JOC Article

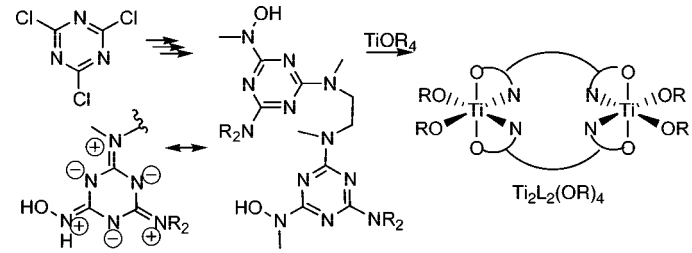
Synthesis and Conformational Analysis of Constrained Ethylene-Bridged Bis(hydroxylamino-1,3,5-triazine) Compounds as Tetradentate Ligands; Structure of Rigid Dinuclear Ti(IV) Complex

Tal Hermon and Edit Y. Tshuva*

Institute of Chemistry, The Hebrew University of Jerusalem, 91904 Jerusalem, Israel

tshuva@chem.ch.huji.ac.il

Received May 7, 2008

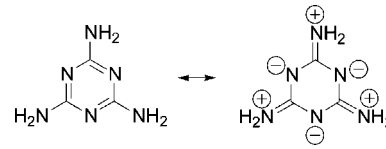


Ethylene-bridged bis(hydroxylamino-1,3,5-triazine) compounds, that may serve as tetradentate ligands, were synthesized in three steps from 2,4,6-trichloro-1,3,5-triazine. These compounds demonstrate different rotation restrictions around the $C_{Ar}-N$ bonds due to their distinctive electronic structure as apparent from their resonative contributors. A dinuclear complex $Ti_2(\mu\text{-}L)_2(OiPr)_4$ (L = bis(triazine)) was synthesized where each octahedral Ti(IV) center is also bound to two isopropoxo groups. The complex rigidity is manifested in a significant deviation from planarity of the aromatic systems, and relatively long Ti−N bonds compared to mononuclear analogous complexes. Increased ligand lability in this complex brings about diminished cytotoxicity toward colon and ovarian cells.

Introduction

1,3,5-Triazine-based compounds have been studied for decades and have been employed for various applications of organic synthesis, including those relating to construction of supramolecular composites.[1–5] One particularly interesting feature of 2,4,6-triamino substituted 1,3,5-triazine compounds, also known as melamine derivatives, is the high electron density of the triazine nitrogen atoms, which results from the resonative contribution of electrons of the amino substituents (Scheme 1). This contribution is also pronounced by the observed high planarity of this compound and thus the large sp^2 character of the substituting nitrogen atoms.[6] This feature makes the triazine nitrogen atoms especially good ligands to various transition metals.[7–13] Particularly, we have recently introduced bis(hydroxylamino)triazine ligands, featuring two covalent aminoalkoxo donors in addition to a coordinative triazine nitrogen

SCHEME 1



* To whom correspondence should be addressed. Fax: +972 2 6584282. Tel.: +972 2 6586084.

(1) Giacomelli, G.; Porcheddu, A.; Luca, L. D. *Curr. Org. Chem.* **2004**, *8*, 1497.
(2) Blotny, G. *Tetrahedron* **2006**, *62*, 9507.
(3) Mooibroek, T. J.; Gamez, P. *Inorg. Chim. Acta Inorg. Chem.* **2007**, *360*, 381.
(4) Kaminski, Z. J. *Biopolymers* **2000**, *55*, 140.
(5) Gamez, P.; Reedijk, J. *Eur. J. Inorg. Chem.* **2006**, 29.
(6) Cousson, A.; Nicolai, B.; Fillaux, F. *Acta Crystallogr., Sect. E* **2005**, *61*, 222.
(7) Gun, J.; Ekeltchik, I.; Lev, O.; Shelkov, R.; Melman, A. *Chem. Commun.* **2005**, 5319.
(8) Ekeltchik, I.; Gun, J.; Lev, O.; Shelkov, R.; Melman, A. *Dalton Trans.* **2006**, 1285.
(9) Carrion, M. C.; Guerrero, A.; Jalon, F. A.; Manzano, B. R.; de la Hoz, A.; Claramunt, R. M.; Milata, V.; Elguero, J. *Inorg. Chem.* **2003**, *42*, 885.
(10) Gelling, A.; Orrell, K. G.; Osborne, A. G.; Sik, V. *J. Chem. Soc., Dalton Trans.* **1996**, 3371.
(11) Ma, D.-L.; Che, C.-M.; Siu, F.-M.; Yang, M.; Wong, K.-Y. *Inorg. Chem.* **2007**, *46*, 740.
(12) Lu, H.-J.; Fan, Y.-T.; Gao, J.; Hou, H.-W. *J. Coord. Chem.* **2004**, *57*, 693.
(13) Sivashankar, K.; Ranganathan, A.; Pedireddi, V. R.; Rao, C. N. R. *J. Mol. Struct.* **2001**, *559*, 41.

