Published in final edited form as:

Inorganica Chim Acta. 2007 April 20; 360(6): 2115–2120.

Synthesis, Solution and Solid State Structure of Titanium-Maltol Complex

José L. Lamboy¹, Antonio Pasquale², Arnold. L. Rheingold², and Enrique Meléndez¹

¹University of Puerto Rico, Department of Chemistry PO Box 9019, Mayaguez, PR 00681

²University of California, San Diego Department of Chemistry and Biochemistry, San Diego, La Jolla, California 92093-0358

Abstract

The reaction of Cp_2TiCl_2 with two equivalents of maltol (3-hydroxy-2-methyl-4-pyrone) in water, at room temperature and pH of 5.4, leads to a complete replacement of Cp and chloride ligands affording, $\text{Ti}(\text{maltolato})_2(\text{OH})_2$. The complex has been characterized by IR, NMR and ESI-MS spectroscopic and cyclic voltammetry methods. In DMSO-d_6 solution, the complex shows two isomers in a ratio of 4:1, in which one OH signal can be identified per isomer. This suggests that in solution the complex is monomeric, most likely a chiral cis- $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ and trans- $\text{Ti}(\text{maltolato})_2(\text{OH})_2$. The monomeric nature of the complex (in water/methanol 1:1) was verified by ESI-MS spectroscopy, showing a parent peak at 329 m/z. Electrochemical behavior of $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ using cyclic voltammetry experiments showed the complex undergoes irreversible reduction in aprotic solvents. In D_2O solution, at pH of 8.4, the ^1H NMR spectrum of the complex shows a mixture of monomer and tetramer $\text{Ti}(\text{IV})$ -maltol complexes in a ratio of 1:1. The crystallization of $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ at pH of 8.4 leads to the formation of $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O}_4)] \cdot 18\text{H}_2\text{O}$. A single crystal of $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O}_4)] \cdot 18\text{H}_2\text{O}$ was analyzed by X-ray diffraction methods. The complex crystallizes in a monoclinic space group $\text{P2}(1)/c$ with $a = 12.617(4) \text{ \AA}$, $b = 24.058(8) \text{ \AA}$, $c = 22.686(7) \text{ \AA}$, $\beta = 97.678(4)^\circ$ and $V = 6824(4) \text{ \AA}^3$ for $Z = 4$. Solid state structure determination of the Ti-maltol complex showed to be tetrameric, containing two bridging oxides (in cis position) and two bidentate maltol ligands per titanium in a pseudo-octahedral coordination geometry.

Keywords

maltol; titanium(IV)-maltol; titanocene dichloride; budotitane

1. Introduction

Maltol (3-hydroxy-2-methyl-4-pyrone), is a naturally occurring, non-toxic compound and common food additive [1]. Many biologically important metals form stable complexes with maltol. Its stability arises from the easiness to deprotonate and to behave as an anionic, bidentate metal chelator. There are numerous metal-maltol complexes used in biomedical application. For instance, iron(III)-maltol complex has been used in the treatment of anemia [2] and tris (maltolato)aluminum complex has been found applications in the Alzheimer disease [3-5]. Perhaps the most significant is bis(maltolato)oxovanadium(IV), which has been the subject of

many chemical and physiological studies due to its potent insulinomimetic properties [6-8]. This complex is an excellent glucose- and lipid-lowering insulin mimetics and it is currently evaluated in clinical trials [6-8].

Titanium(IV) complexes are widely used for a variety of purposes, mainly as catalysts in a diversity of organic reactions [9-14]. But titanium(IV) complexes also have a role in the bioinorganic chemistry with two classical examples: titanocene dichloride (Cp_2TiCl_2) and budotitane ($\text{Ti}(\text{bza})_2(\text{OEt})_2$), which exhibit anti-cancer activities [15-25]. With the discovery of the biological properties of these two Ti(IV) complexes, many research groups have devoted their efforts to synthesize new titanium complexes with enhanced antitumor activity.

