Note

Structural characterization of dinuclear Ti(IV) complexes of rigid tetradentate dianionic diamine bis(phenolato) ligands; effect of steric bulk on coordination features

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ABSTRACT

A small difference in diamine bis(phenolato) ligands, namely an additional single methylene unit, directs formation of dinuclear Ti(IV) complexes rather than mononuclear ones as characterized by X-ray crystallography. Varying steric bulk of the ligand affects the coordination number in the dinuclear complexes and the ligand to metal ratio. A ligand with reduced steric bulk leads to a $L_2Ti_2(OiPr)_4$ type complex featuring two octahedral metal centers bridged only by the two phenolato ligands, whereas a bulky ligand leads to a $Ti_2(\mu\text{-}L^1)(\mu\text{-}OiPr)_2(OiPr)_4$ type complex with a single chelating ligand, two bridging isopropoxo ligands, and two terminal isopropoxo groups on each of the two metal centers, which are of trigonal bipyramidal geometry.

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1. Introduction

Ti(IV) complexes of salan-type diamine bis(phenolato) ligands have been reported to be useful for different applications, ranging from catalysis to biological activity [1–3]. In these complexes, the diamine bis(phenolato) ligands of various R groups including *ortho* Me and *t*Bu and various R″ groups including H and –(CH$_2$)$_4$–, were shown to lead to well-defined mononuclear C_2-symmetrical complexes upon reaction with a Ti(IV) precursor (Scheme 1) [1,4–7]. We reported several such complexes that were studied for biological applications, and some were found to be highly cytotoxic against colon and ovarian cells [3]. Herein, we report the synthesis of rigid ligands of this family that include an additional single methylene bridge between the two N-donors (Scheme 2) [8], as well as the synthesis and structural characterization of their Ti(IV) complexes. The small structural difference adds significantly to the ligand rigidity and thus has a major effect on the complexes formed.

2. Results and discussion

The synthesis of H_2L^{1-2} is based on a single-step Mannich condensation between the primary diamine, two equivalents of the substituted phenol, and formaldehyde (Scheme 3) [8,9]. As second-

ary diamines conveniently give flexible ligands with a single ethylene linker between the N-atoms, the additional NH group in the corresponding products derived from the primary diamines is able to further react with formaldehyde to give a stable five-membered ring. Notably, this reaction is possible both with a flexible ethylene bridge (H_2L^1) as well as with a more constrained *trans*-cyclohexylene bridge (H_2L^2). Thus, H_2L^1 and H_2L^2 were obtained in 88% and 54% yields, respectively, as colorless powders. The diastereotopic nature of the four benzylic hydrogen atoms in H_2L^2 is manifested by two doublets in its ^1H NMR spectrum of an AX system, while these protons appear as a single singlet in the spectrum of H_2L^1.

Reacting H_2L^1 with one equivalent of Ti(O*i*Pr)$_4$ in THF at RT gave a yellow solution. Single crystals suitable for X-ray crystallography were obtained from dichloromethane at −35°. An ORTEP presentation of the structure is presented in Fig. 1, and a list of selected bond lengths and angles is given in Table 1.

The structure features a dinuclear species of the formula $Ti_2(\mu\text{-}L^1)(\mu\text{-}OiPr)_2(OiPr)_4$ where a single chelating ligand bridges the two Ti(IV) centers in a total of Ti:L ratio of 2:1 providing one covalent O donor and one coordinative N-donor to each metal center. Two additional bridging isopropoxo groups give a Ti···Ti distance of 3.28 Å. Each Ti(IV) center is also bound to two terminal isopropoxo groups that complete an octahedral geometry. Interestingly, an almost planar –Ti–O–Ti–O– array is observed, with a Ti(1)–O(3)–Ti(2)–O(4) torsion angle of 0.6°. This complex exhibits an approximate C_2-symmetrical dinuclear core.
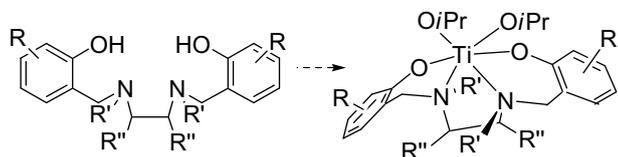
It is thus obvious that the large *t*Bu groups in H_2L^1 preclude binding of a second dianionic bis(phenolato) ligand in replacement

