DOI: 10.1002/ejic.200701233

Preparation and X-ray Structures of Ti^{IV} Complexes of Bis(carboxylato) Ligands – Formation of Mono-, Di-, Tetra-, and Hexanuclear Complexes with or without OR and μ-O Ligands

Michal Shavit[a] **and Edit Y. Tshuva***[a]

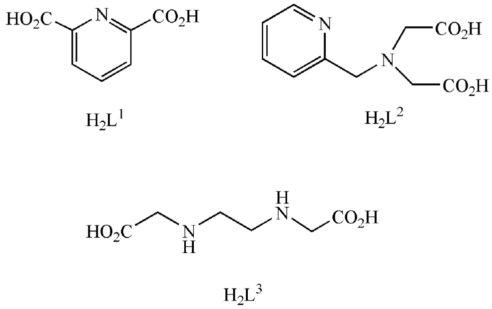
Keywords: Titanium(IV) / Carboxylato ligands / Oxido ligands / Cluster compounds / Coordination modes

Treating the amine bis(carboxylato) ligand precursor pyridine-2,6-dicarboxylic acid (H_2L^1) with titanium tetra(isopropoxide) gave the mononuclear octacoordinate complex $L^1{}_2Ti^{IV}(dmf)_2$ (**1**), in which each carboxylato ligand binds in an η^1 fashion and two solvent molecules are also coordinated to the metal. In contrast, employing the diamine bis(carboxylic acid) ligand precursor H_2L^2 gave a unique hexanuclear Ti^{IV} complex $[Ti^{IV}{}_6(O\mathit{i}Pr)_{16}(\mu_2\text{-}O\mathit{i}Pr)_4(\mu\text{-}L^2)_2]$ (**2**), where L^2 = (pyridin-2-ylmethyl)amino diacetate. The crystal structure reveals that all Ti^{IV} atoms exhibit octahedral geometry, where both carboxylate and isopropoxide groups serve as bridging ligands. Surprisingly, no oxido ligands appear in the structure, which indicates that the complex, obtained at room temp., was not exposed to any traces of water. The diamine bis(carboxylato) ligand coordinates in η^2 modes of both carboxyl groups to give a total of six coordination sites. Employing the same ligand with a slight change in reaction conditions, which included heating to 35 °C, led to the formation of two *O*-bridged complexes: dinuclear $[Ti^{IV}{}_2(\mu_2\text{-}O)(O\mathit{i}Pr)_2(L^2)_2]$ (**3**) and tetranuclear $[Ti^{IV}{}_4(\mu_2\text{-}O)_4(L^2)_4]$ (**4**), where each bis(carboxylato) ligand binds to a single Ti center in an η^1 fashion, and the only bridging ligands are oxide groups, with Ti–O–Ti angles of 180.0° and 166.6° for **3** and **4**, respectively, indicating π interactions in the dinuclear species. Employing a different diamine bis(carboxylato) ligand featuring a sequential connectivity of donor atoms allowed the identification of a mononuclear C_2-symmetrical bis(isopropoxido) complex, $L^3Ti^{IV}(O\mathit{i}Pr)_2$, (**5**) where L^3 = ethylenediamine diacetate. In **5**, as opposed to **2** and similarly to **1**, **4**, and **5**, the carboxylato ligand binds in an η^1 fashion. Complexes **3**, **4**, and **5** are all inactive against ovarian OVCAR-1 and colon HT-29 cells.

Introduction

Simple carboxylato ligands are known to support mononuclear Ti^{IV} structures,[1] but they may also form polynuclear Ti^{IV} clusters under suitable reaction conditions, where the carboxylato unit may bind in an η^2 mode and frequently bridges two Ti^{IV} centers.[2–8] Such clusters may be of various structures and symmetries, even when quite similar carboxylato units are employed. Generally, in such clusters oxide groups also bridge two or three Ti^{IV} ions,[2–11] in addition to alkoxide groups (OR) that may function as bridging or terminal ligands.[2–8] The oxide groups are excellent ligands for the oxidophilic Ti^{IV} metal and thus add to the total thermodynamic stability of the complex and serve as a driving force for cluster formation. These oxido ligands usually come from traces of water molecules in the reaction mixture.[3,5,6,8]

The antitumor activity observed for complexes of the type L_nTiX_2 (n = 1,2; X = Cl, OR)[12–18] prompted us to investigate the conditions required to prepare well-defined Ti^{IV} complexes of chelating bis(carboxylato) ligands[19–25] for such applications. For this purpose, we employed the amine bis(carboxylato) ligand and the two diamine bis(carboxylato) ligands presented in Scheme 1. Herein we report several mono- and polynuclear structures obtained with these ligands under varying reaction conditions.



Scheme 1.

Results and Discussion

The 2,6-pyridine dicarboxylato (L^1, Scheme 1) ligand, featuring a single coordinative N-donor in addition to the two carboxylato groups, may be regarded as a tridentate

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[a] Institute of Chemistry, The Hebrew University of Jerusalem,
91904 Jerusalem, Israel
Fax: +972 2 6584282
E-mail: tshuva@chem.ch.huji.ac.il