Titanocene dichloride and budotitane possess the same limitation, low hydrolytic stability at physiological pH [15,17,26]. As a result, the mechanistic aspects and hydrolysis products of these antitumor species remain mostly uncharacterized. The synthesis of hydrolytically stable Ti(IV) complexes at physiological pH (both organometallic and inorganic) with biological properties is still a challenge. Among oxygen containing chelating ligands, maltol has shown to form non-toxic complexes. Therefore, we synthesized, at low pH, a new Ti(IV)-maltol complex with two reactive OH ligands. At high pH, this species further reacts to form a tetrameric species. These complexes could have potential for applications in catalysis and in the biomedical field. Herein, we report our initial finding.

2. Results and Discussion

The synthesis of Ti(IV)-maltol complex was accomplished by interaction of titanocene dichloride with two equivalents of maltol in aqueous solution at pH 5.4, leading to the formation of $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ as a slightly water soluble yellow product.

Not surprisingly, Ti(IV) being a hard acid and oxyphilic, readily reacts with maltol, an oxygen containing chelating ligand, to form dihydroxobis(maltolato)titanium(IV) complex. The initial product was characterized by spectroscopic and electrochemical methods. IR spectrum for $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ shows four bands in the region of $1400\text{--}1620 \text{ cm}^{-1}$, which are typical of coordinated maltol ligand [27,28]. The band at 1660 cm^{-1} assigned to $\nu(\text{C}=\text{O})$ in free maltol is shifted to 1620 cm^{-1} while the combination bands of the $\nu(\text{C}=\text{O})$ and $\nu(\text{C}=\text{C})$ vibration modes at 1626 cm^{-1} and 1565 cm^{-1} are shifted to 1585 cm^{-1} and 1518 cm^{-1} . A broad band at 3396 cm^{-1} is observed and is attributed to the OH stretching.

To detect the exchangeable protons, ^1H NMR spectrum in DMSO-d_6 was recorded. Two broad signals corresponding to the OH protons are evident, in addition to two set of doublets for the H-5 and H -6 protons of each isomer in a ratio of 4:1 (cis:trans). Addition of D_2O into the DMSO-d_6 solution produces the disappearance of these broad singlets, indicating that these signals belong to exchangeable OH protons.

To assign signals on the ^1H NMR spectral data, we should consider few structural criteria. For the cis isomers, the limited symmetry of the complex conferred by two chelating maltolate and two mutually cis-hydroxo ligands, makes the metal center chiral. Given the fact that we observe two set of resonances for the maltolato and hydroxo ligands *at different ratios*, we can envision the presence of two different isomers with a C_2 axis or plane of symmetry. There are two possibilities: a mixture of two cis- $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ distereoisomers **IA** and **IB** (containing the maltol methyl groups in the same and opposite directions, syn and anti to each other) or a mixture of cis **IA** and trans- dihydroxobis(maltolato)titanium(IV) complex **IIA or IIB**.

Extrapolating from the X-ray results (vide infra), IA should exist in solution. This isomer exhibits one set of maltol H-5 and H-6 signals as well as one OH signal. IA has a C_2 rotation axis. Therefore, in DMSO- d_6 solution, the 1H NMR spectrum should have four signals: two doublets for H-5, H-6 and two singlets for OH and CH_3 protons. On the other hand, isomer IB lacks of a C_2 rotation axis or plane of symmetry and two sets of H-5 and H-6 signals should be observed (the maltol ligands are not magnetically equivalent) as well as 2OH and 2 CH_3 signals. Since this is not the case, the second isomer should be IIA or IIB, trans-Ti(maltolato) $_2$ (OH) $_2$, containing one set of H-5, H-6, OH and CH_3 signals.

The identity of these species in solution was investigated using ESI-MS spectroscopic techniques. In a mixture of $H_2O/MeOH$ we can easily identify the predominant species in solution as $[Ti(maltolato)_2(OH)_2 - H]^+$ with a parent peak at 329 m/z. Further fragmentation of this parent peak, by ion trap methodology, demonstrated the loss of OH ligand. Elemental analysis corroborated this formula. This strongly suggests that the complex in solution at low pH is monomeric.