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of two additional isopropoxo groups, even when a 1:1 ligand to metal ratio was employed. Since binding of a second tetradentate ligand should enhance the complex hydrolytic stability, it was interesting to explore the complex obtained with the less sterically crowded ligand H_2L^2, featuring Me groups instead of the tBu substituents.
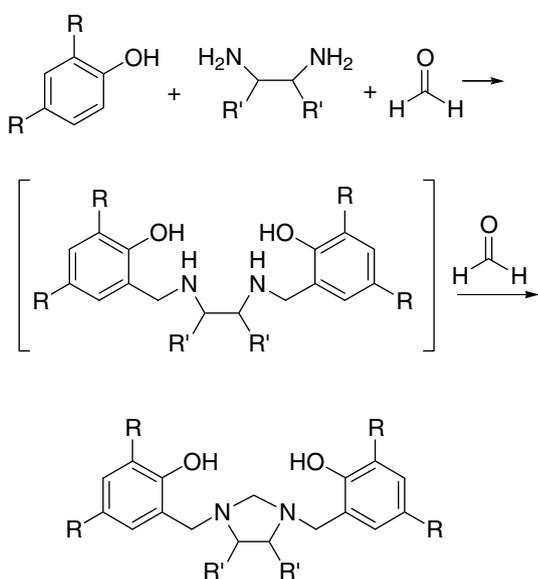
Reacting H_2L^2 with one equivalent of Ti(OiPr)$_4$ in THF at RT gave another yellow solution. Trace amounts of single crystals suitable for X-ray crystallography were obtained from dichloromethane/hexane at RT. An ORTEP presentation of the structure is presented in Fig. 2, and a list of selected bond lengths and angles is given in Table 2.
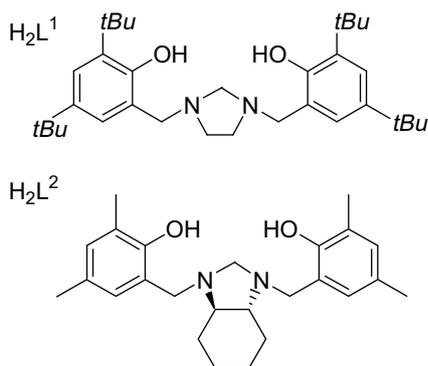
The structure features another dinuclear complex, of the formula Ti$_2$(μ-L^2)$_2$(OiPr)$_4$, exhibiting a C_i-symmetry. In this structure, two chelating ligands are able to bridge the two Ti(IV) centers due to their reduced steric bulk, giving a much larger Ti···Ti distance of 7.77 Å, since no additional single-atom bridging isopropoxo ligands are present. The second bridging ligand may be regarded as a replacement for the two bridging isopropoxo groups observed in Ti$_2$(μ-L^1)(μ-OiPr)$_2$(OiPr)$_4$, however, since only one N-donor in each chelating ligands provides a coordinative bond due to the larger Ti···Ti distance, each Ti(IV) center is penta-coordinate with a trigonal bi-pyramidal geometry (Ti···N(2): 4.35, 5.18 Å). The two isopropoxo groups are in a cis configuration on each Ti(IV) center, and the cyclohexyl rings adopt a chair-like conformation. The planes of the two central phenolato rings of two separate ligands are parallel to one another with <2° deviation. It appears that overall, despite the incomplete coordination sphere, binding of the second chelating ligand is achieved on the expense of binding to two bridging isopropoxo groups.

Cytotoxicity was only measured of the coordinativelly saturated Ti$_2$(μ-L^1)(μ-OiPr)$_2$(OiPr)$_4$, as Ti$_2$(μ-L^2)$_2$(OiPr)$_4$ of the penta-coordinate metal centers demonstrated significant hydrolytic instability in air. The measurements were performed on colon HT-29 and ovarian OVCAR-1 cells based on the MTT (methylthiazolyldiphenyl-tetrazolium bromide) assay as previously described [3]. No substantial activity was observed for this complex towards both cell types. Given the activity we observed for some mononuclear counterparts towards these particular cells and its dependence on steric bulk [3], we may conclude that a combination of coordinative saturation, strong ligand binding, and small steric groups are required for obtaining fruitful biological interactions and cytotoxic activity [3].

Scheme 1.

Scheme 2.

H_2L^1: R = tBu; R' = H
H_2L^2: R = Me; R' = -CH$_2$CH$_2$CH$_2$CH$_2$-

Scheme 3.