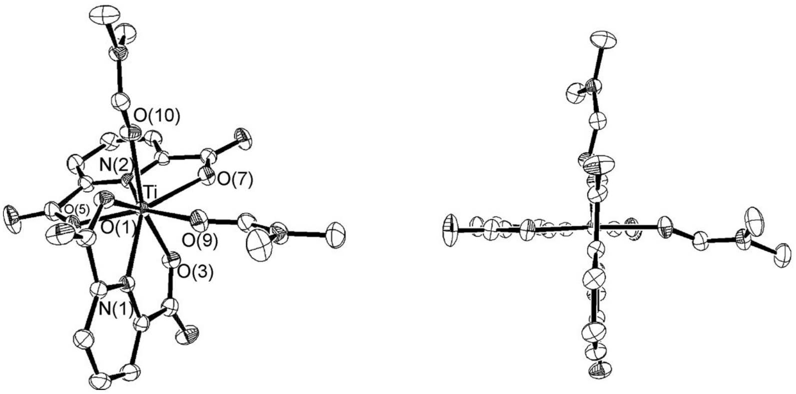


Figure 1. ORTEP drawing of $L^1_2Ti^{IV}(dmf)_2$ (**1**) with 50% probability ellipsoids, presented from two angles (H atoms and an additional solvent molecule were omitted for clarity in both drawings).

ligand to a single metal ion where binding in an η^1 fashion of the carboxylato groups is expected because of the rigidity of the ligand, or as a pentadentate bridging ligand if both carboxylato units bind in an η^2 mode. We thus were interested in examining the coordination features of such a ligand to a Ti^{IV} center, in terms of nuclearity and ligand-to-metal ratio.

When H_2L^1 was treated with titanium tetra(isopropoxide) in thf, an orange crystalline product was obtained. Single crystals suitable for X-ray crystallography were grown from dmf, and the crystal structure (Figure 1) revealed the product to be $L^1_2Ti^{IV}(dmf)_2$ (**1**). Selected bond lengths and angles are presented in Table 1.

Table 1. Selected bond lengths [Å] and angles [°] for $L^1_2Ti^{IV}(dmf)_2$ (**1**).

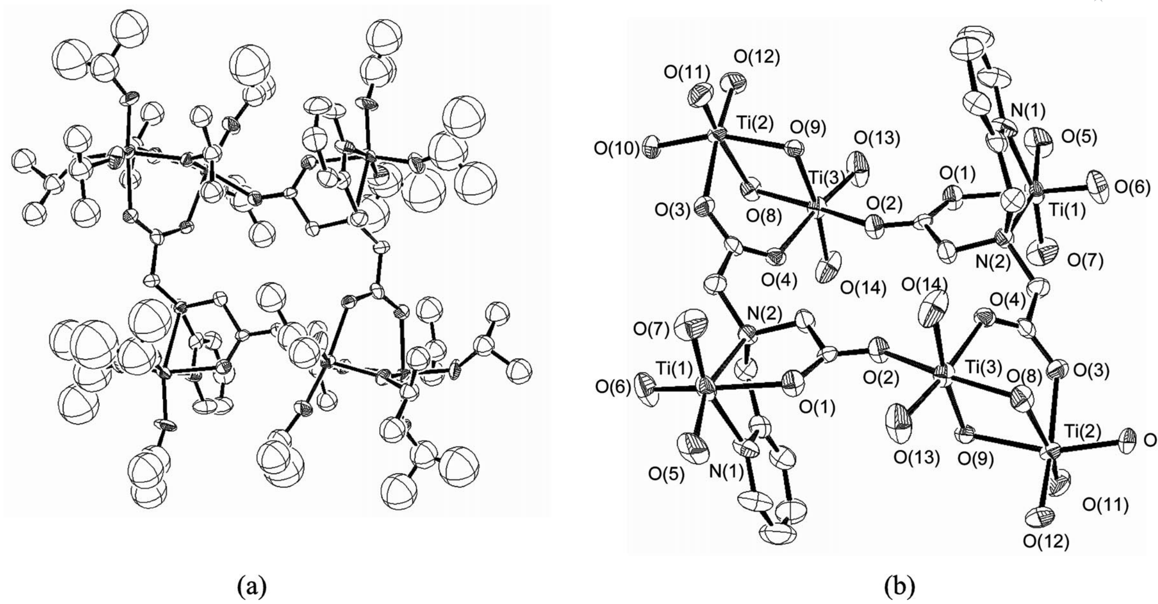
Lengths			
O(1)–Ti	2.1176(12)	O(9)–Ti	2.0964(12)
O(3)–Ti	2.0116(12)	O(10)–Ti	2.1046(12)
O(5)–Ti	2.0128(12)	N(1)–Ti	2.1911(13)
O(7)–Ti	2.0862(12)	N(2)–Ti	2.1905(13)
Angles			
O(3)–Ti–O(5)	94.51(5)	O(1)–Ti–N(1)	70.70(5)
O(3)–Ti–O(7)	78.17(5)	O(3)–Ti–N(1)	71.52(5)
O(5)–Ti–O(7)	142.30(5)	O(5)–Ti–N(1)	77.42(5)
O(3)–Ti–O(9)	95.03(5)	O(7)–Ti–N(1)	132.01(5)
O(5)–Ti–O(9)	143.60(5)	O(9)–Ti–N(1)	72.54(5)
O(7)–Ti–O(9)	74.10(5)	O(10)–Ti–N(1)	144.46(5)
O(3)–Ti–O(10)	143.82(5)	O(1)–Ti–N(2)	133.29(5)
O(5)–Ti–O(10)	92.17(5)	O(3)–Ti–N(2)	74.08(5)
O(7)–Ti–O(10)	74.97(5)	O(5)–Ti–N(2)	71.39(5)
O(9)–Ti–O(10)	100.37(5)	O(7)–Ti–N(2)	71.04(5)
O(3)–Ti–O(1)	142.20(5)	O(9)–Ti–N(2)	144.90(5)
O(5)–Ti–O(1)	76.38(5)	O(10)–Ti–N(2)	74.54(5)
O(7)–Ti–O(1)	130.29(5)	N(1)–Ti–N(2)	130.83(5)
O(9)–Ti–O(1)	74.63(5)		
O(10)–Ti–O(1)	73.84(5)		