Ti(maltolato) $_2$ (OH) $_2$ is slightly soluble in water at low pH (5.4). However, at pH of 8.4 the complex becomes soluble in water but promotes tetramerization of the $[Ti(maltolato)_2(OH)_2]$ species. In fact, this can be monitored by NMR spectroscopy. A pure sample of cis- $[Ti(maltolato)_2(OH)_2]$ was dissolved in D_2O at pH of 8.4. The 1H NMR spectrum of this solution showed two species in a ratio of 1:1. These two species belong most likely to cis- $[Ti(maltolato)_2(OH)_2]$ and $[Ti_4(maltolato)_8(\mu-O)_4]$. After 24 hours the tetrameric species continues increasing while the monomeric species decreases. Upon standing for two weeks, at pH of 8.4, this solution yields orange crystals suitable for X-ray diffraction. Evidently, Ti(maltolato) $_2$ (OH) $_2$ further reacts to form a tetranuclear titanium complex, which crystallizes as a hydrate, $[Ti_4(maltolato)_8(\mu-O)_4] \cdot 18H_2O$. Single crystal X-ray structure determination was

pursued on this high pH species. Figure 1 depicts the solid state structure. Tables 1 presents the crystal data and structure refinement details and Tables 2 presents the bonding parameters. Torsion angles are included in the supplementary material.

As shown by X-ray diffraction study, the subject compound is tetrameric. Solid state structure of $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$ consist of four Ti(IV) in a pseudo octahedral configuration linked by four oxo ligands. Similar structure but with guaiacolato ligand (a structural isomer of maltol) has been reported, $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$ [29]. The Ti_4O_4 moiety in $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$ is non-planar, with alternate bridging oxygens above and below the Ti_4 plane. Since the four Ti coordination spheres and bonding parameters are similar, although not identical, we will discuss only one unit, Ti(1). As mentioned previously, Ti(1) consists of a pseudo-octahedral configuration with two bidentate maltolate and two mutually cis- μ -oxo ligands.

Two sets of Ti-O bonds can be identified in the titanium-maltol interaction. The Ti-O (deprotonated) bonds (Ti-O(5) and Ti-O(2)) are trans to each other, with bond distances (Ti-O(5) 1.9583(17) Å and Ti-O(2) 1.9706(17) Å) substantially shorter than the Ti-O(ketonic) bonds (Ti-O(1) 2.1797(17) Å and Ti-O(4) 2.1495(17) Å). This demonstrates the greater coordination and donating ability of the hydroxyl oxygens compared to ketonic oxygens. Ti-O(oxo) bonds are almost identical, 1.799(16) and 1.8050(16) Å.

The chelating angles (O(4)-Ti(1)-O(5), 76.75(7)° and O(1)-Ti(1)-O(2), 76.64(6)°) are smaller than 90°, reflecting the strain created by the five member ring chelate while the cis-O(25)-Ti(1)-O(28) angle (100.18(7)°) shows a deviation of 10° from the octahedral angles. In terms of the maltolato ligand, there is a small lengthening in the C=O(ketone) bonds (C(1)-O(10) 1.266(3) Å and C(7)-O(4) 1.276(3) Å) compared to free maltol, 1.248-1.254 Å [30]. Within the maltol ring, carbon-carbon bond distances ranged from 1.328 to 1.436 Å. If we consider a typical single carbon-carbon bond with length of 1.54 Å and a double bond with 1.32 Å [31], it is evident that there is some degree of delocalization of the double bonds in the maltol ring.