3. Experimental

The synthesis of ligands was generally based on a published procedure [9]. Paraformaldehyde (95%), aqueous formaldehyde (30–38%), ethylenediamine (99%), $trans$-1,2-diaminocyclohexane (99%), 2,4-di-$tert$-butylphenol (99%), 2,4-dimethylphenol (97%), and titanium tetra(isopropoxide) (97%) were purchased and used as is. All solvents for Ti(IV) complex preparation were distilled from K or K/benzophenone under nitrogen. All experiments requiring dry atmosphere were performed in a M. Braun dry-box or under nitrogen atmosphere using Schlenck line techniques. NMR data were recorded using AMX-400 MHz Bruker spectrometer. X-ray diffraction data were obtained with Bruker Smart Apex diffractometer. Elemental analyses were performed in the microanalytical laboratory in our institute. Cytotoxicity was measured on HT-29 colon and OVCAR-1 ovarian cells obtained from ATCC Inc. using the methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay as previously described [3,10].

H_2L^1 was synthesized as previously described [8] in 88% yield. ^{13}C NMR (400 MHz; CCl$_3$D): δ 154.1, 140.7, 135.7, 123.3, 123.1, 120.8, 74.4, 59.2, 51.8, 34.9, 34.2, 31.7, 29.6. Anal. Calc. for C$_{33}$H$_{52}$N$_2$O$_2$: C, 77.90; H, 10.30; N, 5.51. Found: C, 78.11; H, 10.31; N, 5.59%.

H_2L^2 was synthesized similarly by reacting paraformaldehyde (8 mmol) with $trans$-1,2-diaminocyclohexane (4 mmol) and 2,4-dimethylphenol (9 mmol) in refluxing methanol. A colorless powder precipitated in 54% yield. ^{1}H NMR (400 MHz; CCl$_3$D): δ 10.48 (s, 2H, OH), 6.83 (s, 2H, Ar), 6.57 (s, 2H, Ar), 4.15 (d, J = 14 Hz, 2H, ArCH$_2$), 3.51 (s, 2H, NCH$_2$N), 3.36 (d, J = 14 Hz, 2H, ArCH$_2$), 2.32 (m, 2H, cy), 2.18 (s, 6H, CH$_3$), 2.17 (s, 6H, CH$_3$), 2.08 (m, 2H, Cy), 1.84(m, 2H, cy), 1.29 (m, 4H, cy). ^{13}C NMR (400 MHz; CCl$_3$D): δ
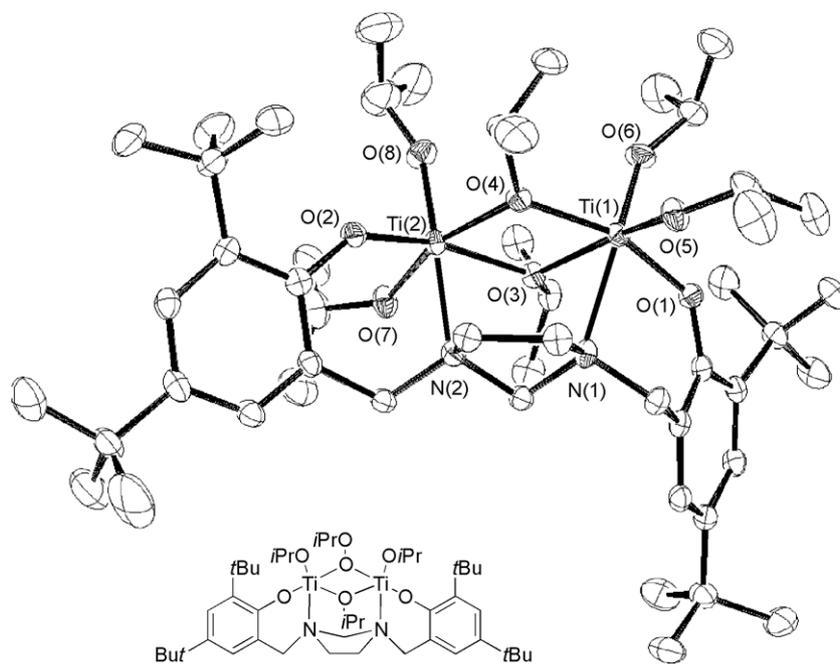
Fig. 1. ORTEP drawing of Ti$_2$(μ-L^1)(μ-OiPr)$_2$(OiPr)$_4$ in 50% probability ellipsoids; CH$_2$Cl$_2$ solvent and H atoms were omitted for clarity.

