot 27H_2O$[7] in NaOAc buffer solution (1M, pH 4.6) at room temperature (yield 0.105 g, 10.3 %). However, the crystals of **Na-1** were not suitable for single crystal X-ray analysis. Therefore, we also isolated the hydrated, mixed sodium-cesium salt $Na_{17.5}Cs_{2.5}[Ti_6(TiO_6)(AsW_9O_{33})_4]\cdot 72H_2O\cdot 2NaCH_3COO$ (**NaCs-1**, yield 0.030 g, 2.8 %), which was suitable for X-ray analysis (see Scheme S1 and ESI† for synthetic details). As expected, the FTIR spectra of **Na-1** and **NaCs-1** are virtually identical in the

POM fingerprint region 400-1000 cm^{-1}, indicating the presence of the same polyanion in both cases (see Figure S1). Elemental analysis on **Na-1** and **NaCs-1** suggested 63 vs 72 water molecules of hydration, respectively (see Supp. Info. for details). Furthermore, for **NaCs-1** the presence of two equivalents of cocrystallized sodium acetate was identified, supported by IR (extra peaks at 1559 and 1411 cm^{-1}) and ^{13}C NMR (two signals at 181.5 and 23.3 ppm, respectively, see also Figure S4). Bond valence sum (BVS) calculations confirmed that **1** is not protonated (Table S3).[8] In the present work, all bulk studies were performed on **Na-1**, due to the higher yield as compared to **NaCs-1**.

Single crystal X-ray analysis revealed that polyanion **1** contains a novel Ti_7-core, comprising a central TiO_6 octahedron surrounded by six TiO_5 square-pyramids, capped by four $\{As^{III}W_9\}$ trilacunary fragments, leading to an assembly with T_d point-group symmetry (see Figures 1a, b). The structure of **1** somewhat resembles the tetra-Keggin polyanion $[Nb_4O_6(Nb_3SiW_9O_{40})_4]^{20-}$,[9] as well as the Wells-Dawson based tetramer $\{(Ti_3P_2W_{15})_4\}$,[10] which also have an overall tetrahedral shape. However, in **1** the lone pair of electrons on the As hetero atom in $\{B\text{-}\alpha\text{-}AsW_9O_{33}\}$ does not allow formation of a tri-Ti^{4+}-substituted Keggin unit. As a result, the four $\{B\text{-}\alpha\text{-}AsW_9O_{33}\}$ units in **1** are linked via six square-pyramidal TiO_5 groups, with the apical oxo ligand O12T ($d_{Ti2–O12T}$ = 1.75(2) Å) pointing at the centre of the polyanion, and bridging to the central, unique Ti^{4+} ion, which is hence octahedrally coordinated. As a result, **1** contains Ti^{4+} ions in two different coordination geometries, square-pyramidal and octahedral. In the other known polyanions containing square-pyramidal TiO_5 groups the apical oxygen is terminal.[5,11] The central Ti_7 core in **1** has an octahedral shape, with ideal bond angles of 90° and 180°, respectively, around the central Ti1 (see Figure 1c). For structural clarity, we can simplify the four $\{B\text{-}\alpha\text{-}AsW_9O_{33}\}$ groups in **1** as the four vertices of a regular tetrahedron, with the six five-coordinated Ti^{4+} ions being located at the edge centers, thus forming an ideal octahedron, surrounding the central, unique Ti^{4+} ion (see Figure 1d).

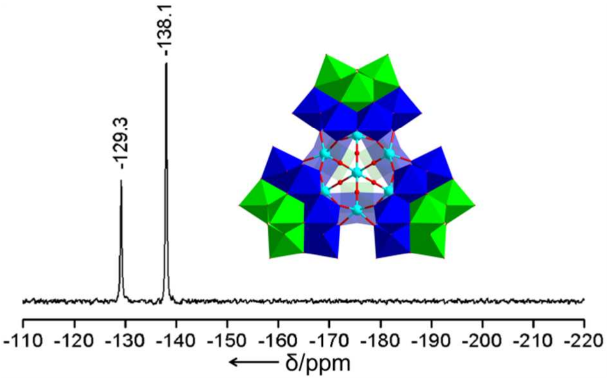

Figure 2. Room temperature ^{183}W NMR spectrum of **Na-1** in D_2O/H_2O. The signal at -129.3 ppm originates from the 12 capping tungstens (green WO_6 octahedra), whereas the signal at -138.1 ppm corresponds to the 24 equatorial tungstens (blue WO_6 octahedra).

As **Na-1** is well-soluble in water, we also performed ^{183}W NMR in D_2O/H_2O. The resulting spectrum (see Figure 2) consists of two singlets at -129.3 and -138.1 ppm, respectively, with relative intensities of 1:2, in complete agreement with the solid state structure of **1**, indicating that the tetrahedral assembly is maintained in solution.

These observations are further supported by UV-vis spectroscopy. The UV-vis spectrum of **Na-1** dissolved in water displays an absorption maximum at 256 nm (see Figure S5a), and we showed that polyanion **1** is stable in water and LiOAc solution at pH 4 - 7 for at least 24 hours (see Figures S5b-d).

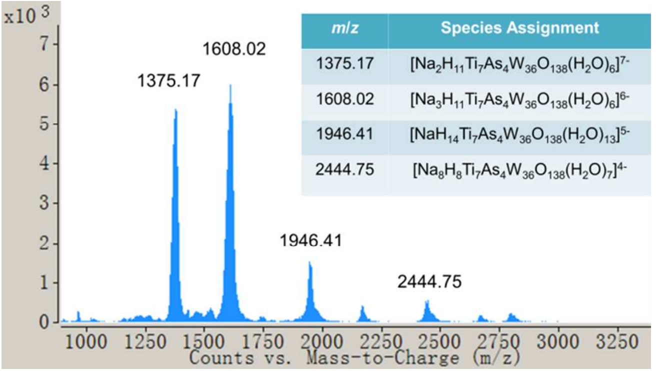

Figure 3. Negative ion mass spectrum of **Na-1** in water showing a series of species derived from $[Na_xH_yTi_7As_4W_{36}O_{138}(H_2O)_z]^{(20-x-y)-}$.