The structure features a mononuclear Ti^{IV} center with a coordination number of eight resulting from additional coordination of two dmf solvent molecules. This is rather an unusually high coordination number, considering the small radius of the Ti^{IV} ion, especially since monodentate coordinative ligands are involved.[26–30] Due to the rigidity of the L^1 ligand and its inability to bind in an η^2 mode to a single Ti^{IV} center, two tridentate bis(carboxylato) ligands are required to complete the coordination sphere of the Ti^{IV} ion, where all carboxylato ligands bind in an η^1 mode. Somewhat surprisingly, all Ti–O bond lengths, including those of the coordinative dmf molecules as well as those of the covalent carboxylato units, are within the range 2.0–2.1 Å. The relatively long covalent bonds are thus a result of the high coordination number. Each dmf molecule is coplanar with one of the carboxylato ligands, and the two planes are approximately perpendicular to one another with a maximal value for distortion of 10° (Figure 1). This structure may thus be considered as a distorted dodecahedron.

Since we generally aim for complexes of the type $LTiX_2$, which include two monodentate labile ligands on a coordinatively saturated Ti^{IV} center, we turned to diamine bis(carboxylato) ligands featuring a second coordinative N-donor. We thus treated titanium tetra(isopropoxide) with one equivalent of (pyridin-2-ylmethyl)amino diacetic acid (H_2L^2)[31] (Scheme 1) in toluene as the solvent. The free ligand demonstrated incomplete solubility in toluene, and thus its effective concentration in solution throughout the reaction was lower than that of the Ti^{IV} species. The reaction mixture was allowed to stir at room temp. for several days, and the product was crystallized from toluene at –35 °C. Single crystals were obtained, which, despite their poor quality, allowed structure characterization by X-ray crystallography, and the ORTEP structure of product **2** is presented in Figure 2. A schematic chemical representation of **2** is shown in Scheme 2, and a list of selected bond lengths and angles is presented in Table 2.

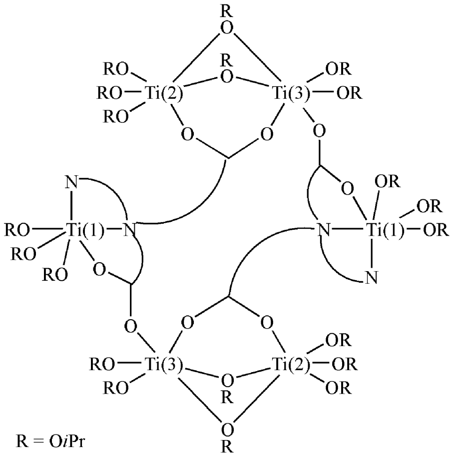
The X-ray structure indicates formation of a compound of the general unique structure $[Ti^{IV}_6(O\textit{i}Pr)_{16}(\mu_2\text{-}O\textit{i}Pr)_4(\mu_4\text{-}L^2)_2]$. The cluster has a crystallographic inversion center *i* and thus only three different Ti ions are observed, and they are marked as Ti(1), Ti(2) and Ti(3), while their counterparts are marked Ti(1_2), Ti(2_2) and Ti(3_2). The symmetry assigned to this complex is thus C_i.

The six Ti^{IV} centers of this hexamer all manage to complete an octahedral coordination sphere with a total charge of zero. Only two diamine bis(carboxylato) ligands are present in the structure. Each one binds through all six possible coordination sites; the carboxylato units bind in an η^2 mode



(a) (b)

Figure 2. ORTEP drawing of $[Ti^{IV}_6(OiPr)_{16}(\mu_2\text{-}OiPr)_4(\mu\text{-}L^2)_2]$ (**2**) with 50% probability ellipsoids, presented in full (a) and where isopropyl groups were omitted for clarity (b). H atoms and disorder were also omitted in both schemes.



Scheme 2.

and bridge two Ti^{IV} centers each. Altogether, each such ligand coordinates to four different Ti^{IV} ions (Scheme 2). Each one of the four oxygen donors in the two carboxylato units binds to a different Ti atom, while one of these four Ti^{IV} centers also accepts the coordination from the two nitrogen donors on the ligand. Isopropoxide groups are found to bridge two metal centers, these are the two that are not bound to the diamine moiety, but are also bridged by one carboxylato unit of the diamine ligand, forming altogether two pairs of carboxylato-bridged, bis(alkoxido)-bridged dinuclear species in the general bigger structure. One of these Ti centers is bound to an additional oxygen donor from the second diamine bis(carboxylato) ligand and is bridged by this carboxylato ligand to the third Ti canter which allows the entire structure to hold together as a hexamer. The Ti(2)···Ti(3) distance for the dinuclear core is 3.24 Å, which is typical of bridged dinuclear Ti^{IV} centers.[3,5,7,8] The four Ti atoms, marked Ti(1), Ti(1_2), Ti(3) and Ti(3_2), are coplanar, while the approximate planar array of the dinuclear $[(\mu_2\text{-}OiPr)_2Ti_2]$ moiety, which includes Ti(2) and Ti(3), is approximately perpendicular to the plane containing them. Surprisingly, no additional oxido ligands were found to hold this structure together, which indicates that no traces of water were present during formation of **2** and esterification reactions do not occur under the conditions employed.[3,5,6,8] The Ti(1)···Ti(3_2) distance for the ions bridged only by a carboxylato unit (Scheme 2) is 5.70 Å, whereas other Ti···Ti distances were found to be Ti(1)···Ti(2): 7.55 Å and Ti(1)···Ti(3): 7.23 Å. The coordination sphere of all Ti centers is completed by two or three additional terminal isopropoxido ligands per nuclei, while no μ_3-O ligands are found. Additional bond lengths and angles mostly have typical values (Table 2).