153.1, 130.8, 127.8, 126.2, 124.6, 120.6, 75.8, 69.1, 56.3, 29.0, 24.1, 20.4, 15.6. Anal. Calc. for C$_{25}$H$_{34}$N$_2$O$_2$: C, 76.10; H, 8.69; N, 7.10. Found: C, 75.83; H, 8.84; N, 7.03%.

Ti$_2$(μ-L^1)(μ-OiPr)$_2$(OiPr)$_4$ was synthesized by reacting Ti(OiPr)$_4$ (0.67 mmol) with H$_2$L^1 (0.69 mmol) in THF at RT under nitrogen atmosphere. Following removal of the isopropanol with the solvent, yellow single crystals were obtained from dichloromethane at −35 °C (10%). ^{1}H NMR (400 MHz; CCl$_3$D): δ 7.22 (d, J = 2.4 Hz, 2H, Ar), 6.91 (d, J = 2.4 Hz, 2H, Ar), 4.88 (m, 6H, CH), 4.23 (s, 4H, CH$_2$), 4.20 (s, 2H, CH$_2$), 3.05 (s, 4H, CH$_2$), 1.47 (s, 18H, C(CH$_3$)$_3$), 1.29 (s, 18H, C(CH$_3$)$_3$), 1.27 (d, J = 6.2 Hz, 36H, CH$_3$). ^{13}C NMR (400 MHz; CCl$_3$D): δ 158.9, 139.8, 135.7, 124.7, 124.4, 123.1, 76.2, 59.0, 34.9, 34.1, 31.7, 29.7, 26.7. Anal. Calc. for C$_{51}$H$_{90}$N$_2$O$_8$Ti$_2$: C, 64.14; H, 9.50; N, 2.93. Found: C, 63.77; H, 9.84; N, 2.92%.

Table 1
Selected bond lengths (Å) and angles (°) for Ti$_2$(μ-L^1)(μ-OiPr)$_2$(OiPr)$_4$.

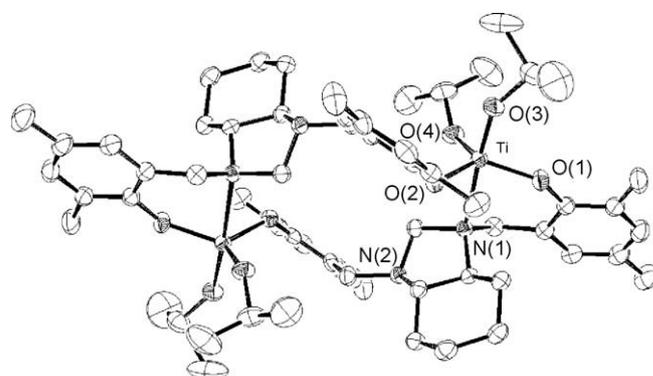| Lengths			
Ti(1)–O(1)	1.9190(17)	Ti(2)–O(2)	1.9121(17)
Ti(1)–O(3)	2.0914(17)	Ti(2)–O(3)	2.0116(17)
Ti(1)–O(4)	2.0206(17)	Ti(2)–O(4)	2.0966(17)
Ti(1)–O(5)	1.8144(18)	Ti(2)–O(7)	1.8182(18)
Ti(1)–O(6)	1.7888(18)	Ti(2)–O(8)	1.7936(19)
Ti(1)–N(1)	2.438(2)	Ti(2)–N(2)	2.430(2)
Angles			
O(6)–Ti(1)–O(5)	101.40(9)	O(8)–Ti(2)–O(7)	101.37(9)
O(6)–Ti(1)–O(1)	92.61(8)	O(8)–Ti(2)–O(2)	96.35(8)
O(5)–Ti(1)–O(1)	96.61(8)	O(7)–Ti(2)–O(2)	94.16(8)
O(6)–Ti(1)–O(4)	101.03(8)	O(8)–Ti(2)–O(3)	103.29(8)
O(5)–Ti(1)–O(4)	93.16(8)	O(7)–Ti(2)–O(3)	92.70(8)
O(1)–Ti(1)–O(4)	161.33(7)	O(2)–Ti(2)–O(3)	157.47(8)
O(6)–Ti(1)–O(3)	96.64(8)	O(8)–Ti(2)–O(4)	92.35(8)
O(5)–Ti(1)–O(3)	159.64(8)	O(7)–Ti(2)–O(4)	162.93(8)
O(1)–Ti(1)–O(3)	91.87(7)	O(2)–Ti(2)–O(4)	94.37(7)
O(4)–Ti(1)–O(3)	74.04(7)	O(3)–Ti(2)–O(4)	74.11(7)
O(6)–Ti(1)–N(1)	174.11(8)	O(8)–Ti(2)–N(2)	168.62(8)
O(5)–T(1)–N(1)	83.41(8)	O(7)–Ti(2)–N(2)	87.74(8)
O(1)–Ti(1)–N(1)	83.41(7)	O(2)–Ti(2)–N(2)	76.01(7)
O(4)–Ti(1)–N(1)	81.94(7)	O(3)–Ti(2)–N(2)	82.85(7)
O(3)–Ti(1)–N(1)	79.21(7)	O(4)–Ti(2)–N(2)	80.02(7)