10.1021/jo800966s CCC: $40.75
Published on Web 06/24/2008

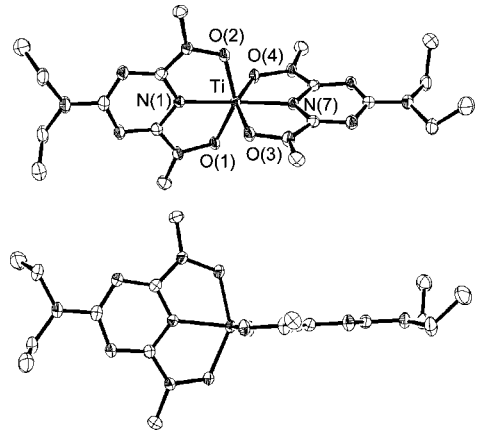
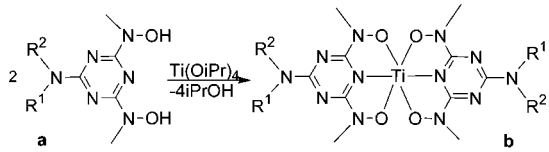


FIGURE 1. ORTEP drawing of **4b** shown from two angles at 50% probability ellipsoids (H atoms and solvent were omitted for clarity).

SCHEME 2

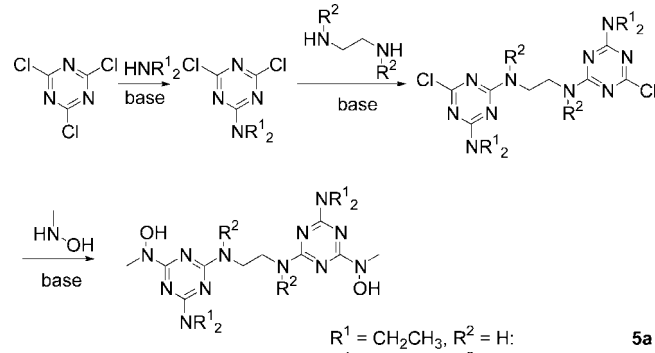


1 $R^1 = R^2 = c\text{-}C_6H_{11}$
2 $R^1, R^2 = -CH_2CH_2OCH_2CH_2-$ (morpholino)
3 $R^1 = R^2 = CH_2CO_2CH_2CH_3$
4 $R^1 = R^2 = CH_2CH_3$

donor, for Ti(IV) metal (Scheme 2).[14] We reported formation of homoleptic $[ONO]_2$Ti-type mononuclear complexes, which exhibit exceptionally short Ti−N coordinative bonds owing to the ligand distinctive electronic features, pronounced by especially high hydrolytic stability.[14]

The recent interest in identifying new cytotoxic non-Pt based metal compounds,[15–26] and the promising results observed with Ti(IV) complexes,[18,19,27–34] prompt us to investigate our aminoalkoxo complexes for biological applications. Surprisingly, the inert complex **3b** (Scheme 2) exhibits some cytotoxicity against colon HT-29 and ovarian OVCAR-1 cells,[35] despite having no labile groups (Cl, OR) generally assumed to be essential for activity.[36,37] As tetradentate [2−] ligands may coordinatively saturate a bis(alkoxo) Ti(IV) center[38] and may thus allow the exploration of the labile ligand effect, we became interested in the synthesis of more complex bis(triazine) compounds featuring two particularly electron-rich coordinative N-atoms (Scheme 3).