Ti^{IV} complexes having no bridging oxide groups are rare,[32–34] especially among complexes with nuclearity higher than two.[11,35] Some other single-atom bridges, such as chlorido or fluorido, are also known; however, they normally do not hold clusters of more than two Ti^{IV} centers.[33–35] To the best of our knowledge, this particular core structure is unprecedented.

Using the same reactants and only applying slightly different reaction conditions led to a different product. Treating H_2L^2 with one equivalent of titanium tetra(isopropoxide) in thf, in which enhanced solubility was observed, and heating to 35 °C overnight led to the formation of $[Ti^{IV}_2(\mu_2\text{-}O)(OiPr)_2(L^2)_2]$ (**3**), which crystallized from a thf/hexane mixture at room temp. The X-ray structure of **3** is presented in Figure 3, and a list of selected bond lengths and angles is summarized in Table 3.

The structure of **3** features a dinuclear Ti^{IV} center with C_i symmetry that does not include bridging carboxylato ligands but is rather bridged solely by a single oxido ligand,

Table 2. Selected bond lengths [Å] and angles [°] for [$Ti^{IV}_6(OiPr)_{16}(\mu_2\text{-}OiPr)_4(\mu\text{-}L^2)_2$] (**2**).

Lengths			
N(1)–Ti(1)	2.278(9)	O(10)–Ti(2)	1.829(6)
N(2)–Ti(1)	2.362(7)	O(11)–Ti(2)	1.805(7)
O(1)–Ti(1)	2.093(6)	O(12)–Ti(2)	1.807(7)
O(2)–Ti(3)	2.103(6)	O(13)–Ti(3)	1.768(7)
O(3)–Ti(2)	2.156(6)	O(14)–Ti(3)	1.818(8)
O(4)–Ti(3)	2.131(6)		
O(5)–Ti(1)	1.790(7)		
O(6)–Ti(1)	1.793(8)		
O(7)–Ti(1)	1.779(8)		
O(8)–Ti(3)	1.925(6)	*Ti(2)···Ti(3)*	*3.24*
O(8)–Ti(2)	2.156(7)	*Ti(1)···Ti(2)*	*7.55*
O(9)–Ti(3)	2.038(6)	*Ti(1)···Ti(3)*	*7.23*
O(9)–Ti(2)	2.055(6)	*Ti(1)···Ti(3_2)*	*5.70*
Angles			
O(7)–Ti(1)–O(5)	105.3(4)	O(11)–Ti(2)–O(3)	88.4(3)
O(7)–Ti(1)–O(6)	100.7(4)	O(12)–Ti(2)–O(3)	171.7(3)
O(5)–Ti(1)–O(6)	103.6(4)	O(10)–Ti(2)–O(3)	83.9(3)
O(7)–Ti(1)–O(1)	90.8(3)	O(9)–Ti(2)–O(3)	81.5(2)
O(5)–Ti(1)–O(1)	92.5(3)	O(8)–Ti(2)–O(3)	82.4(2)
O(6)–Ti(1)–O(1)	156.8(3)	O(13)–Ti(3)–O(14)	97.4(4)
O(7)–Ti(1)–N(1)	162.1(3)	O(13)–Ti(3)–O(8)	102.0(3)
O(5)–Ti(1)–N(1)	88.8(4)	O(14)–Ti(3)–O(8)	101.0(3)
O(6)–Ti(1)–N(1)	86.3(4)	O(13)–Ti(3)–O(9)	95.1(4)
O(1)–Ti(1)–N(1)	77.4(3)	O(14)–Ti(3)–O(9)	167.5(3)
O(7)–Ti(1)–N(2)	91.7(3)	O(8)–Ti(3)–O(9)	77.4(3)
O(5)–Ti(1)–N(2)	159.0(3)	O(13)–Ti(3)–O(2)	94.6(3)
O(6)–Ti(1)–N(2)	84.9(3)	O(14)–Ti(3)–O(2)	91.4(3)
O(1)–Ti(1)–N(2)	74.6(2)	O(8)–Ti(3)–O(2)	157.7(3)
N(1)–Ti(1)–N(2)	72.4(3)	O(9)–Ti(3)–O(2)	86.4(2)
O(11)–Ti(2)–O(12)	99.5(4)	O(13)–Ti(3)–O(4)	170.8(3)
O(11)–Ti(2)–O(10)	98.5(3)	O(14)–Ti(3)–O(4)	84.1(3)
O(12)–Ti(2)–O(10)	97.4(3)	O(8)–Ti(3)–O(4)	86.5(3)
O(11)–Ti(2)–O(9)	94.2(3)	O(9)–Ti(3)–O(4)	83.4(2)
O(12)–Ti(2)–O(9)	95.2(3)	O(2)–Ti(3)–O(4)	76.3(2)
O(10)–Ti(2)–O(9)	160.3(3)		
O(11)–Ti(2)–O(8)	164.5(3)		
O(12)–Ti(2)–O(8)	89.3(3)		
O(10)–Ti(2)–O(8)	92.9(3)		
O(9)–Ti(2)–O(8)	72.1(2)		

