anisotropically refined. For 4420 observed reflections [$I > 2\sigma(I)$] and 804 parameters the conventional R factor is 0.0593 ($wR_2 = 0.1627$ for 9410 independent reflections). Crystal structure analysis of **4**: ($C_{128}H_{132}Ca_3I_2N_{12}$) · C_7H_8 · 4(C_2H_3N), $M_r = 2468.85$, orthorhombic, space group *Pnna* (No. 52), $a = 16.566(3)$, $b = 34.562(7)$, $c = 24.996(5)$ Å, $V = 14312(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.146$ g cm^{-3}, $F(000) = 5152$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71070$ Å), $\mu(Mo_{K\alpha}) = 0.598$ mm^{-1}; crystal dimensions 0.13 × 0.10 × 0.07 mm. Data collection and solution of the structure was done as above. For 4480 observed reflections [$I > 2\sigma(I)$] and 742 parameters the conventional R factor is 0.1138 ($wR_2 = 0.3662$ for 9138 independent reflections). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-153000 (**3**) and -153001 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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$[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_6O_4)_2]^{4-}$: A Flexible, Pillared Oxothiotungstate Wheel[**]

Emmanuel Cadot,[*] Jérôme Marrot, and
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The design of clusters containing a large number of metal centers represents an intellectually stimulating challenge for the chemist since these compounds are situated at the boundary of molecular and condensed matter. The properties of such compounds are expected to envelop diverse fields such as biochemical processes,[1] catalysis,[2] and material science.[3] In this context, transition metal ringlike clusters based on the $\{M_2S_2O_2\}$ building block represent a fascinating emerging class of compounds.[4] Two years ago, we reported the synthesis and characterization of the neutral ring-shaped polyoxothio molybdenum compound $[Mo_{12}S_{12}O_{12}(OH)_{12}(H_2O)_6]$.[5] The cyclic architecture of this cluster delimits a central cavity which has a significant cationic character and is the origin of striking properties related to supramolecular[6] or host–guest chemistry.[7] Anionic reagents such as phosphate or dicarboxylate ions have been inserted into the cavity replacing the water molecules which initially line the cavity. This substitution led to size-controlled molecular wheels, distorted to a greater or lesser extent, and containing from eight[8] to twelve[9] molybdenum atoms. However, compared to heteropolyoxometalates, which are generally built upon Mo, W, and V centers,[10] cyclic oxothiocompounds are restricted exclusively to molybdenum, herein we aim to fill this void.

By acido–basic self-condensation of the $\{W_2S_2O_2\}^{2+}$ building block we have prepared compound **1** which is the largest known discrete cyclic oxothioanion. The W_{16} anion was synthesized through successive steps consisting of the formation of the oxothio precursor $[(S_x)_2W_2S_2O_2]^{2-}$ ($x = 2$, 4)[11] followed by the selective oxidation of the two terminal polysulfido ligands with stoichiometric amounts of iodine in DMF.[12] The acido–basic self-condensation was performed in the presence of glutarate which acts as a templating agent. The cesium salt of **1** was isolated as a pale yellow precipitate and after recrystallization at room temperature gave two types of crystals (**1a** and **1b**). A minimum of three weeks was required for the crystallization of orthorhombic crystals of **1a** while the monoclinic phase **1b** crystallized within two or three days.