If we compare the subject structure with the $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$ [29], we can observe several differences. First, the Ti-O(deprotonated) bonds of $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$ (1.901 Å) are shorter than Ti-O(deprotonated) bonds (1.9583(17) Å and 1.9706(17) Å) in $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$, while the Ti-O(alkoxy) bonds in guaiacol complex (2.273(11) Å and 2.289(12) Å) are longer than the Ti-O(ketonic) (2.1797(17) Å and 2.1495(17) Å) in the maltol complex, as a result of the different binding capabilities of these two oxygens. Second, the maltol ligands on adjacent titanium (i.e. Ti(1) and Ti(2) in $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$) are arranged parallel to each other while the guaiacolate ligands are arranged perpendicular in $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$. In the Ti_4O_4 moiety, $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$ has two alternate bridging oxygens (O(25) and O(27)) above and the other two (O(26) and O(28)), below the Ti_4 plane, while for $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$, two bridging oxygen are in the Ti_4 plane and the remaining two are one above and the other below the plane. On the other hand, similar expansion is observed in the cis-Ti-O(oxo) angles, 103° for $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$ and 100° for $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$.

Characterization of this tetrameric complex by NMR, IR and MS spectroscopic methods have been pursued. The ^1H NMR spectrum of the freshly dissolved $[\text{Ti}_4(\text{maltol})_8(\mu\text{-O})_4]$ crystals, in DMSO-d_6 , shows one species, corresponding to the tetramer. In D_2O , the crystals also showed one species corresponding to $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$ but after 3 hours, the presence of the cis-monomer is evident, reaching a ratio of the tetramer to cis-monomer of 7:1 (tetramer:monomer). This suggests that partial dissociation of the tetramer is taking place. The $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4] \cdot 18\text{H}_2\text{O}$ crystals are unstable and undergoes dehydration when removed from the mother liquor. Therefore, analytical data has been obtained consistent to

$[\text{Ti}_4(\text{maltolato})_8(\text{O})_4] \cdot 5.5\text{H}_2\text{O}$. This was further corroborated by TGA analysis which showed that this compound has five molecules of water (Supplementary Material). In addition, solution characterization by MS has been pursued. ESI-MS of this complex did not show a parent peak but showed fragments such as $[\text{Ti}(\text{maltolato})_2(\text{OTi})_2]^+$, 423.1 m/z and $[\text{Ti}(\text{maltolato})_2(\text{OH})]^+$, 315.1 m/z. This data suggests that the complex in solution tends to be monomeric at low pH, and in the solid state the species isolated at high pH is tetrameric.

Electrochemical behavior of $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ was investigated using cyclic voltammetry (cv). $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ in $\text{CH}_2\text{Cl}_2/[\text{NBu}_4][\text{BF}_4]$ showed an irreversible cathodic wave at a potential of (E_{red}) -1.36 V, suggesting irreversible reduction of Ti(IV) to Ti(III), while no anodic wave was detected up to the solvent-electrolyte discharge potential. If we compare this potential with previously reported Ti(IV)-maltol and Ti(IV)-guaiacol complexes [29], it resembles to reduction potentials of monomeric species such as $\text{Ti}(\text{maltolato})_2(\text{OEt})_2$ (-1.0 V) and $\text{Ti}(\text{maltolato})_2(\text{Cl})_2$ (-1.55 V) and not to the tetrameric species $[\text{Ti}_4(\text{guaiacolato})_8(\mu\text{-O})_4]$ (-1.94 V). This evidence further suggests that the complex isolated at low pH is monomeric. Attempts to characterize the $[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$ by cyclic voltammetry failed due to the lack of solubility in CH_2Cl_2 and, in solvents such as DMSO or water no anodic/cathodic waves were detected up to the solvent-electrolyte discharge potential.

3. Final remarks

The coordination capabilities of maltol to transition metal have been investigated for many years [1-8]. Maltol has proven to be a versatile and non-toxic chelating ligand that has made a major contribution to the bioinorganic chemistry and catalysis. Therefore, we investigated the coordinating capabilities of maltol to Ti(IV) center. First, maltol is able to replace organic ligands (in water) such as the well reputed Cp leading to the formation of a coordination compound. To our knowledge, this is the first tetrameric titanium(IV) complex containing maltolate ligand. Similar tertameric complex has been reported with the guaiacol, a structural isomer of maltol but the bonding patterns between these two complexes are different. As investigated by spectroscopic methods, this complex can exist as a mixture of the monomeric/tetrameric species and their ratio is a function of the solution pH. The fate of these Ti(IV)-maltol complexes in the bioinorganic chemistry or catalysis has not been determined at the present time but it is a area that we will be looking in the near future. In particular the antitumor properties of these species will be explored.

