# Distinctive structural features of hydroxyamino-1,3,5-triazine ligands leading to enhanced hydrolytic stability of their titanium complexes

Dani Peri,<sup>a</sup> Jacob S. Alexander,<sup>a</sup> Edit Y. Tshuva<sup>\*a</sup> and Artem Melman<sup>b</sup>

Received 28th April 2006, Accepted 21st June 2006 First published as an Advance Article on the web 4th July 2006 DOI: 10.1039/b606072b

Three bis(homoleptic) titanium complexes of hydroxyamino-1,3,5-triazine ligands **3a–c** were synthesized and characterized, and their kinetic behavior in THF–water solutions was studied at various pH conditions using UV-vis, based on the characteristic Ti–O band at 380 nm. One of these complexes, **3c**, was analyzed by X-ray crystallography. Due to the characteristic electronic structure of the triazine rings, high electron density on the nitrogen atoms leads to strong N–Ti bonds, as indicative by the 2.0 Å coordinative bond lengths in the X-ray structure. Consequently, these complexes exhibit high hydrolytic stability over a wide pH range, where hydrolysis was observed to be promoted by basic conditions. At neutral pH,  $t_{1/2}$  was estimated to be >200 h, whereas at pH = 5.5, no hydrolysis was observed for a period of at least three days.

# Introduction

Complexes of titanium(IV) metal are widely studied for a variety of purposes, mainly serving as catalysts in different organic reactions.<sup>1-6</sup> Known ligands for titanium(IV) include numerous cyclopentadienyl systems, as well as nitrogen- and oxygen-based compounds. One general feature common to most titanium complexes is their hydrolytic instability, due to their d<sup>o</sup> configuration and thus highly oxophilic nature. Therefore, in the presence of water, hydroxide groups replace other ligands, followed by the formation of oxo-bridged polynuclear aggregates, with the final thermodynamic product being titanium dioxide.<sup>7-11</sup>

Hydrolytically stable titanium complexes have the advantage of easier handling, both for industrial applications<sup>12,13</sup> as well as for small-scale laboratory work. In addition, water-stable titanium complexes may have medicinal applications in anti-cancer therapy.14 More specifically, titanocene dichloride and budotitane complexes are active against certain types of tumor cells, however, their decomposition in aqueous solutions impeded mechanistic investigations, lowered their efficiency, and ultimately resulted in failure in clinical trials. Thus, identifying parameters affecting hydrolytic stability, and producing titanium(IV) complexes of inert ligands exhibiting enhanced water resistance, is extremely valuable. Following the discovery of their possible therapeutic value, only a few most relevant titanium systems were studied thus far in actual aqueous solutions at various pH conditions in order to evaluate the hydrolysis rate of their inert ligands, which mostly hydrolyze within several hours.14-19 We are interested in exploring additional ligand families that may produce stable complexes, and investigate their hydrolysis and the relevant factors affecting it.

Resistance towards hydrolysis should increase with the complex thermodynamic stability. Therefore, we searched for electron-rich oxygen-based ligands that may lead to strong hard acid-hard base binding.<sup>7,16,20,21</sup> More specifically, we chose the hydroxylamine ligand family presented in Scheme 1.



Simple hydroxylamine based ligands have been reported to form complexes with titanium as well as aluminium and gallium cations<sup>22-26</sup> but to the best of our knowledge did not find substantial use. The presence of alkyl and aryl hydroxyamino groups as metal ligands is deterred by their low stability toward oxidizing reagents and relatively weak binding. In this paper we describe a new family of chelating hydroxylamine based ligands for Ti(IV) cations, possessing two hydroxy(alkyl)amino groups attached to a 1,3,5-triazine scaffold. The strong electronwithdrawing properties of the 1,3,5-triazine cycle results in a substantial increase of acidity of OH groups and prevents oxidation of hydroxy(alkyl)amino units. In addition, the nitrogen atom at position 1 of the 1,3,5-triazine cycle, which is at a suitable location for coordination to the metal center, should be relatively electron-rich due to the resonative structure presented in Scheme 2. Stable octahedral titanium complexes of two tridentate bis(hydroxyamino)triazine ligands could thus be envisioned.