$[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_6O_4)_2]^{4-}$ **1**

The compositions of **1a** and **1b** are quite similar, differing only in the water content. The molecular structure of **1** (Figure 1) consists of a cyclic neutral backbone $\{W_{16}S_{16}O_{16}(OH)_{16}\}$ (noted W_{16}) encapsulating two glutarate ions $[C_5H_6O_4]^{2-}$ (noted glu^{2-}). Eight $[W_2S_2O_2]^{2+}$ units are mutually connected by hydroxo double bridges giving two types of W···W separations in the cluster: short W–W distances within the building blocks (2.825(1)–2.818(1) Å) for **1a**; 2.813(1)–2.789(1) Å for **1b**) and long inter-block distances (3.413(1)–3.415(1) Å for **1a** and 3.298(1)–3.403(1) Å for **1b**. The two carboxylate groups are symmetrically arranged in the open cavity and exhibit the same type of binding mode with oxygen atoms bonded to the tungsten atoms. The cavity contains four water molecules, each being bonded to a tungsten atom through long $W{-}OH_2$ bonds (2.376(9) Å for **1a** and 2.363(10)–2.403(9) Å for **1b**). Probably because of steric constraints induced by the presence of the two glutarate ions in the cavity, four tungsten atoms adopt a pyramidal arrangement. Compounds **1a** and **1b** differ in their packing, the symmetry of the wheel is also significantly affected. In **1a** (orthorhombic), the discrete $\{W_{16}\}$ cluster has D_{2h} symmetry (Figure 1a) while in **1b** (monoclinic), the symmetry of the wheel is lowered to C_2 (Figure 1b). Both the structures are formally related through "soft" deformations which can be described as antiparallel stretching modes

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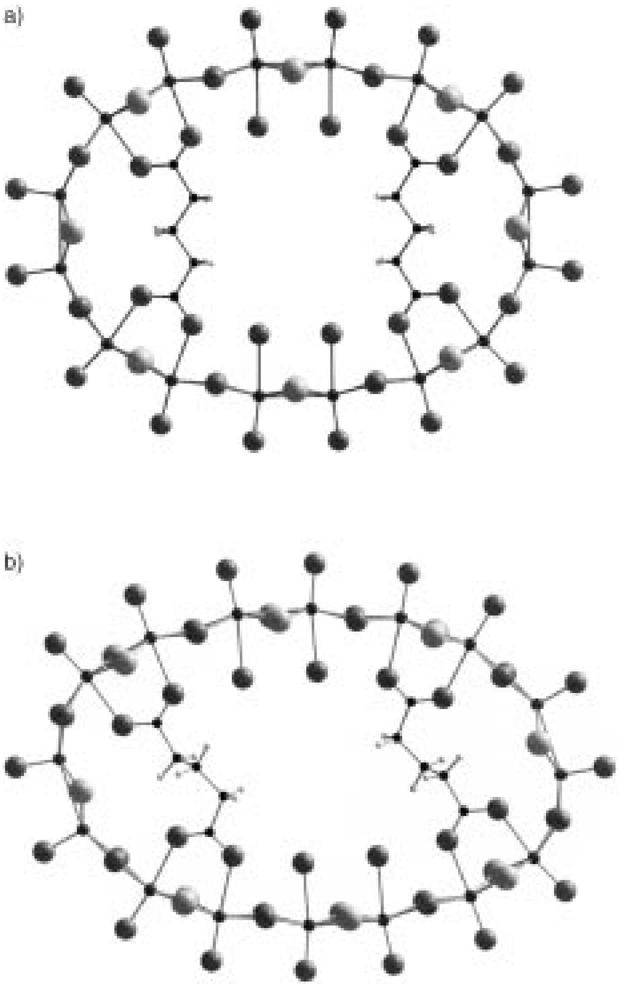

Figure 1. Ball and Stick representations of **1;** a) view of **1a** illustrating the regular $\{W_{16}S_{16}O_{16}(OH)_{16}\}$ elliptic backbone pillared by two glutarate anions; b) view of **1b** showing the distorted elliptic backbone with the two glutaric pillars: (small black sphere: C, small light-gray sphere = H, small dark-gray sphere = W, large light-gray sphere = S, large medium-gray sphere = O).

(Figure 2). Such a result illustrates the high flexibility of a cyclic arrangement, also observed in the analogous Mo_{12}-cyclic oxothiomolybdate compound[7]in which the $\{Mo_{12}\}$ ring can adopt circular or pronounced elliptic geometry provoking strong variations in the Mo-Mo-Mo angles which change from 150° to 130° and 180°.[5] The two conformations of $\{W_{16}\}$ can be viewed as two snapshots of the molecule, each reflecting the dynamic of the wheel in aqueous solution and the sensitivity of the system to weak interactions.