4. Experimental Section

4.1 Methods and Materials

Titanocene dichloride was handled under dried nitrogen in Schlenk type anaerobic lines. The Cp_2TiCl_2 complex was obtained from Aldrich and used without further purification. Maltol was obtained from Sigma-Aldrich and used as received. The purity of titanocene dichloride and maltol were checked by IR and/or by ^1H NMR spectroscopy. Water was doubly distilled, deionized and thoroughly saturated with dried nitrogen. All solvents for NMR measurements were 99.9% D purity grade. The dichloromethane (CH_2Cl_2) was distilled twice over CaH_2 and stored under nitrogen over molecular sieves.

4.2 Physical measurements

FTIR spectra were recorded on a Bruker Vector-22 spectrophotometer with the samples as compressed KBr discs. The ^1H spectra were recorded on a 500 MHz Avance Bruker spectrometers under controlled temperature. Tetramethylsilane (TMS) and 3-(trimethylsilyl)propanesulfonic acid (DSS) were used as internal reference. Mass spectral data was obtained on a Bruker Daltonics Esquire 6000. The complexes were dissolved in a mixture of water/

methanol (1:1) prior to mass spectral analysis. The electrospray positive ion was used as ionization mode during the MS experiment.

Electrochemical characterization was carried out on a BAS CV-50W voltammetric analyzer. Dichloromethane (Aldrich) was used as a solvent for all electrochemical experiments. Once the solvent was dried over calcium hydride and distilled under nitrogen, it was stored in a round bottom flask over molecular sieves. Tetrabutylammonium tetrafluoroborate ($[\text{NBu}_4][\text{BF}_4]$) (Aldrich) was used as supporting electrolyte in all electrochemical measurements. The supporting electrolyte was recrystallized from methanol and dried in vacuo prior to use.

A three-electrode configuration consisting of a glassy carbon working electrode, a platinum wire (Pt-wire) counter electrode, and a non-aqueous silver wire in contact with a solution of approximately (0.1M) $[\text{NBu}_4][\text{BF}_4]$ in dichloromethane (CH_2Cl_2) separated from the bulk solution by a fine glass frit as pseudo reference electrode. The internal reference is $[\text{Fe}(\text{C}_5\text{H}_5)_2]^{0/+}$ and potentials are quoted relative to SCE. The working electrode was polish with $0.05\mu\text{m}$ alumina slurry for 1-2 min, and then rinsed with deionized water. This cleaning process was done before each cyclic voltammetry (CV) experiment. A sweep between 1.9 and -2.0mV was performed.

The thermal analysis experiments were performed using a TAQ500 (TGA) instrument. The heating rate was $10^\circ\text{C}/\text{min}$ for TGA analysis.