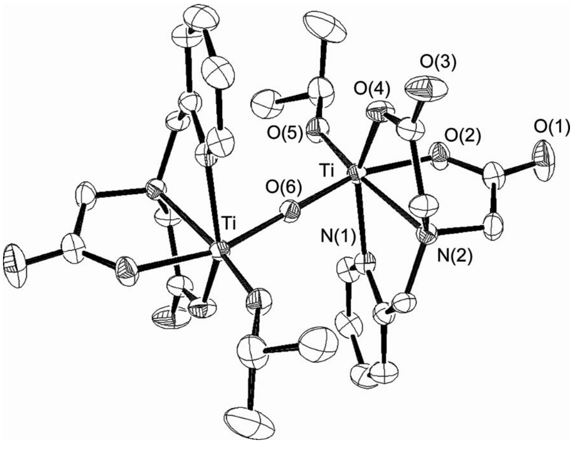


Figure 3. ORTEP drawing of [$Ti^{IV}_2(\mu_2\text{-}O)(OiPr)_2(L^2)_2$] (**3**) with 50% probability ellipsoids (H atoms were omitted for clarity).

Table 3. Selected bond lengths [Å] and angles [°] for [$Ti^{IV}_2(\mu_2\text{-}O)(OiPr)_2(L^2)_2$] (**3**).

Lengths			
O(2)–Ti	2.0010(12)	N(1)–Ti	2.1628(14)
O(4)–Ti	1.9505(13)	N(2)–Ti	2.2543(14)
O(5)–Ti	1.7800(12)		
O(6)–Ti	1.8218(4)	*Ti···Ti*	*3.64*
Angles			
Ti–O(6)–Ti	180.0	O(6)–Ti–N(1)	85.04(4)
O(5)–Ti–O(6)	102.13(4)	O(4)–Ti–N(1)	151.79(5)
O(5)–Ti–O(4)	105.93(6)	O(2)–Ti–N(1)	84.31(6)
O(6)–Ti–O(4)	95.27(4)	O(5)–Ti–N(2)	168.39(5)
O(5)–Ti–O(2)	91.17(5)	O(6)–Ti–N(2)	88.24(4)
O(6)–Ti–O(2)	164.39(4)	O(4)–Ti–N(2)	77.91(5)
O(4)–Ti–O(2)	88.79(6)	O(2)–Ti–N(2)	77.85(5)
O(5)–Ti–N(1)	101.55(6)	N(1)–Ti–N(2)	73.90(5)

apparently as a result of water release from the esterification reaction between the carboxylic acid and 2-propanol formed, which takes place upon the slight heating.[3,5,6,8] Each Ti^{IV} atom is bound to one terminal chelating L^2 ligand, where each one of the two carboxylato ligands binds in a *cis* configuration and in an η^1 fashion. Interestingly, a shorter Ti–N bond length is observed for the side pyridine arm (2.16 Å) relative to that of the central nitrogen atom (2.25 Å). One additional terminal isopropoxide group is bound to each Ti^{IV} center. This compound may thus be regarded as a partial hydrolysis product of an imaginary mononuclear bis(isopropoxido) complex of the type $LTi(OiPr)_2$. An interesting feature of this structure is the linear Ti–O–Ti angle of 180.0°, which may suggest some π interaction between the bridging oxygen atom of some sp-type character and an empty d orbital of the metal center.[14,36,37] Nevertheless, the two Ti–O(6) bonds are not particularly short, with a length of 1.82 Å each, which sum up to a Ti···Ti distance of 3.64 Å, a distance that is longer than that of Ti(2)···Ti(3) observed for the bridged dinuclear substructure of **2** (Figure 2).

Interestingly, in the same reaction flask where **3** was obtained, trace amounts of different single crystals were observed, which were found suitable for lower quality X-ray crystallographic analysis. The ORTEP structure of the second product, **4**, is presented in Figure 4, and a list of selected bond lengths and angles is given in Table 4.[19]

The structure of **4** features a tetranuclear complex, which may be regarded as a further hydrolyzed product of two molecules of **3**, reacting with two water molecules while releasing a total of four molecules of *i*PrOH. In the structure, the two Ti^{IV} centers are octahedral, the ligand wrapping around the metal in a similar manner to that observed in **3**. One main difference between the structures of **3** and **4** lies in the Ti–O–Ti angles, which deviate from linearity in **4** with a value of 166.6°. This suggests that enhanced steric interactions between the ligands packed closely together prohibit the π interactions observed in **2**.[14,36,37] This angle is also similar to that observed in a similar tetrameric structure of a tris(carboxylato) ligand[19,22] and other similar core structures.[38–44] A shorter Ti–O(5) bond length of

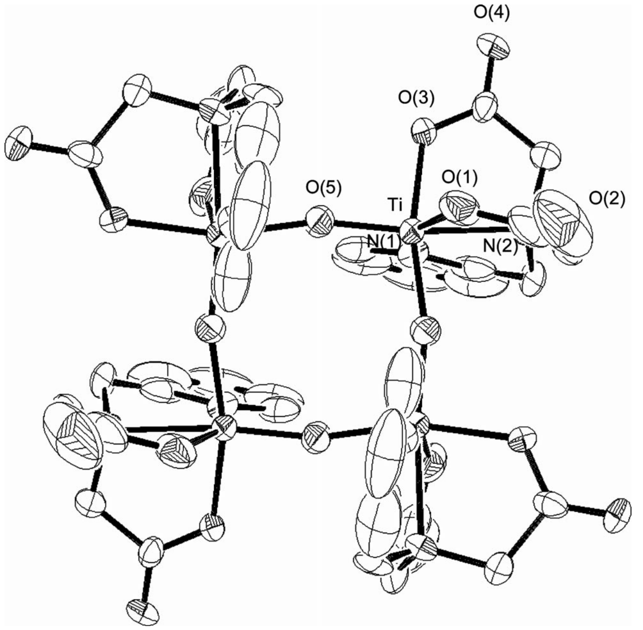


Figure 4. ORTEP drawing of $[Ti^{IV}_4(\mu_2\text{-}O)_4(L^2)_4]$ (**4**) with 50% probability ellipsoids (H atoms and a water molecule were omitted for clarity).