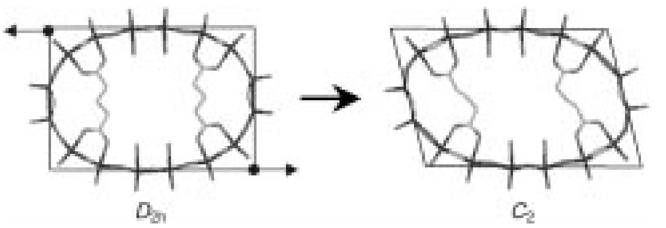

Figure 2. Schematic representation of the $D_{2h}-C_2$ correlation upon "soft" deformations: arrows symbolize the antiparallel stretching directions.

The ^1H NMR spectra of **1a** or **1b** in D_2O are shown in Figure 3. The encapsulation of the glu^{2-} ion by the $\{W_{16}\}$ ring is characterized by a significant shielding of the ^1H nuclei of the methylene unit of the glutarate alkyl chain ($\delta = 0.22$ and -0.26). Resonance signals corresponding to trace amounts of uncoordinated glu^{2-} ions indicate that template exchange can occur, but only in dilute solutions (0.005 M), and only to a small extent (uncoordinated glu^{2-} ions represent less than 2% of the resonance signals arising from the glu^{2-} ions). The effect of the concentration on the ^1H NMR spectra was studied (Figure 4). As the concentration of the $[W_{16}(glu)_2]^{4-}$ ion was increased, four broad resonances at $\delta = 0.5, 0.0, -0.2$ and -0.35 grew; the ^1H NMR spectra show clear features attributable to other glutarate-containing species revealing that equilibria exist involving the $[W_{16}(glu)_2]^{4-}$ ion. Infrared (solid state) and Raman (solution in H_2O) spectra are given in Figure 5. The Raman spectrum is dominated by intense bands corresponding to the $W{=}O_t$ stretching vibrations (971 cm^{-1} and 955 cm^{-1}) and to the $W{-}E_{br}$ breathing modes (E = S or O; 433 cm^{-1} and 418 cm^{-1}). Correlative with Raman features, the infrared spectrum displays in the inorganic region intense absorption bands at 952 cm^{-1}, 530 cm^{-1}, and 425 cm^{-1}, which were tentatively attributed to $W{-}O_t$, $W{-}E_{br}$ stretching vibrations, and $W{-}E_{br}$ breathing modes, respectively. The hydrolytic stability of the complex in solution was studied by UV/Vis spectroscopy. In the pH 4–6 range, the $[W_{16}glu_2]^{4-}$ ion appears stable, but acidification gives back the starting

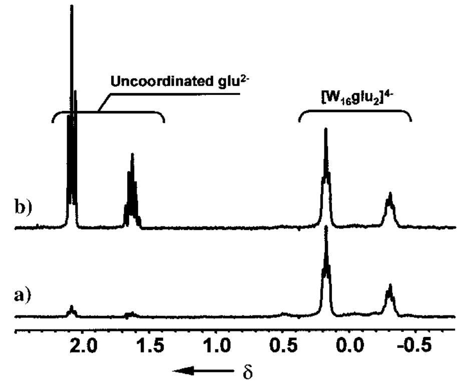

Figure 3. ^1H NMR spectra in D_2O of a) pure $Cs_4[W_{16}glu_2]$ and b) a mixture of $Cs_4[W_{16}glu_2]$ and glu^{2-}.