SCHEME 3



$R^1 = CH_2CH_3$, R^2 = H: **5a**
$R^1 = CH_2CH_3$, $R^2 = CH_3$: **6a**
$R^1 = CH_2CO_2CH_2CH_3$, $R^2 = CH_3$: **7a**

Several examples of the synthesis of diamino-bridged 1,3,5-triazine rings were reported;[39–47] however, bridged hydroxylamino-1,3,5-triazine compounds were never synthesized. Herein we present in particular the synthesis of tetradentate bis(triazine) compounds, **5a**−**7a**, which vary in the substituents of the N donors (Scheme 3), and discuss their dynamic behavior in solution. The structure and properties of a resulting Ti(IV) complex is compared to those of the homoleptic complexes of tridentate triazine ligands.

Results and Discussion

The synthesis of **4a** (Scheme 2) was achieved by reacting 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) with excess amounts of diethylamine in THF as a solvent in an ice bath and stirring them for 0.5 h, after which the colorless precipitate was filtered and discarded and the solution was evaporated. The crude product was recrystallized from 2-propanol. The formation of the monosubstituted product was verified by ^{1}H NMR, and consequently, double substitution with methylhydroxylamine was undertaken by employing excessive amounts of *N*-methylhydroxylamine hydrochloride previously stirred with NaOH in water, and refluxing the solution mixture overnight. Evaporat-

(14) Peri, D.; Alexander, J.; Tshuva, E. Y.; Melman, A. *Dalton Trans.* **2006**, 4169.
(15) Clarke, M. J.; Zhu, F.; Frasca, D. R. *Chem. Rev.* **1999**, *99*, 2511.
(16) Kratz, F.; Schütte, M. T. *Cancer J.* **1998**, *11*, 176.
(17) Köpf-Maier, P. *Eur. J. Clin. Pharmacol.* **1994**, *47*, 1.
(18) Köpf-Maier, P.; Köpf, H. *Chem. Rev.* **1987**, *87*, 1137.
(19) Christodoulou, C. V.; Eliopoulos, A. G.; Young, L. S.; Hodgkins, L.; Ferry, D. R.; Kerr, D. J. *Br. J. Cancer* **1998**, *77*, 2088.
(20) Desoize, B. *Anticancer Res.* **2004**, *24*, 1529.
(21) Xu, G.; Cui, Y. B.; Cui, K.; Gou, S. H. *Prog. Chem.* **2006**, *18*, 107.
(22) Galanski, M.; Arion, V. B.; Jakupec, M. A.; Keppler, B. K. *Curr. Pharm. Des.* **2003**, *9*, 2078.
(23) Ott, I.; Gust, R. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 117.
(24) Katsaros, N.; Anagnostopoulou, A. *Crit. Rev. Oncol. Hemat.* **2002**, *42*, 297.
(25) Kostova, I. *Curr. Med. Chem.* **2006**, *13*, 1085.
(26) Evangelou, A. M. *Crit. Rev. Oncol. Hemat.* **2002**, *42*, 249.
(27) Meléndez, E. *Crit. Rev. Oncol. Hemat.* **2002**, *42*, 309.
(28) Caruso, F.; Rossi, M.; Pettinari, C. *Expert Opin. Ther. Pat.* **2001**, *11*, 969.
(29) Köpf-Maier, P.; Köpf, H. *Struct. Bonding (Berlin)* **1988**, *70*, 103.
(30) Kelter, G.; Sweeney, N. J.; Strohfeldt, K.; Fiebig, H.-H.; Tacke, M. *Anti-Cancer Drugs* **2005**, *16*, 1091.
(31) Keppler, B. K.; Friesen, C.; Moritz, H. G.; Vongerichten, H.; Vogel, E. *Struct. Bonding (Berlin)* **1991**, *78*, 97.
(32) Caruso, F.; Rossi, M.; Tanski, J.; Sartori, R.; Sariego, R.; Moya, S.; Diez, S.; Navarrete, E.; Cingolani, A.; Marchetti, F.; Pettinari, C. *J. Med. Chem.* **2000**, *43*, 3665.
(33) Caruso, F.; Rossi, M. *Mini-Rev. Med. Chem.* **2004**, *4*, 49.
(34) Shavit, M.; Peri, D.; Manna, C. M.; Alexander, J. S.; Tshuva, E. Y. *J. Am. Chem. Soc.* **2007**, *129*, 12098.
(35) Shavit, M.; Peri, D.; Melman, A.; Tshuva, E. Y. *J. Biol. Inorg. Chem.* **2007**, *12*, 825.
(36) Yang, P.; Guo, M. *Coord. Chem. Rev.* **1999**, *189*, 185–186.
(37) Caruso, F.; Rossi, M.; Opazo, C.; Pettinari, C. *Bioinorg. Chem. Appl.* **2005**, *3*, 317.
(38) Tshuva, E. Y.; Versano, M.; Goldberg, I.; Kol, M.; Weitman, H.; Goldschmidt, Z. *Inorg. Chem. Commun.* **1999**, *2*, 371.
(39) Lai, L.-L.; Wang, L.-Y.; Lee, C.-H.; Lin, Y.-C.; Cheng, K.-L. *Org. Lett.* **2006**, *8*, 1541.
(40) Chen, H.-T.; Neerman, M. F.; Parrish, A. R.; Simanek, E. E. *J. Am. Chem. Soc.* **2004**, *126*, 10044.
(41) Umali, A. P.; Simanek, E. E. *Org. Lett.* **2003**, *5*, 1245.
(42) de Hoog, P.; Gamez, P.; Driessen, W. L.; Reedijk, J. *Tetrahedron Lett.* **2002**, *43*, 6783.
(43) Yang, X.; Lowe, C. R. *Tetrahedron Lett.* **2003**, *44*, 1359.
(44) Marsh, A.; Carlisle, S. J.; Smith, S. C. *Tetrahedron Lett.* **2001**, *42*, 493.
(45) Zhang, W.; Simanek, E. E. *Tetrahedron Lett.* **2001**, *42*, 5355.
(46) Borkovec, A. B.; DeMilo, A. B. *J. Med. Chem.* **1967**, *10*, 457.
(47) Reddy, N. D.; Elias, A. J.; Vij, A. *J. Chem. Res. Synop.* **1998**, 504.