# **Results and discussion**

Synthesis of the bis(hydroxyamino)triazine ligands was based on facile nucleophilic substitution at the 1,3,5-triazine rings (Scheme 1). Sequential substitution of three chlorine atoms in

<sup>&</sup>lt;sup>a</sup>Department of Inorganic Chemistry, The Hebrew University of Jerusalem, 91904, Jerusalem, Israel. E-mail: tshuva@chem.ch.huji.ac.il; Fax: +972 2 6585319; Tel: +972 2 6586084

<sup>&</sup>lt;sup>b</sup>Department of Organic Chemistry, The Hebrew University of Jerusalem, 91904, Jerusalem, Israel



2,4,6-trichloro-1,3,5-triazine proceeded with high selectivity in all stages thus providing ligands with general formula 2a-c.<sup>27,28</sup> This method allows an easy adjustment of the structural properties of the ligands by introducing different substituents at position 4. More complex structures can be introduced using tethered carboxylic groups in compounds of type **2b**.

The reaction of Ti(OiPr)<sub>4</sub> with two equivalents of **2a** (Scheme 1) in THF at room temperature gave a dark-yellow product which precipitated out of solution. The <sup>1</sup>H NMR spectrum of the crystalline product indicated the formation of a single isomer of the homoleptic TiL<sub>2</sub> type complex **3a** (Scheme 3) in quantitative yield. A single singlet representing all four N–CH<sub>3</sub> groups and a single morpholine system are observed, indicative of a  $D_{2d}$  symmetry. The ESI-MS spectrum of **3a** supported formation of a TiL<sub>2</sub> species of molecular weight of 556 with a typical isotope pattern of titanium.



**a**  $R^1$ ,  $R^2 = -CH_2CH_2OCH_2CH_2$ - (morpholino) **b**  $R^1 = R^2 = CH_2CO_2Et$ **c**  $R^1 = R^2 = c-C_8H_{11}$ 

#### Scheme 3

In a similar manner, the reactions of  $Ti(OiPr)_4$  with two equivalents of **2b** or **2c** (Scheme 1) in THF or diethyl ether at room temperature gave clear yellow or orange solutions. The NMR spectra of the products were consistent with formation of single isomers of **3b** and **3c**, respectively (Scheme 3). Cooling a solution of **3c** in diethyl ether afforded single crystals suitable for X-ray crystallography. The crystal structure is presented in Fig. 1.

The complex **3c** has a highly distorted octahedral geometry. The cyclohexyl units appear to be different both in the solid state and in solution due to restricted rotation, which reduces the symmetry from  $D_{2d}$  to  $C_2$ .<sup>29</sup> The two planes of the [ONO] binding atoms of the two ligands are approximately perpendicular to one another possessing a *mer* geometry. Additional interesting structural features are the following: (a) an extremely short Ti–N coordinative bond is observed, of 2.0 Å;<sup>20</sup> this value nearly falls in the range of covalent bonds, rather than coordinative bonds; (b) highly twisted hexagons of the aromatic ring of the triazine moieties, where all C–N–C angles are around 115° and all N–C–N angles are around 125°; for example, a C(1)–N(5)–C(3) angle of



Fig. 1 ORTEP drawing of 3c at 50% probability ellipsoids, presented from two angles (H atoms and solvent molecules in the unit cell were omitted for clarity). Selected bond lengths (Å) and angles (°): Ti–N(5) 2.018(3), Ti–N(10) 2.025(3), Ti–O(1) 1.953(3), Ti–O(2) 1.959(3), Ti–O(3) 1.965(3), Ti–O(4) 1.956(3), O(2)–N(4) 1.385(4); N(5)–Ti–N(10) 165.7(2), O(1)–Ti–O(2) 143.7(1), O(1)–Ti–O(3) 96.7(1).

115.8° and a N(2)–C(1)–N(5) angle of 125.0° (Fig. 1);<sup>30</sup> and (c) highly planar arrays of the bodies of each ligand including all six N atoms, the inner ring as well as out-of-ring nitrogen atoms; this may be observed by the sum of bond angles of nearly 360° surrounding the out-of-ring nitrogen atoms, two such examples are summarized in Table 1. These facts are all in agreement with a large contribution of the resonative structure presented in Scheme 2, according to which all out-of-ring nitrogen atoms are of approximately sp<sup>2</sup> configuration, while the inner ring nitrogen atoms, including the one coordinating to the titanium, possess high electron densities. Therefore, a strong electron donation to the titanium center is observed in the form of a short bond. This complex also exhibits a single singlet in the <sup>1</sup>H NMR spectrum for the four N–CH<sub>3</sub> groups as observed with **3a** and **3b** (Scheme 3).