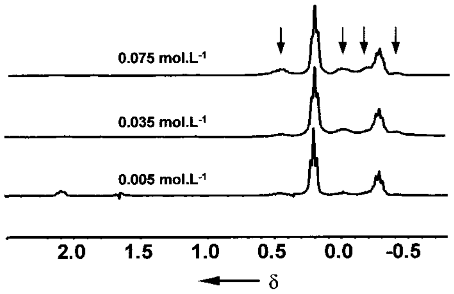

Figure 4. ^1H NMR spectra of $Li_4[W_{16}glu_2]$ in D_2O with variable concentrations in $Li_4[W_{16}glu_2]$. Arrows indicate the resonances attributable to other glu-containing species in equilibrium with $[W_{16}glu_2]^{4-}$.

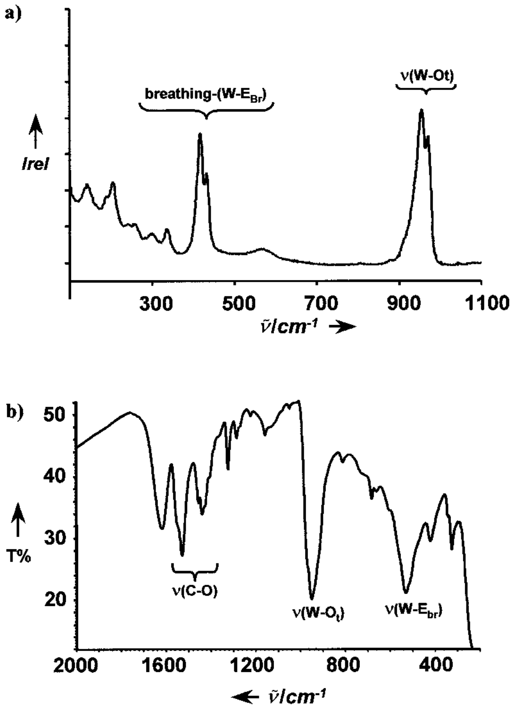

Figure 5. Vibrational spectra of $[W_{16}glu_2]^{4-}$: a) infrared spectrum of $Cs_4[W_{16}glu_2]$ in the solid state and b) Raman spectrum of $Li_4[W_{16}glu_2]$ in aqueous solution, t = terminal, br = bridging.

material $[W_2O_2S_2]^{2+}$ which slowly decomposes with H_2S evolution into insoluble unidentified products.

The results reported herein lead the way to original host–guest chemistry. The use of organic or inorganic templates not only permits the control of the nuclearity of the cyclic cluster (dimension of the wheel) but also the inclusion of specific anionic substrates, a property that is important in transport and extraction processes. Indeed, the possibility to enclose several molecules of substrate in the ring offers some perspectives in the field of homogeneous catalysis, with the inorganic cluster playing the role of a molecular reactor.

Experimental Section

Cs salt of **1**: Iodine (0.585 g; 2.30 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL) and slowly added to a stirred solution of $(NMe_4)_2[W_2O_2S_{10}]$ (1 g, 1.15 mmol) in dimethylformamide (10 mL). After the mixture was stirred for 60 min at room temperature, the resulting insoluble material (mainly solid sulfur and tetramethylammonium iodide) was removed by filtration and the red filtrate cooled to 0 °C to complete the precipitation of the remaining NMe_4I. Glutaric acid, $C_5H_8O_4$ (0.15 g; 0.75 mmol) was dissolved in distilled water (15 mL) and the pH of the solution was adjusted to five by addition of NaOH (1.6 mL; 1 molL^{-1}). The red solution was slowly added to the glutarate solution while the pH was maintened at five by dropwise addition of 1 molL^{-1} NaOH (about 2.4 mL of sodium hydroxide was added). The resulting turbid solution was clarified by filtration through a glass frit (D4). The crude product Cs-**1** (yellow solid) was precipitated by addition of cesium chloride (1 g; 6 mmol), collected by filtration, washed with ethanol and dried with diethyl ether (by suction), yield: 0.45 g (50 % based on W).