Electrospray-ionization mass spectrometry (ESI-MS) has proven to be a valuable analytical technique, allowing to extract structural information of POMs.[12] The major peaks observed in the ESI-MS spectrum of **Na-1** dissolved in water showed an ensemble of adducts derived from $[Na_xH_yTi_7As_4W_{36}O_{138}(H_2O)_z]^{(20-x-y)-}$ with different numbers of sodium ions, protons and water molecules associated with the title polyanion (see Figure 3). For instance, the most intense peaks centred at *m*/*z* 1375.17 and 1608.02, respectively, can be assigned to the 7- charged $[Na_2H_{11}Ti_7As_4W_{36}O_{138}(H_2O)_6]^{7-}$ and the 6- charged

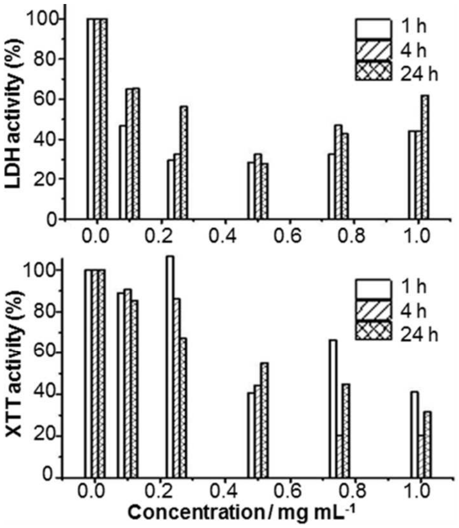

Figure 4. LDH (top) and XTT (bottom) assays of A431 cells incubated with **1** for different incubation times. Activity is expressed in percent (compared to control) and is related to the appropriate protein content. Data are means of 6 replicates for each POM concentration. SD ± 15%.

$[Na_3H_{11}Ti_7As_4W_{36}O_{138}(H_2O)_6]^{6-}$ adducts. These results further provide evidence of the high stability of polyanion **1** in solution, even allowing transfer to the gas phase.

We have also performed biological studies on **1**. It has been shown previously that Ti^{4+}-containing POMs can exhibit anticancer activities.[13] We investigated the cytotoxicity of **1** in the epidermoid carcinoma cell line A431 (see Figure 4). These *in vitro* studies indicated low cytotoxicity of **1** (EC50 ~2.5 mg/ml after 24 hours), in agreement with other Ti^{4+}-containing POMs.[14] However, there was neither cell growth nor death detectable. A reason for this could be poor cellular accumulation of **1**. Hence, it is likely that a main mechanism of the pharmacological effect of **1** is based on inhibiting the binding of native ligands to membrane receptors such as growth factors. Such possible interference in cell signaling and proliferation can be beneficial in cancer treatment.

In summary, we have prepared $[Ti_6(TiO_6)(AsW_9O_{33})_4]^{20-}$ (**1**), comprising a Ti_7 core comprising five- and six-coordinated Ti^{4+} ions, surrounded by four {*B*-*α*-AsW_9O_{33}} capping units, resulting in a tetrahedral assembly. The novel polyanion **1** was characterized by various analytical methods including single crystal X-ray diffraction, FTIR, UV-vis, TGA, NMR and ESI-MS. *In vitro* studies revealed low cytotoxicity in a model cancer cell line, but cell proliferation was inhibited. Currently we investigate these and other properties in more detail.

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Notes and references

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† Crystallographic data of **NaCs-1**: $C_4H_{150}As_4Cs_{2.5}Na_{19.5}O_{214}Ti_7W_{36}$, λ = 0.71073 Å, M = 11657.39, cubic, space group Fd-$3m$, a = 38.955(2) Å, V = 59114(9) $Å^3$, Z = 8, T = 100K, D_{calc} = 2.620 g cm^{-3}, μ = 14.985 mm^{-1}, 199037 total reflections, 2403 unique [R_{int} = 0.2058], final R_1 = 0.0482, wR_2 = 0.1217 [$I > 2\sigma(I)$]. CSD number: 427928.

Electronic Supplementary Information (ESI) available: synthetic details, XRD data, selected bond lengths and angles, FTIR, TGA, ^{13}C NMR, UV-vis, bond valence sum calculations, and toxicity test results. See DOI: 10.1039/c000000x/

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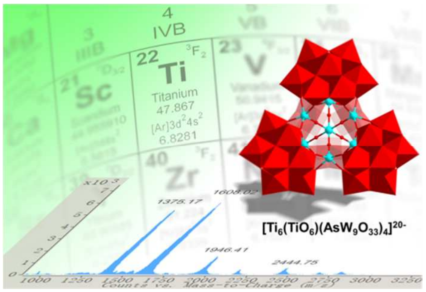

The Ti_7-containing $[Ti_6(TiO_6)(AsW_9O_{33})_4]^{20-}$ (**1**) comprises a central, octahedrally coordinated Ti^{4+} ion bridged to six square-pyramidally coordinated Ti^{4+} ions, and this titanium-oxo core is surrounded by four $\{AsW_9O_{33}\}$ capping units, resulting in an overall tetrahedral assembly. Polyanion **1** was characterized in solution and in the solid state by multiple techniques. *In vitro* studies revealed low cytotoxicity in a model cancer cell line, but inhibited cell proliferation.