4.3 Synthesis of dihydroxobis(maltolato) titanium(IV), $\text{Ti}(\text{maltolato})_2(\text{OH})_2$ complex

In 80 ml of deionized water, under nitrogen, was charged with 200 mg (1.6 mmol) of maltol and, 200 mg (0.80 mmol) of titanocene dichloride. The pH was adjusted to 5.4 with 0.1M NaOH. After 96hrs of stirring at room temperature, the reaction mixture was filtered and the yellow precipitate was dried under vacuum. Yield: 60 %. IR(KBr disc): 3396(br), 3074(w), 1620(m), 1586(s), 1518(m), 1476(s), 1276(s), 1246(w), 1204(m), 928(w), 854(sh), 796(m), 728(m), 630(w), 543(w), 475(w). ^1H NMR ($\text{DMSO}-d_6$, ambient, isomer I) δ : 8.273(bs, 1H), 6.529 (bs, 1H), 6.219(bs, 1H (OH)), 2.340 (bs, 3H). ^1H NMR ($\text{DMSO}-d_6$, ambient, isomer II) δ : 8.405 (d, 1H, $J = 5\text{ Hz}$), 7.999 (bs, 1H (OH)), 6.728 (d, 1H, $J = 5\text{ Hz}$), 2.395 (s, 3H). ^1H NMR (D_2O , pH 8.4, ambient, isomer I, monomer) δ : 8.066 (d, 1H, $J = 5\text{ Hz}$), 6.375 (d, 1H, $J = 5\text{ Hz}$), 2.457(s, 3H). ESI-MS (positive mode), m/z (relative intensity): $[\text{Ti}(\eta^2\text{-maltolato})_2(\text{OH})_2 - \text{H}]^+$ 327.2 (9.9), 328.2 (9.4), 329.1 (100), 330.1 (23), 331.1 (10.1); $[\text{Ti}(\eta^2\text{-maltolato})_2(\text{OH})]^+$, m/z (relative intensity): 313.1 (6.7), 314.1 (10.8), 315.0 (100), 316.0 (18.1), 317 (26.7). Anal. Calc. for $\text{C}_{12}\text{H}_{12}\text{O}_8\text{Ti}$: C, 43.40; H, 3.64. Found: C, 43.25; H, 3.64.

$[\text{Ti}_4(\text{maltolato})_8(\mu\text{-O})_4]$ (tetramer) IR(KBr disc): 3418(br), 3074(w), 2920(vw), 1619(s), 1587(vs), 1516(m), 1472(s), 1392(w), 1368(w), 1276(s), 1243(m), 1203(s), 1092(w), 1040(w), 928(w), 854(sh), 796(s), 722(s), 628(w), 610(w), 543(m), 469(w). ^1H NMR ($\text{DMSO}-d_6$, ambient) δ : 8.016 (d, 1H, $J = 5\text{ Hz}$), 6.350(d, 1H, $J = 5\text{ Hz}$), 2.389(s, 3H). ^1H NMR (D_2O , pH 8.4, ambient) δ : 7.835 (d, 1H, $J = 5.5\text{ Hz}$), 6.504 (d, 1H, $J = 5.5\text{ Hz}$), 3.42(bs, H_2O), 2.314(s, 3H). ESI-MS (positive mode): m/z (relative intensity): $[\text{Ti}(2\text{-maltolato})_2(\text{OTi})_2]^+$, 422.2 (12.1), 423.1 (100), 424.9 (31.1), 425.0 (13.6); $[\text{Ti}(2\text{-maltolato})_2(\text{OH})]^+$, 313.2 (5.8), 314.2 (7.3), 315.1 (100), 315.9 (46.3), 317.0 (8.5). Anal. Calc. for $[\text{Ti}_4(2\text{-maltolato})_8(\text{O})_4] \cdot 5.5\text{H}_2\text{O}$: C, 42.53; H, 3.79. Found: C, 42.70; H, 3.70.

4.4 X-ray crystallographic analysis

An orange plate cut to $0.30 \times 0.20 \times 0.20\text{ mm}$ in size was mounted on a cryoloop with Paratone® oil. Data was collected in a nitrogen gas stream at -173°C . Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.5° . Data collection was 99.9% complete to 25° in θ . A total of 57,671 reflections were collected covering the

indices, $h = -15$ to 15 , $k = -31$ to 30 , $l = -29$ to 28 . 15,416 reflections were found to be symmetry independent, with an R_{int} of 0.0702 indicating that the data was of average quality (0.07). Indexing and unit cell refinement indicated a P centered, monoclinic lattice. The space group was found to be $P 2_1/c$ (No. 14). The data was integrated using the Bruker SAINT software program and scaled using the Bruker SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model and their positions constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. 18 H₂O molecules co-crystallized with the target complex. The water molecules were treated by removal of their electron contributions using the Squeeze routine in the PLATON software package. A CIF file containing the refined cocrystallized waters involved in the hydrogen bonding are included as Supplementary Material.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

EM is grateful to the NIH-MBRS for financial support and NSF-MRI for providing funds for the 500 MHz NMR instrument.