The UV-vis spectrum of **3c** in THF shows a characteristic LMCT signal of the O–Ti binding at 380 nm ( $\varepsilon = 7000 \text{ M}^{-1} \text{ cm}^{-1}$ ),<sup>16</sup>

Table 1 Bond angles (°) indicating planarity of out-of-ring nitrogen atoms



**Table 2** Kinetic behavior of ligand hydrolysis in 3c in 1 : 1 THF-water solutions at RT

	pН	Buffer	Reaction time/h	<i>t</i> <sub>1/2</sub> /h
1 2 3	5.0 7.1 11.5	CH <sub>3</sub> COOH/CH <sub>3</sub> COONa H <sub>2</sub> KPO <sub>4</sub> /HK <sub>2</sub> PO <sub>4</sub> HK <sub>2</sub> PO <sub>4</sub> /K <sub>3</sub> PO <sub>4</sub>	80 80 40	Not detected >200 <sup>a</sup> 34
<sup><i>a</i></sup> Estimated based on trend-line.				

which does not appear in the free ligand spectrum. This signal was used as the basis for kinetic studies upon addition of water at different pH conditions to give a solution of 50% THF and 50%  $H_2O$ , † The signal was monitored for 40–80 h at room temperature. The results are summarized in Table 2. No change in absorbance was observed at pH = 5.0 for a period of at least 3 days, indicating that 3c is very stable under these conditions (Fig. 2). Under higher pH conditions, however, ligand dissociation is observed within a few hours. The  $t_{1/2}$  at pH = 11.5 was found to be 34 h, while at neutral pH the  $t_{1/2}$  was calculated to be significantly higher (Table 2). This indicates that hydroxide ion attack is the favored hydrolysis mechanism, rather than protonation followed by ligand dissociation, similarly to the findings previously obtained with other titanium systems, including titanocene dichloride and Ti-O based compounds.15,16 It is also noteworthy that in comparison to the previously reported systems studied under similar conditions, including metallocenes and budotitane complexes,14-18 our system indeed exhibits very high water stability.



**Fig. 2** Dependence of the absorbance at 380 nm with time of **3c** in 1 : 1 THF–water solution at RT under different pH conditions.

### Conclusion

It is thus apparent that our titanium complexes are not only "air stable" but are also highly resistant towards hydrolysis in THF-water solutions at a relatively wide pH range compared to previously reported compounds due to the unique electronic structure introduced by the triazine ligands, leading to the interesting structural features that contribute to the complex thermodynamic stability. In addition, the steric crowding of two such ligands probably adds a kinetic barrier to hydroxide attack, which is the main hydrolysis route based on the pH dependence observed. We are currently studying the structure and reactivity of systems featuring different ligands and properties, such as complexes exhibiting enhanced water solubility due to hydrophilic substituents.

### Experimental

Synthesis of ligands was achieved as previously described.<sup>28</sup> 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 dry atmosphere were performed in a M. Braun dry-box or under nitrogen atmosphere using Schlenk-line techniques. NMR data were recorded using an AMX-300 MHz Bruker spectrometer. X-Ray diffraction data were obtained with Bruker Smart Apex diffractometer. UV/Vis at different pH values were recorded on a Jasco V-530 UV/Vis spectrophotometer at room temperature using 1 cm path length cells. Elemental analyses were performed in the microanalytical laboratory in our institute.

# Bis[2,6-bis(*N*-hydroxo-*N*-methylamino)-4-morpholino-1,3,5-triazine]titanium, 3a

A solution of Ti(OiPr)<sub>4</sub> (0.039 mmol) in tetrahydrofuran (5 mL) was added to a solution of **2a** (0.078 mmol) in tetrahydrofuran (5 mL) at room temperature under nitrogen atmosphere. The colour changed instantly from colourless to yellow. The reaction mixture was stirred for additional 2 h and the tetrahydrofuran was removed under reduced pressure to give crude **3a** as a single isomer in a quantitative yield (Found: C, 39.22; H, 5.16; N, 29.44. Calc. for C<sub>18</sub>H<sub>28</sub>N<sub>12</sub>O<sub>6</sub>Ti: C, 38.86, H, 5.07, N, 30.21%). <sup>1</sup>H NMR  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 3.9 (8 H, t, *J* 4.7, CH<sub>2</sub>), 3.7 (8 H, t, *J* 4.7, CH<sub>2</sub>), 3.4 (12 H, s, NMe). <sup>13</sup>C NMR  $\delta_{\rm C}$  (300 MHz; CDCl<sub>3</sub>) 164.5 (Ar), 159.0 (Ar), 66.9 (CH<sub>2</sub>), 44.5 (CH<sub>2</sub>), 36.1 (NCH<sub>3</sub>).  $\lambda_{\rm max}$ (CH<sub>2</sub>Cl<sub>2</sub>)/nm 376 ( $\varepsilon$ /M<sup>-1</sup> cm<sup>-1</sup> 7000) and 252 (52000).