TABLE 1. Selected Bond Lengths (Å) and Angles (deg) for 4b

atoms	value	atoms	value	atoms	value
		Lengths			
O(1)−Ti	1.9652(13)	O(3)−Ti	1.9576(13)	N(1)−Ti	2.0186(15)
O(2)−Ti	1.9556(13)	O(4)−Ti	1.9482(13)	N(7)-Ti	2.0221(15)
		Angles			
O(4)−Ti−O(2)	94.10(6)	O(3)−Ti−O(1)	95.27(6)	O(4)−Ti−N(1)	117.61(6)
O(4)−Ti−O(3)	146.02(6)	N(1)−Ti−N(7)	167.82(6)	O(1)−Ti−N(7)	113.03(6)
O(2)−Ti−O(3)	96.48(6)	O(1)−Ti−N(1)	73.36(6)	O(2)−Ti−N(7)	101.71(6)
O(4)−Ti−O(1)	94.17(6)	O(2)−Ti−N(1)	72.87(6)	O(3)−Ti−N(7)	73.12(6)
O(2)−Ti−O(1)	145.21(6)	O(3)−Ti−N(1)	96.37(6)	O(4)−Ti−N(7)	73.14(6)

ing the organic solvent and recrystallization from 2-propanol gave **4a**, as verified by ^{1}H NMR, in a total yield for both steps of 23%.

The homoleptic titanium complex **4b** was also synthesized similarly to **1b**−**3b**[14] by reacting titanium tetra(isopropoxide) with 2 equiv of **4a** at room temperature in THF. Single crystals suitable for X-ray crystallography were obtained from THF at −35 °C, and an ORTEP view of the structure is presented in Figure 1 with a summary of selected bond lengths and angles given in Table 1.

The structure features an octahedral Ti(IV) center bound to two approximately perpendicular tridentate triazine ligands in a *mer*−*mer* geometry similarly to a related complex of this class.[14] A particularly unique feature of this family of complexes is exceptionally short Ti−N coordinative bonds of 2.0 Å, which is in accordance with a large contribution of the resonative structure presented in Scheme 1 that includes negative charge on the coordinative N-donors.