Table 4. Selected bond lengths [Å] and angles [°] for $[Ti^{IV}_4(\mu_2\text{-}O)_4(L^2)_4]$ (**4**).

Lengths			
O(1)–Ti	1.915(7)	N(1)–Ti	2.153(8)
O(3)–Ti	1.997(6)	N(2)–Ti	2.285(8)
O(5)–Ti	1.754(6)		
Angles			
Ti–O(5)–Ti	166.6(4)	O(3)–Ti–N(1)	82.7(3)
O(5)–Ti–O(1)	106.2(4)	O(5)–Ti–N(2)	170.5(3)
O(5)–Ti–O(3)	93.7(3)	O(1)–Ti–N(2)	78.3(4)
O(1)–Ti–O(3)	91.3(3)	O(3)–Ti–N(2)	77.8(3)
O(5)–Ti–N(1)	101.2(3)	N(1)–Ti–N(2)	73.9(4)
O(1)–Ti–N(1)	152.2(3)		

1.75 Å and a shorter Ti···Ti distance of 3.61 Å are observed. An additional water molecule appears in the structure, which forms a hydrogen bond to a carbonyl oxygen with an O(6)–O(4) distance of 2.84 Å.

We made numerous attempts to identify a mononuclear bis(isopropoxido)titanium(IV) complex of L^2, namely $L^2Ti^{IV}(O\mathit{i}Pr)_2$, by treating the ligand precursor with the Ti^{IV} starting material under various reaction conditions, including different solvents, temperatures, etc. Unfortunately, we could not identify the desired product. However, employing a different bis(carboxylato) ligand with a sequential connectivity of donor atoms rather than a branched one allowed us to obtain a mononuclear species. Thus, reaction of the commercially available ethylenediamine diacetic acid (EDDA) (H_2L^3) (Scheme 1) with excess pyridine followed by addition of one equivalent of titanium tetra(isopropoxide) and stirring in dmf at room temp. for 14 d led to the formation of a very light yellow solution, from which crystals suitable for X-ray crystallography precipitated at –35 °C. The crystal structure of product **5** is presented in Figure 5, and a list of selected bond lengths and angles is given in Table 5.

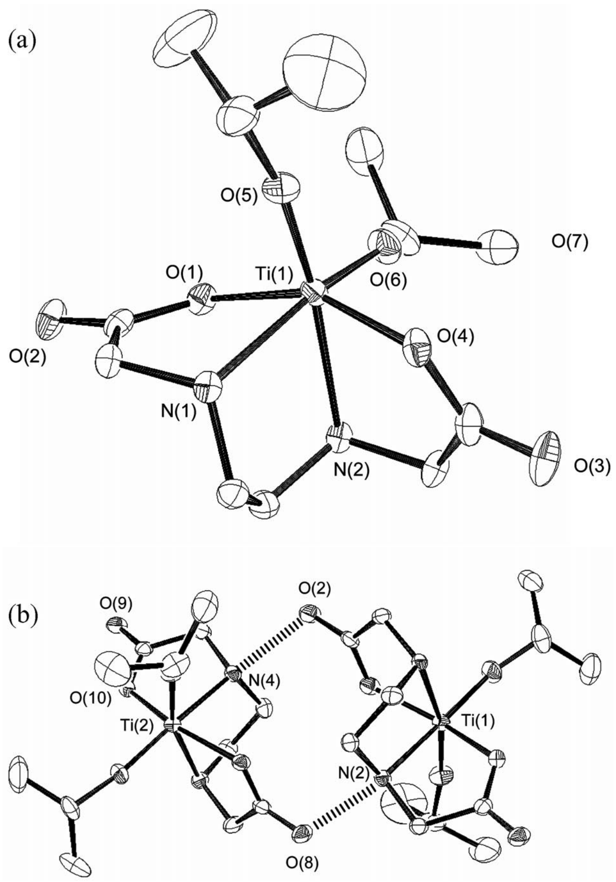


Figure 5. ORTEP drawing of $L^3Ti^{IV}(O\mathit{i}Pr)_2$ (**5**) with 50% probability ellipsoids: (a) one molecule of the two found in the asymmetric unit; (b) the two molecules in the asymmetric unit and their hydrogen bonding (H atoms and one C atom disorder were omitted for clarity).

The structure of **5** features a bis(isopropoxido) complex of a somewhat distorted octahedral geometry, where the carboxylato units bind in an η^1 fashion and in a *trans* configuration (Figure 5). The two isopropoxide groups are in a *cis* configuration, and the complex has an approximate C_2 symmetry. The asymmetric unit contains two molecules of **5**, which are held together by hydrogen bonding between the carbonyl oxygen atoms and the secondary amine units of the tetradentate ligand, with O(2)–N(4) and O(8)–N(2) distances of 2.87 and 2.85 Å, respectively.