### Bis[2,6-bis(*N*-hydroxo-*N*-methylamino)-4-bis(ethoxycarbonylmethyl)amino-1,3,5-triazine]titanium, 3b

Similarly to the procedure described for **3a**, **3b** was obtained quantitatively as a single isomer by reacting Ti(OiPr)<sub>4</sub> (0.58 mmol) with **2b** (0.116 mmol) in tetrahydrofuran at room temperature (Found: C, 40.64; H, 5.29; N, 22.50. Calc. for  $C_{26}H_{40}N_{12}O_{12}Ti$ : C, 41.06, H, 5.30, N, 22.10%). <sup>1</sup>H NMR  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 4.4 (8 H, s, NCH<sub>2</sub>CO), 4.2 (8 H, q, *J* 7.2, CH<sub>2</sub>CH<sub>3</sub>), 3.4 (12 H, s, NMe), 1.3 (12 H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta_{\rm C}$  (300 MHz; CDCl<sub>3</sub>) 169.8 (CO), 165.2 (Ar), 158.3 (Ar), 61.1 (CH<sub>2</sub>), 50.2 (CH<sub>2</sub>), 35.9 (NCH<sub>3</sub>), 14.2 (CH<sub>3</sub>).  $\lambda_{\rm max}$ (THF)/nm 376 ( $\varepsilon/M^{-1}$  cm<sup>-1</sup> 7000) and 244 (56000).

### Bis[2,6-bis(*N*-hydroxo-*N*-methylamino)-4-dicyclohexylamino-1,3,5-triazine]titanium, 3c

Similarly to the previous procedures, **3c** was obtained quantitatively as a single isomer by reacting Ti(OiPr)<sub>4</sub> (0.21 mmol) with of **2c** (0.42 mmol) in diethyl ether at room temperature (Found: C, 54.73; H, 7.58; N, 22.41. Calc. for C<sub>34</sub>H<sub>56</sub>N<sub>12</sub>O<sub>4</sub>Ti: C, 54.83, H, 7.58, N, 22.57%). <sup>1</sup>H NMR  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 3.4 (12 H, s, NMe), 1.1–1.8 (44 H, m, Cy). <sup>13</sup>C NMR  $\delta_{\rm C}$  (300 MHz;

<sup>&</sup>lt;sup>†</sup>THF was employed both to provide a reference and allow accurate monitoring of absorbance change as well as to enhance solubility (3a-c are all poorly soluble in pure aqueous solutions).

### Crystal data

**3c** was crystallized from diethyl ether at -30 °C. The unit cell contains two molecules of diethyl ether.  $C_{34}H_{56}N_{12}O_4Ti \cdot 2C_4H_{10}O$ , M = 893.05, triclinic, space group  $P\overline{1}$ , a = 11.9542(12), b = 12.6502(12), c = 17.5705(17) Å, a = 79.126(2),  $\beta = 80.599(2)$ ,  $\gamma = 66.344(2)^{\circ}$ , U = 2378.7(4) Å<sup>3</sup>, T = -102 K, Z = 2,  $\mu$ (Mo-K $\alpha$ ) = 0.237 cm<sup>-1</sup>, 13465 reflections measured, 9135 unique ( $R_{int} = 0.0420$ ).  $R(F_o^2)$  for  $[I > 2\sigma(I)] = 0.0916$ , Rw for  $[I > 2\sigma(I)] = 0.1827$ .

CCDC reference number 604238.

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606072b

### Acknowledgements

We thank the Allon Foundation as well as the friends of the HU USA for financial support. We also thank Dr Shmuel Cohen for solution of the X-ray structure.