The synthesis of compounds **5a**−**7a** was achieved by a three-step procedure, starting with 2,4,6-trichloro-1,3,5-triazine. The first step for the synthesis of **5a** is similar to the first step in the preparation of **4a**. The monosubstituted product was further reacted in the second step with 0.5 equiv of ethylenediamine in the presence of triethylamine as a base in dichloromethane/acetonitrile at room temp, and after stirring overnight, the reaction mixture was filtered, evaporated, and the resulting product was recrystallized from 2-propanol to give a colorless powder. ^{1}H NMR has confirmed the product to be the ethylene-bridged compound (Scheme 3).

The bis(triazine) compound as a THF solution was finally reacted with an excess of *N*-methylhydroxylamine hydrochloride previously stirred with NaOH in water, and the mixture was refluxed for 1 day. Evaporating the organic solvent gave a colorless powder, which was recrystallized from acetonitrile in a total yield for all steps of 24%. ^{1}H NMR confirmed the product to be **5a** (Scheme 3), featuring one type of ethyl group and two additional singlets. It was observed that the hydroxylamino substituent activates the triazine ring for further substitution and thus is best to be inserted last.

6a (Scheme 3) was synthesized in a similar manner, by reacting the diethylamino monosubstituted compound with 0.5 equiv of *N*,*N*′-dimethylethylenediamine and recrystallization from acetonitrile, followed by the hydroxylamino substitution to give **6a** in a total of 22% yield following recrystallization from acetonitrile. The ^{1}H NMR of **6a** is consistent with that of **5a**, featuring three singlets in addition to a single type of ethyl group.

7a (Scheme 3) was also synthesized in a similar manner, starting with 1 equiv of diethyliminodiacetate for the first substitution in the presence of 1 equiv of diisopropylethylamine (DIPEA) as a base, which was employed for the second step as well. The final product was recrystallized from 2-propanol in a total yield of 16%. Interestingly, multiple broad signals were observed in the ^{1}H NMR of both the final product and the product of the second step, suggesting a dynamic behavior. 2D HSQC measurements supported this notion.

Dynamic NMR measurements were performed on **3a**−**7a** (Scheme 2,3) at 190−390 K. Indeed, cooling **7a** to 280 K in d_8-THF gave ^{1}H NMR and ^{13}C NMR spectra with well separated signals, where each type of NMe is separated into four different singlets, the methylene bridge appears as two singlets and two triplets in the ^{1}H NMR and as four signals in the ^{13}C NMR, and eight different signals are observed for the NCH_2CO$_2$Et group as particularly revealed by HSQS measurements at this temperature (Figure 2a; Figure S11−S18 in Supporting Information). Heating **7a** to 390 K revealed complete coalescence for all signals to give a highly symmetrical molecule (Figure 2b). In contrast, for **5a** and **6a**, only after cooling to 290 K, multiple peaks began to appear. We may thus conclude that

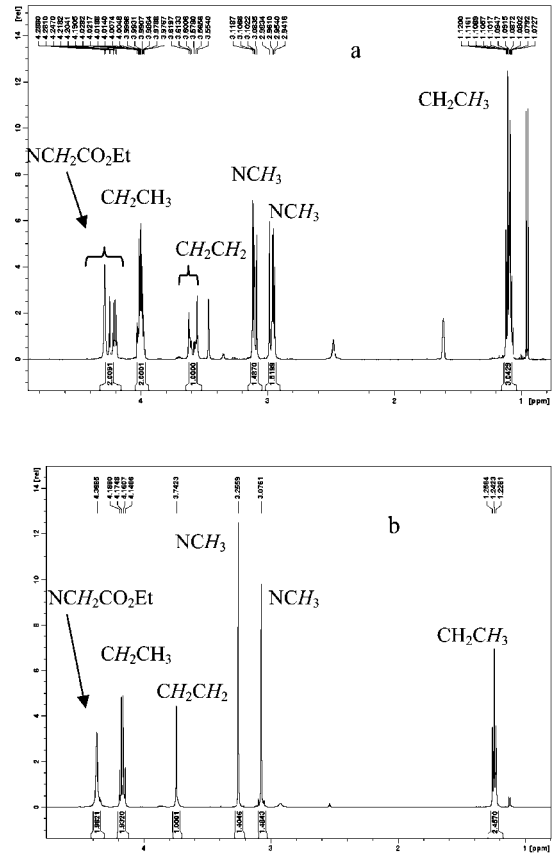
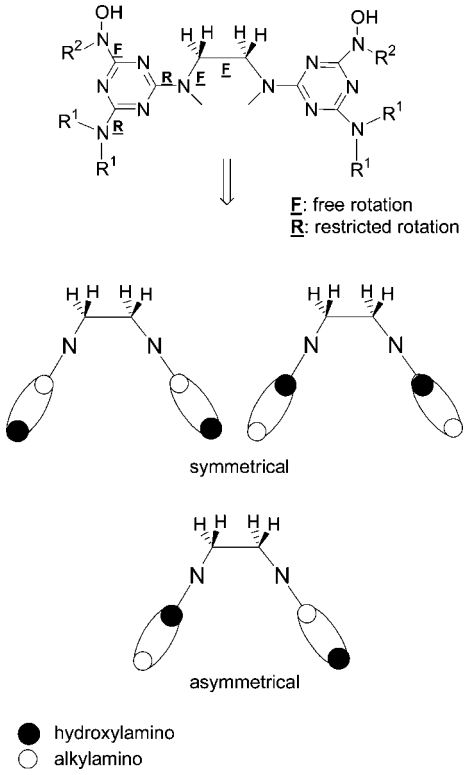