References

1. Schenck JR, Speilmen MA. J. Am. Chem. Soc 1945;67:2276.
2. Ahmet MT, Frampton CS, Silver J. J. Chem. Soc., Dalton Trans 1988:1159.
3. Finnegan MM, Rettig SJ, Orvig C. J. Am. Chem. Soc 1986;108:5033.
4. Nelson WO, Karpishin TB, Rettig SJ, Orvig C. Inorg. Chem 1988;27:1045.
5. Yu P, Phillips BL, Olmstead MM, Casey WH. J. Chem. Soc. Dalton Trans 2002:2119.
6. Saatchi K, Thompson KH, Patrick BO, Pink M, Yuen VG, McNeill JH, Orvig C. Inorg. Chem 2005;44:2689. [PubMed: 15819554]
7. Thompson KH, Chiles J, Yuen VG, Tse J, McNeill JH, Orvig C. J. Inorg. Chem 2004;98:683.
8. Thompson KH, Liboiron BD, Sun Y, Bellman KDD, Setyawati IA, Patrick BO, Karunaratne V, Rawji G, Wheeler J, Sutton K, Bhanot S, Cassidy C, McNeill JH, Yuen VG, Orvig C. J. Biol. Inorg. Chem 2003;8:66. [PubMed: 12459900]
9. Duthaler RO, Hafner A. Chem. Rev 1992;92:807.
10. Qian Y, Huang J, Bala MD, Lian B, Zhang H, Zhang H. Chem. Rev 2003;103:2633. [PubMed: 12848582]
11. Beckhaus R, Santamaría C. J. Organometal. Chem 2001;617-618:81.
12. Vites JC, Lynam MM. Coord. Chem. Rev 1995;138:71.
13. Vites JC, Lynam MM. Coord. Chem. Rev 1995;146:1.
14. Manek E, Hinz D, Meyer G. Coord. Chem. Rev 1997;164:5.
15. Keppler BK, Friesen C, Moritz HG, Vongerichten H, Vogel E. Struct. Bonding 1991;78:97-127.
16. Clarke MJ, Zhu F, Frasca DR. Chem. Rev 1999;99:2511. [PubMed: 11749489]
17. Schilling T, Keppler BK, Heim ME, Niebch G, Dietzfelbinger H, Rastetter J, Hanauske AR. Invest. New Drugs 1996;13:327. [PubMed: 8824351]
18. Köpf H, Köpf-Maier P. Angew. Chem. Int. Ed. Engl 1979;18:477. [PubMed: 111586]
20. Köpf-Maier P. Eur. J. Clin. Pharmacol 1994;47:1. [PubMed: 7988618]
21. Köpf-Maier P, Köpf H. Structure and Bonding 1988;70:103.
22. Köpf-Maier P, Köpf H. Chem. Rev 1987;87:1137.

23. Köpf-Maier, P.; Köpf, H. Metal Compounds in Cancer Therapy, Organometallic Titanium, Vanadium, Niobium, Molybdenum and Rhenium Complexes - Early Transition Metal Antitumor Drugs. Fricker, SP., editor. Chapman and Hall; London: 1994. p. 109-146.
24. Harding MM, Mokdsi G. Current Medicinal Chemistry 2000;7:1289. [PubMed: 11032972]
25. Meléndez E. Crit. Rev. Onc. Hem 2002;47:309.
26. Toney JH, Marks TJ. J. Am. Chem. Soc 1985;107:947.
27. Hsieh W-Y, Zaleski CM, Pecoraro VL, Fanwick PE, Liu S. Inorg. Chim. Acta 2006;359:228.
28. Lord SJ, Epstein NA, Paddock RL, Vogels CM, Hennigar TL, Zaworotko MJ, Taylor NJ, Driedzic WR, Broderick TL, Westcott SA. Can. J. Chem 1999;77:1249.
29. Sobota P, Przybylak K, Utko J, Jerzykiewicz LB, Pomberio AL, Guedes da Silva MFC, Szczegot K. Chem. Eur. J 2001;7:951.
30. Burges J, Fawcett J, Russell DR, Hider RC, Hossain MB, Stoner CR, Van der Helm D. Acta Cryst 1996;C52:2917.
31. Pauling, L. The Nature of the Chemical Bond. third edition. Cornell University Press; Ithaca, New York: 1960.