To evaluate the suitability of carboxylato ligands for biological applications of Ti^{IV} complexes, in vitro cytotoxicity measurements were performed for the mononuclear complex **5** as well as for the *O*-bridged clusters **3** and **4** on colon HT-29 and ovarian OVCAR-1 cells according to the MTT assay that we previously published.[45] No significant biological activity was observed for any of these compounds. As previous reports suggested that *O*-bridged polynuclear Ti compounds are the active species obtained upon hydrolysis of cytotoxic Ti^{IV} complexes, and those featuring wide

Table 5. Selected bond lengths [Å] and angles [°] for $L^3Ti^{IV}(OiPr)_2$ (**5**).

Lengths			
N(1)–Ti(1)	2.2569(17)	N(3)–Ti(2)	2.2729(17)
N(2)–Ti(1)	2.2373(16)	N(4)–Ti(2)	2.2537(17)
O(1)–Ti(1)	1.9800(15)	O(7)–Ti(2)	1.9929(14)
O(4)–Ti(1)	2.0055(14)	O(10)–Ti(2)	1.9847(14)
O(5)–Ti(1)	1.7854(15)	O(11)–Ti(2)	1.7900(15)
O(6)–Ti(1)	1.7655(15)	O(12)–Ti(2)	1.7744(15)
O(2)···N(4)	*2.867*		
O(8)···N(2)	*2.846*		
Angles			
O(6)–Ti(1)–O(5)	105.00(7)	O(12)–Ti(2)–O(11)	104.56(7)
O(6)–Ti(1)–O(1)	96.94(7)	O(12)–Ti(2)–O(10)	94.39(6)
O(5)–Ti(1)–O(1)	101.04(7)	O(11)–Ti(2)–O(10)	102.01(6)
O(6)–Ti(1)–O(4)	99.26(7)	O(12)–Ti(2)–O(7)	100.46(6)
O(5)–Ti(1)–O(4)	93.60(6)	O(11)–Ti(2)–O(7)	92.09(6)
O(1)–Ti(1)–O(4)	154.53(6)	O(10)–Ti(2)–O(7)	156.29(6)
O(6)–Ti(1)–N(2)	89.40(7)	O(12)–Ti(2)–N(4)	164.22(7)
O(5)–Ti(1)–N(2)	163.77(7)	O(11)–Ti(2)–N(4)	90.07(7)
O(1)–Ti(1)–N(2)	84.26(6)	O(10)–Ti(2)–N(4)	76.50(6)
O(4)–Ti(1)–N(2)	76.42(6)	O(7)–Ti(2)–N(4)	84.60(6)
O(6)–Ti(1)–N(1)	165.41(7)	O(12)–Ti(2)–N(3)	90.23(6)
O(5)–Ti(1)–N(1)	89.20(7)	O(11)–Ti(2)–N(3)	162.67(7)
O(1)–Ti(1)–N(1)	76.66(6)	O(10)–Ti(2)–N(3)	85.51(6)
O(4)–Ti(1)–N(1)	82.88(6)	O(7)–Ti(2)–N(3)	76.11(6)
N(2)–Ti(1)–N(1)	77.01(6)	N(4)–Ti(2)–N(3)	76.39(6)

Ti–O–Ti and relatively short Ti–O bonds are especially active,[13,46] the lack of activity observed for **3** indicates that some other particular features of the ligand are of significance for cytotoxicity, and that the carboxylato ligands employed are not suitable for this purpose.

Conclusions

We have obtained several bis(carboxylato)titanium(IV) complexes of different nuclearities, bridging ligands, and ligand-to-metal ratios by varying the reaction conditions and the particular ligand employed. It appears that, under the various conditions tested, the electron-poor d^0 Ti^{IV} center seeks to complete at least an octahedral coordination sphere, which governs the number of chelating ligands bound to each Ti center, considering their effective molar ratio in solution. In addition, the number of bridging oxide groups is dependent on the possibility of esterification reactions, which are enhanced upon heating. Particularly, an interesting unusual hexanuclear complex of low symmetry was obtained at room temp. where the complicated structure holds together without bridging oxide groups, but solely [1-] isopropoxido ligands and η^2 carboxylato bridges. In contrast, heating to 35 °C allowed the identification of two hydrolysis products presumably coming from a bis(isopropoxido) mononuclear precursor. These structures suggest that the hydrolysis mechanism of $LTiX_2$-type complexes of such ligands proceed in a stepwise manner, where first, two single metal centers react with a water molecule, giving a bis(isopropoxide) *O*-bridged dinuclear species, followed by reaction of two such products with two additional water molecules to give the O*i*Pr-free tetranuclear compounds. Nevertheless, the bis(carboxylato) complexes described herein do not show any promise for antitumor applications.

Experimental Section

Synthesis of the ligand H_2L^2 was achieved as described previously.[31] H_2L^1 and H_2L^3 are commercially available and were purchased from Aldrich Chemical Company, Inc. Titanium tetra(isopropoxide) (97%) was purchased from Aldrich Chemical Company, Inc. All solvents were distilled from K or K/benzophenone under nitrogen. All experiments requiring a dry atmosphere were performed in a M. Braun dry-box or under a nitrogen atmosphere by using Schlenk line techniques. X-ray diffraction data were obtained with a Bruker Smart Apex diffractometer, running the SMART software package. After collection, the raw data frames were integrated by the SAINT software package. The structures were solved and refined with the SHELXTL software package. UV/Vis was recorded with a Jasco V-530 UV/Vis spectrophotometer at room temp. Cytotoxicity measurements were performed as described previously.[45]

$L^1{}_2Ti^{IV}(dmf)_2$ (1): $Ti(OiPr)_4$ (0.34 mmol) was added to a solution of H_2L^1 (1.00 mmol) in thf (5 mL), and the reaction mixture was heated to 35 °C under a nitrogen atmosphere and allowed to stir overnight. The thf was removed under reduced pressure, and the orange product was crystallized from dmf at –35 °C. Crystal data: The asymmetric unit contains one molecule of dmf solvent. The crystal data is summarized in Table 6.