FIGURE 2. ^{1}H NMR spectra (500 MHz) of **7a** in d_8-THF at 280 K demonstrating restricted rotation (a) and in d_6-DMSO at 390 K demonstrating free rotation (b).

SCHEME 4. Schematic Representation of Stereoisomers Resulting from Restricted Rotation



restricted rotation around the $C_{Ar}-N$ bonds, due to the highly contributing resonative structure where the amino substituents on the triazine rings are of sp^2 character (Scheme 1), results in several conformations in solution that do not interconvert in the NMR time scale under certain temperature conditions. As the monotriazine molecules **3a** and **4a** (Scheme 2) do not show multiple NMe peaks at temperatures as low as 190 K, with $\Delta G^{\ddagger}$ for rotation of 36.5−38.5 ± 1.3 kJ mol^{-1}, we conclude that the rotation around the $C_{Ar}-N$(OH)Me is relatively free for the bis(triazine) compounds as well under the conditions employed. We thus conclude that the rotations around the two $C_{Ar}-NCH_2$ bonds in **7a** are restricted owing to steric interference giving altogether three isomers, two symmetrical and one asymmetrical (Scheme 4), where each includes two different ester groups on each triazine ring. The average $\Delta G^{\ddagger}$ calculated based on coalescence of the two NMe and the two NCH_2 signals for rotation around the $C_{Ar}-N(Me)CH_2CH_2$ bond is 69.0 ± 1.3 kJ mol^{-1}, whereas the $\Delta G^{\ddagger}$ calculated based on coalescence of NCH_2CO_2 signals for rotation around the $C_{Ar}-N(CH_2CO_2Et)_2$ bond is 78.7 ± 1.3 kJ mol^{-1}. Clearly, the compounds **5a** and **6a** demonstrate lower $\Delta G^{\ddagger}$ values of 61.9 ± 1.3 and 64.9 ± 2.1 kJ mol^{-1}, respectively, for rotation around the $C_{Ar}-N$(Me/H)CH_2CH_2 bond due to their reduced steric bulk, with higher restriction in the bulkier compound, as expected.

Reacting **7a** with 1 equiv of titanium tetra(isopropoxide) in THF at room temperature overnight gave a dark-yellow solution. Single crystals suitable for X-ray crystallography were grown from diethylether, and an ORTEP view of the structure is presented in Figure 3 with selected bond lengths and angles summarized in Table 2.

The structure features a C_i-symmetrical dinuclear species, of the formula $Ti_2(\mu\text{-L})_2(OiPr)_4$ (L = bis(triazine)), where the two Ti(IV) centers are of a highly distorted octahedral configuration.