$Cs_4[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_6O_4)_2]\cdot 33H_2O$ (**1a**): Cs-**1** (0.2 g) was dissolved in hot water (about 50 °C; 30 mL). After cooling to room temperature, the solution was filtered. The crystallization vessel was covered with a film of paraffin, and the solution allowed to stand for crystallization at room temperature. After three weeks, rectangular parallalepipedic yellow crystals were isolated; yield: 0.06 g; elemental analysis calcd (%): Cs 9.78, W 54.07, S 9.41, C 2.20; found: Cs 10.08, W 54.03, S 9.45, C 2.12.

$Cs_4[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_6O_4)_2]\cdot 34H_2O$ (**1b**): Cs-**1** (0.2 g) was dissolved in hot water (about 50 °C; 20 mL). Then, the solution was filtered and allowed to stand for crystallization in the fume-hood. After three days, yellow diamond-shaped parallalepipedic crystals were isolated; elemental analysis calcd (%): Cs 9.74, W 53.90, S 9.38, C 2.19; found: Cs 10.37, W 54.15, S 9.33, C 2.03.

Synthesis of $Li_4[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_6O_4)_2]\cdot nH_2O$. The lithium salt was prepared from crystals of **1a** or **1b** which were dissolved in water and then passed through a cation exchange resin in Li^+ form (Dowex 50WX2). The resultant solution was evaporated to dryness. The purity of the Li salt was checked by ^1H NMR.

Crystal structure analysis: **1a**: crystal dimensions (0.26 mm × 0.14 mm × 0.10 mm); orthorhombic; space group *Pnnm*; $a = 11.7504(1)$, $b = 20.3808(2)$, $c = 24{,}9664(3)$ Å, $V = 5979.02(11)$ Å^3; $Z = 2$; total reflections collected: 32000; independent reflections: 7998; $R(\text{int}) = 0.0742$; a hemisphere of data was collected up to a $2\theta_{\max}$ value of 59.30° (92.50 % coverage); an empirical absorption correction was applied (SADABS), ($\mu = 16.883$ mm^{-1}; min/max transmission 0.0966/0.2831); structure solution with direct methods and refined by full-matrix least-squares procedure; 263 parameters; $R_1 = 0.0496$ for 5499 independent reflections ($F_o > 4\sigma(F_o)$); highest residual electron density 2.048 Å^3. **1b** : crystal dimensions (0.28 mm × 0.16 mm × 0.14 mm); monoclinic; space group $P2_1/n$; $a = 18.941(3)$, $b = 16.272(2)$, $c = 20.698(3)$ Å, $\beta = 107.728(11)°$, $V = 6076.2(14)$ Å^3; $Z = 2$; 40651 reflections; independent refections:15692; A hemisphere of data was collected up to a $2\theta_{\max}$ value of 59.45° (90.80 % coverage); an empirical absorption correction was applied (SADABS), ($\mu = 16.614$ mm^{-1}; min/max transmission 0.0898/0.2044); structure solution with direct methods and refined by full-matrix least-squares procedure (SHELX-TL package); 475 parameters; $R_1 = 0.0509$ for 7741 independent reflections ($F_o > 4\sigma(F_o)$); highest residual electron density 1.619 Å^3. The hydrogen atoms of the alkyl chain of the glutarate were located with geometrical restraints in the riding mode. The two crystals **1a** and **1b** were mounted in Lindemann tubes to prevent any water loss. Crystal data were collected at room temperature (293 K) with a Siemens SMART three-circle diffractometer equipped with a CCD bidimensionnal detector using $Mo_{K\alpha}$ monochromated radiation ($\lambda = 0.71073$ Å). An empirical absorption correction was applied (SADABS program) based on Blessing's method[13] and the structures were solved and refined with the SHELX-TL package.[14] The structural graphics were generated with the program DIAMOND 2.1 K (K. Brandeburg, Crystal Impact GbR, 1999). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-146999 (**1a**) and -147000 (**1b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Origin and True Nature of the Starter Unit for the Rapamycin Polyketide Synthase**