Fig. 2. ORTEP drawing of Ti$_2$(μ-L^2)$_2$(OiPr)$_4$ in 50% probability ellipsoids; H atoms and disorder were omitted for clarity.
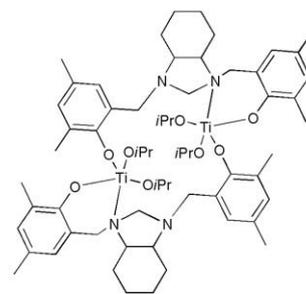
Table 2
Selected bond lengths (Å) and angles (°) for Ti$_2$(μ-L^2)$_2$(OiPr)$_4$.

Lengths			
Ti(1)–O(1)	1.855(2)	Ti(1)–O(4)	1.801(2)
Ti(1)–O(2)	1.8667(19)	Ti(1)–N(1)	2.369(2)
Ti(1)–O(3)	1.775(2)		
Angles			
O(3)–Ti(1)–O(4)	100.85(10)	O(1)–Ti(1)–O(2)	125.40(9)
O(3)–Ti(1)–O(1)	96.37(10)	O(3)–Ti(1)–N(1)	176.26(10)
O(4)–Ti(1)–O(1)	115.19(10)	O(4)–T(1)–N(1)	82.33(9)
O(3)–Ti(1)–O(2)	96.11(10)	O(1)–Ti(1)–N(1)	80.43(8)
O(4)–Ti(1)–O(2)	114.11(10)	O(2)–Ti(1)–N(1)	84.28(8)

Crystal data: $C_{51}H_{92}N_2O_8Ti_2 \cdot CH_2Cl_2$, $M = 1041.99$, triclinic, $a = 10.9072(11)$, $b = 13.5112(13)$, $c = 19.7812(19)$ Å, $\alpha = 85.605(2)°$, $\beta = 82.960(2)°$, $\gamma = 89.553(2)°$, $U = 2884.7(5)$ Å^3, $T = 173(1)$ K, space group $P\bar{1}$, $Z = 2$, μ(Mo Kα) = 0.418 mm^{-1}, Reflections measured 31 637, 12 440 unique ($R_{int} = 0.0336$), $R(F^2)$ for $[I > 2\sigma(I)] = 0.0625$, *Rw* for $[I > 2\sigma(I)] = 0.1451$.

$Ti_2(\mu\text{-}L^2)_2(OiPr)_4$ was synthesized by reacting $Ti(OiPr)_4$ (0.17 mmol) with H_2L^2 (0.17 mmol) in THF at RT under nitrogen atmosphere. Following removal of the isopropanol with the solvent, yellow single crystals were obtained from dichloromethane/hexane at RT (10%). Further characterization of this compound was impeded by its hydrolytic instability.

Crystal data: $C_{62}H_{92}N_4O_8Ti_2$, $M = 1117.20$, monoclinic, $a = 12.2048(9)$, $b = 17.7609(13)$, $c = 14.7463(11)$ Å, $\beta = 106.2130(10)°$, $U = 3069.4(4)$ Å^3, $T = 173(1)$ K, space group $P2_1/n$, $Z = 2$, μ(Mo Kα) = 0.315 mm^{-1}, Reflections measured 33 876, 6706 unique ($R_{int} = 0.0396$), $R(F^2)$ for $[I > 2\sigma(I)] = 0.0757$, *Rw* for $[I > 2\sigma(I)] = 0.1741$.

Acknowledgment

Appendix A. Supplementary material

CCDC 693366 and 693367 contains the supplementary crystallographic data for $Ti_2(\mu\text{-}L^2)_2(OiPr)_4$ and $Ti_2(\mu\text{-}L^1)(\mu\text{-}OiPr)_2(OiPr)_4$. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.09.056.

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