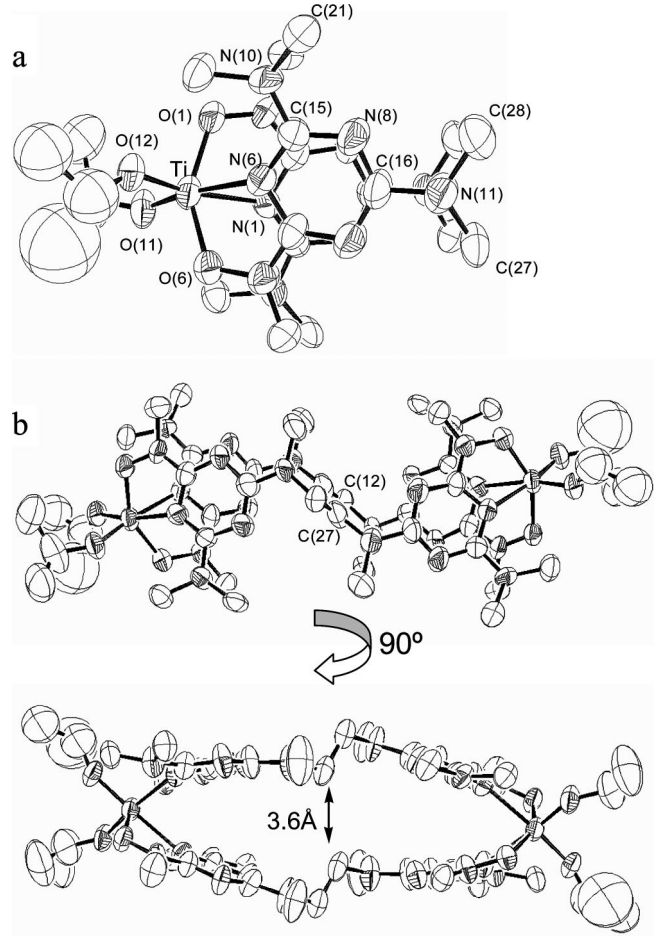


FIGURE 3. ORTEP drawing of **7b** shown at 50% probability ellipsoids (H atoms and ester groups were omitted for clarity) for half of the molecule (a) and two angles of the molecule in full (b).

Since the tetradentate ligand is too rigid to wrap around a single Ti(IV) center owing to the planarity of the aromatic systems (C(12)−C(27): 4.68 Å), two ligand units bridge between the two Ti(IV) ions. The two triazine rings of each ligand thus bind to separate Ti(IV) centers through the aminoalkoxo groups and N-donors of the highest electron density, giving an especially long Ti−Ti distance of 13.8 Å, and the ligand is constrained in the asymmetrical conformation (Scheme 4). The rigidity of the molecule is also pronounced in longer Ti−N coordinative bonds of 2.3−2.4 Å in comparison to the 2.0 Å value observed for the mononuclear homoleptic complexes, as well as in the substantial deviation from planarity of the aromatic moieties of up to 20°. It is also notable that as one cause for the longer Ti−N bonds, the Ti(IV) centers are not coplanar with the aromatic moieties of the triazine systems, unlike the observation with the homoleptic analogues, which is another obvious consequence of the ligand rigidity on one hand, and the tendency of the Ti(IV) center to complete its coordination sphere in an optimal form on the other. Interestingly, a very planar array of the ethylene bridges of the two bridging ligands is observed, with a N(11)−C(27)−C(12′)−N(12′) torsion angle of 176.7° and a 180.0° angle between the two C−C vectors of the ethylene bridges of the two ligands. Each Ti(IV) ion thus fills altogether four coordination sites by donors from the chelating ligand while the two additional covalent bonds are to isopropoxo ligands to give two octahedral Ti(IV) centers. Altogether, this complex includes a total Ti:L (bis(triazine)):OiPr ratio of 1:1:2.