Figure 1. Solid state structure of $[\text{Ti}_4(2\text{-maltol})_8(\mu\text{-O})_4] \cdot 18\text{H}_2\text{O}$. Water molecules have been removed for clarity.

Table 1Crystal data and structure refinement for $[\text{Ti}_4(2\text{-maltol})_8(\mu\text{-O})_4] \cdot 18\text{H}_2\text{O}$.

Empirical formula	C48 H76 O46 Ti4	
Formula weight	1580.69	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.617(4) Å	$\alpha = 90^\circ$.
	b = 24.058(8) Å	$\beta = 97.678(4)^\circ$.
	c = 22.686(7) Å	$\gamma = 90^\circ$.
Volume	6824(4) Å ³	
Z	4	
Density (calculated)	1.538 g/mL	
Absorption coefficient	0.559 mm ⁻¹	
F(000)	3280	
Crystal size	0.30 × 0.30 × 0.20 mm ³	
Theta range for data collection	2.14 to 27.56°	
Index ranges	-15 ≤ h ≤ 15, -31 ≤ k ≤ 30, -29 ≤ l ≤ 28	
Reflections collected	57671	
Independent reflections	15416 [R(int) = 0.0702]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8964 and 0.8503	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	15416 / 0 / 729	
Goodness-of-fit on F ²	0.914	
Final R indices [I > 2sigma(I)]	R1 = 0.0459, wR2 = 0.1031	
R indices (all data)	R1 = 0.0708, wR2 = 0.1094	
Largest diff. peak and hole	0.467 and -0.332 e.Å ⁻³	

Table 2
Selected bond lengths [$\text{\AA}$] and angles [$^{\circ}$] for $[\text{Ti}_4(\eta^2\text{-maltol})_8(\mu\text{-O})_4] \cdot 18\text{H}_2\text{O}$.

C(1)-O(1)	1.266(3)
C(1)-C(2)	1.428(3)
C(1)-C(5)	1.436(3)
C(2)-C(3)	1.328(3)
C(3)-O(3)	1.331(3)
C(4)-C(5)	1.352(3)
C(4)-O(3)	1.367(3)
C(4)-C(6)	1.484(3)
C(5)-O(2)	1.324(3)
O(1)-Ti(1)	2.1797(17)
O(2)-Ti(1)	1.9706(17)
O(4)-Ti(1)	2.1495(17)
O(5)-Ti(1)	1.9583(17)
O(25)-Ti(1)	1.7990(16)
O(25)-Ti(2)	1.8141(16)
O(28)-Ti(1)	1.8050(16)
O(28)-Ti(4)	1.8065(16)
Ti(1)-O(25)-Ti(2)	148.37(10)
Ti(1)-O(28)-Ti(4)	151.45(10)
O(25)-Ti(1)-O(28)	100.18(7)
O(25)-Ti(1)-O(5)	103.16(7)
O(28)-Ti(1)-O(5)	91.73(7)
O(25)-Ti(1)-O(2)	90.91(7)
O(28)-Ti(1)-O(2)	104.30(7)
O(5)-Ti(1)-O(2)	156.55(7)
O(25)-Ti(1)-O(4)	91.30(7)
O(28)-Ti(1)-O(4)	165.38(7)
O(5)-Ti(1)-O(4)	76.75(7)
O(2)-Ti(1)-O(4)	84.37(7)
O(25)-Ti(1)-O(1)	166.92(7)
O(28)-Ti(1)-O(1)	86.97(7)
O(5)-Ti(1)-O(1)	87.43(6)
O(2)-Ti(1)-O(1)	76.64(6)
O(4)-Ti(1)-O(1)	83.60(7)