$[Ti^{IV}{}_6(OiPr)_{16}(\mu_2\text{-}OiPr)_4(\mu_4\text{-}L^2)_2]$ (2): $Ti(OiPr)_4$ (0.10 mmol) was added to a solution of H_2L^2 (0.12 mmol) in toluene (5 mL) at room temp. under a nitrogen atmosphere. The color changed overnight from colorless to orange. The reaction mixture was stirred for 20 d, and the toluene was removed under reduced pressure. Compound **2** was crystallized from toluene at –35 °C. Crystal data: The asymmetric unit contains one half of the molecule and disorder. The crystal data is summarized in Table 6.

$[Ti^{IV}{}_2(\mu_2\text{-}O)(OiPr)_2(L^2)_2]$ (3): $Ti(OiPr)_4$ (0.13 mmol) was added to a solution of H_2L^2 (0.12 mmol) in thf (5 mL) under a nitrogen atmosphere, and the mixture was heated to 35 °C overnight. The pale yellow solution was evaporated, and **3** was recrystallized from thf/hexane at room temp. Crystal data: The asymmetric unit contains one half of the molecule. The crystal data is summarized in Table 6.

$[Ti^{IV}{}_2(\mu_2\text{-}O)_4(L^2)_2]$ (4): Compound **4** was recrystallized as orange crystals from thf/hexane at room temp. under similar conditions as those of **3**. Crystal data: The asymmetric unit contains one quarter of the molecule and a water molecule. The crystal data is summarized in Table 6.

$L^3Ti^{IV}(OiPr)_2$ (5): $Ti(OiPr)_4$ (0.15 mmol) was added to a solution of H_2L^3 (0.13 mmol) in dmf (5 mL) previously stirred with pyridine (1 mL), and the mixture was stirred for two weeks at room temp. under a nitrogen atmosphere. The color changed from colorless to very light yellow. Compound **5** was crystallized from dmf at –35 °C in 18% yield. ^1H NMR (400 MHz, CD_3CN, 25 °C): δ = 4.74 [sept, *J* = 6.1 Hz, 2 H, $C\mathit{H}(CH_3)_2$], 4.07 (s, 2 H, NH), 3.97 (dd, *J* = 17.2, 8.1 Hz, 2 H, CH_2), 3.13 (d, *J* = 17.2 Hz, 2 H, CH_2), 3.09 (m, *J* = 4.3 Hz, 2 H, CH_2), 2.64 (d, *J* = 10.4 Hz, 2 H, CH_2), 1.27 [d, *J* = 6.1 Hz, 6 H, $CH(C\mathit{H}_3)_2$], 1.25 [d, *J* = 6.1 Hz, 6 H, $CH(C\mathit{H}_3)_2$] ppm. λ_{max}(dmf), nm (ε): 268 (ca. 1700). Crystal data: The asymmetric unit contains two molecules of **5**. The crystal data is summarized in Table 6.

Table 6. Crystal data for **1**–**5**.

	1	**2**	**3**	**4**	**5**
Formula	$C_{20}H_{20}N_4O_{10}Ti{\cdot}C_3H_7NO$	$C_{40}H_{806}N_2O_{14}Ti_3$	$C_{26}H_{34}N_4O_{11}Ti_2$	$C_{20}H_{20}N_4O_{11}Ti_2$	$C_{12}H_{24}N_2O_6Ti$
Mass	597.40	956.76	674.37	588.20	340.23
Crystal system	monoclinic	triclinic	monoclinic	tetragonal	monoclinic
Space group	$C2/c$	$P\bar{1}$	$P2_1/c$	$I\bar{4}2d$	$P2_1/c$
a [Å]	30.015(2)	13.506(3)	9.6025(18)	11.993(2)	11.6997(6)
b [Å]	11.5192(9)	14.604(3)	15.028(3)	11.993(2)	16.0850(9)
c [Å]	15.7734(13)	15.277(3)	10.3314(19)	37.382(14)	18.2689(10)
α [°]		105.772(5)			
β [°]	99.4400(10)	95.098(4)	93.546(3)		102.0320(10)
γ [°]		104.814(4)			
U [Å^3]	5379.7(7)	2762.6(10)	1488.0(5)	5377(2)	3362.5(3)
Z	8	2	2	8	8
T [K]	173(1)	173(2)	173(2)	123(1)	100(1)
μ(Mo-K_α) [cm^{-1}]	0.386	0.477	0.602	0.654	0.535
Reflections measured	30529	30944	16880	28777	39263
Reflections unique	6416	11978	3547	2948	7994
R_{int}	0203	0.0993	0.0188	0.0188	0.0361
$R(F_\circ^2)$ for [$I > 2\sigma(I)$]	0.0441	0.1781	0.0379	0.1206	0.0485
Rw for [$I > 2\sigma(I)$]	0.1077	0.3842	0.1031	0.3010	0.1261

CCDC-667776, -667777, -667778, -667779, and -667780 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

We thank the Allon Foundation as well as the friends of the Hebrew University, United States of America for financial support. We also thank Dr. Shmuel Cohen for solution of the X-ray structures.

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Received: November 18, 2007