### References

- 1 R. O. Duthaler and A. Hafner, Chem. Rev., 1992, 92, 807.
- 2 Y. Qian, J. Huang, M. D. Bala, B. Lian, H. Zhang and H. Zhang, *Chem. Rev.*, 2003, **103**, 2633.
- 3 R. Beckhaus and C. Santamaría, *J. Organomet. Chem.*, 2001, **617–618**, 81.
- 4 J. C. Vites and M. M. Lynam, Coord. Chem. Rev., 1995, 138, 71.
- 5 J. C. Vites and M. M. Lynam, Coord. Chem. Rev., 1995, 146, 1.
- 6 E. Manek, D. Hinz and G. Meyer, *Coord. Chem. Rev.*, 1997, **164**, 5.
- 7 V. Ugrinova, G. A. Ellis and S. N. Brown, *Chem. Commun.*, 2004, 468.

- 8 C. F. Campana, Y. Chen, V. W. Day, W. G. Klemperer and R. A. Sparks, J. Chem. Soc., Dalton Trans., 1996, 691.
- 9 N. Peulecke, W. Baumann, R. Kempe, V. V. Burlakov and U. Rosenthal, *Eur. J. Inorg. Chem.*, 1998, 419.
- 10 J. Chen, N. H. Hu, J. Zhan and Y. S. Li, Acta Crystallogr., Sect. C, 2005, 61, M337.
- 11 F. Caruso, M. Rossi, J. Tanski, R. Sartori, R. Sariego, S. Moya, S. Diez, E. Navarrete, A. Cingolani, F. Marchetti and C. Pettinari, J. Med. Chem., 2000, 43, 3665.
- 12 M. Bochmann, J. Chem. Soc., Dalton Trans., 1996, 255.
- 13 X. Wang, X. Wang, H. Guo, Z. Wang and K. Ding, Chem. Eur. J., 2005, 11, 4078.
- 14 E. Meléndez, Crit. Rev. Oncol. Hematol., 2002, 42, 309.
- 15 G. Mokdsi and M. M. Harding, J. Organomet. Chem., 1998, 565, 29.
- 16 M. Guo, H. Sun, S. Bihari, J. A. Parkinson, R. O. Gould, S. Parsons and P. J. Sadler, *Inorg. Chem.*, 2000, **39**, 206.
- 17 J. H. Toney and T. J. Marks, J. Am. Chem. Soc., 1985, 107, 947.
- 18 Y. Pérez, V. López, L. Rivera-Rivera, A. Cardona and E. Meléndez, J. Biol. Inorg. Chem., 2005, 10, 94.
- 19 R. Bína, M. Pavlišta, Z. Černošek, I. Císařová and I. Pavlík, Appl. Organomet. Chem., 2005, 19, 701.
- 20 E. Y. Tshuva, M. Versano, I. Goldberg, M. Kol, H. Weitman and Z. Goldschmidt, *Inorg. Chem. Commun.*, 1999, 2, 371.
- 21 E. Y. Tshuva, I. Goldberg, M. Kol and Z. Goldschmidt, Organometallics, 2001, 20, 3017.
- 22 N. W. Mitzel, S. Parsons, A. J. Blake and D. W. H. Rankin, J. Chem. Soc., Dalton Trans., 1996, 2089.
- 23 V. K. Wieghardt and I. Tolksdorf, Z. Anorg. Allg. Chem., 1982, 490, 182.
- 24 R. Reichenbach-Klinke, M. Zabel and B. Koenig, *Dalton Trans.*, 2003, 141.
- 25 M. K. Mahanthappa, A. P. Cole and R. M. Waymouth, Organometallics, 2004, 23, 1405.
- 26 C. Lustig and N. W. Mitzel, Angew. Chem., Int. Ed., 2001, 40, 4390.
- 27 J. Gun, I. Ekeltchik, O. Lev, R. Shelkov and A. Melman, *Chem. Commun.*, 2005, 5319.
- 28 I. Ekeltchik, J. Gun, O. Lev, R. Shelkov and A. Melman, *Dalton Trans.*, 2006, 1285.
- 29 A. R. Katritzky, I. Ghiviriga, P. J. Steel and D. C. Oniciu, J. Chem. Soc., Perkin Trans. 2, 1996, 443.
- 30 A. Cousson, B. Nicolai and F. Fillaux, Acta Crystallogr., Sect. E, 2005, 61, 222.