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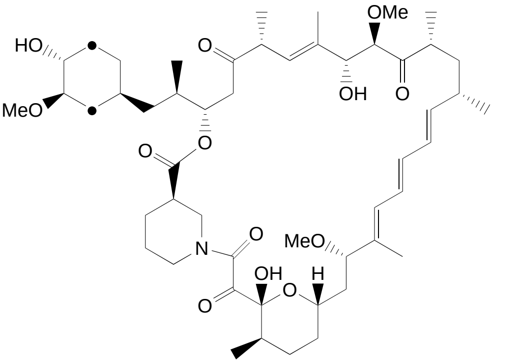
Peter F. Leadlay, and James Staunton*

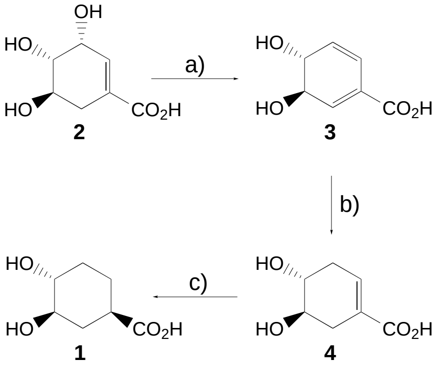
Rapamycin is a polyketide macrolide produced by *Streptomyces hygroscopicus* that displays potent immunosuppressant activity.[1] The recognition that such a property could be therapeutically useful has generated great interest in the chemistry[2] and biology[3] of rapamycin, and of the structurally similar immunosuppressants FK506 and FK520.

Rapid progress has been made in the manipulation of polyketide biosynthesis,[4] and the entire biosynthetic gene cluster for rapamycin has been sequenced.[5] The rapamycin polyketide synthase (PKS) is a modular system in which 14 chain extension modules are housed in three giant multimodular proteins (RAPS1–3).[4, 5] The polyketide origin of rapamycin has been verified through feeding studies with labeled precursors.[6] Rapamycin, FK506, and FK520 share in common an unusual substituted cyclohexane ring, the origins of which have been traced to shikimic acid for rapamycin[7] and FK520,[8] and which undergoes O-methylation post-PKS during the biosynthesis of FK506.[9] The proximal precursor for this unusual starter unit for rapamycin biosynthesis has been shown to be (1*R*,3*R*,4*R*)-3,4-dihydroxycyclohexanecarboxylic acid (**1**, DHCHC).[10] That the saturated molecule **1** is the starter unit of the rapamycin PKS brings into question the function of an apparently catalytically competent enoyl reductase domain (ER) present in the initiation module,[5] the structure of which is also conserved for the PKSs of FK506[11] and FK520.[12]



Rapamycin

The steps between shikimic acid (**2**) and **1** for FK520 have been elucidated and are described in Scheme 1.[8, 13] An initial *anti*-1,4-conjugate elimination of water from **2** provides (4*R*,5*R*)-4,5-dihydroxycyclohexa-1,5-dienecarboxylic acid (**3**). The α,β-double bond is then reduced in a *syn* fashion and the system subsequently undergoes a suprafacial 1,3-allylic rearrangement to form 4,5-dihydroxycyclohex-1-enecarboxylic acid (**4**). A final *anti* reduction of the conjugated double bond provides **1**. This pathway is related to that which was elucidated for the cyclohexanecarboxylic acid (CHC) precursor of ω-cyclohexyl fatty acids in *Alicyclobacillus acidocaldarius*[14] and of ansatrienin A in *Streptomyces collinus*.[15] Herein we will attempt to address the question of the identity of the intermediates between shikimic acid and **1** during rapamycin biosynthesis.



Scheme 1. Biosynthetic pathway to DHCHC (**1**) in FK520 and rapamycin. a) Stereospecific 1,4-*anti*-elimination of water; b) reduction of the Δ^1 double bond and isomerization of the remaining double bond from Δ^2 to Δ^1; c) reduction of the final Δ^1 double bond.

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