TABLE 2. Selected Bond Lengths (Å) and Angles (deg) for 7b

atoms	value	atoms	value	atoms	value
			Lengths		
O(1)−Ti	1.931(7)	N(6)−Ti	2.356(9)	N(8)−C(16)	1.300(14)
O(6)−Ti	1.908(7)	N(4)−O(1)	1.342(10)	C(16)−N(11)	1.387(14)
O(11)−Ti	1.800(8)	N(9)−O(6)	1.401(10)	N(11)−C(28)	1.496(15)
O(12)−Ti	1.794(7)	N(6)−C(15)	1.373(13)	N(11)−C(27)	1.480(14)
N(1)−Ti	2.303(8)	C(15)−N(8)	1.349(13)	C(12)−C(27)	1.465(16)
			Angles		
O(12)−Ti−O(11)	95.2(3)	O(1)−Ti−N(1)	74.7(3)	N(8)−C(16)−N(11)	117.1(11)
O(12)−Ti−O(6)	101.7(3)	O(12)−Ti−N(6)	91.4(3)	C(16)−N(11)−C(28)	118.2(11)
O(11)−Ti−O(6)	100.6(3)	O(11)−Ti−N(6)	171.9(3)	C(28)−N(11)−C(27)	117.4(10)
O(12)−Ti−O(1)	97.1(3)	O(6)−Ti−N(6)	73.4(3)	N(11)−C(27)−C(12)	110.2(11)
O(11)−Ti−O(1)	102.0(4)	O(1)−Ti−N(6)	81.6(3)	N(11)−C(27)−C(12)−N(11)	176.7
O(12)−Ti−N(1)	169.2(3)	N(1)−Ti−N(6)	80.4(3)	C(28)−N(11)−C(27)−C(12)	88.5
O(11)−Ti−N(1)	93.5(3)	N(6)−C(15)−N(8)	125.3(10)	N(6)−C(15)−N(8)−C(16)	177.0
O(6)−Ti−N(1)	82.9(3)	C(15)−N(8)−C(16)	114.0(10)	C(21)−N(10)−C(15)−N(8)	170.6

The cytotoxicity of the dinuclear complex **7b** was tested to evaluate the influence of the labile isopropoxo groups and general ligand lability. Employing the MTT assay,[35] we found that unlike its homoleptic counterpart **3b** (Scheme 2), this complex exhibits essentially no reactivity against colon HT-29 and ovarian OVCAR-1 cells. It therefore appears that the hydrolytic stability observed for **3b** is essential for cytotoxicity, a parameter that is more important than the existence of additional particularly labile monodentate groups, despite the general assumption that such groups are required to allow binding to the biological target following their hydrolysis.[35] Thus, the longer Ti−N bonds in **7b**, which lead to substantially increased hydrolytic instability, appear to play a significant role in abolishing the biological activity.

Experimental Section

4a (Figures S1−S2). Diethylamine (5.6 mL, 54.13 mmol) in THF was added dropwise to a solution of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) (5.0 gr, 27.11 mmol), in THF at 0 °C after which the reaction mixture was stirred for an additional 0.5 h. The colorless solid was filtered, and the THF solution was evaporated to dryness. The crude product was recrystallized from 2-propanol to give the monosubstituted product as crystalline solid (4.1 gr, 67%). This product (1.5 gr, 6.78 mmol) was redissolved in THF; *N*-methylhydroxylamine hydrochloride (2.27 gr, 27.12 mmol) previously contradicted with NaOH (1.09 gr, 27.12 mmol) in water was added, and the reaction mixture was refluxed overnight. The THF was evaporated to yield a colorless precipitate, which was filtered and recrystallized from 2-propanol to give **4a** as a colorless powder (0.55 g, 34%). The total yield is 23%. Anal. Calcd for $C_9H_{18}N_6O_2$: C, 44.62; H, 7.49; N, 34.69. Found: C, 44.60; H, 7.75; N, 34.61. ^{1}H NMR (Figure S1) (500 MHz; $CDCl_3$; rt) δ 3.5 (4 H, q, $J = 7.1$ Hz, CH_2CH_3), 3.4 (6 H, s, NMe), 1.2 (6 H, t, $J = 7.1$ Hz, CH_2CH_3). ^{13}C NMR (Figure S2) (500 MHz; $CDCl_3$; rt) δ 162.9, 162.2, 41.7, 37.0, 13.1; mp 146 °C.

5a (Figures S3−S5). The monosubstituted product was obtained as described above. This product (1.0 g, 4.52 mmol) was redissolved in acetonitrile and triethylamine (0.63 mL, 4.52 mmol) was added. Ethylenediamine (0.15 mL, 2.26 mmol) dissolved in dichloromethane was added dropwise at rt, and consequently the reaction mixture was stirred overnight. The precipitate was filtered, and the solution was evaporated to give a colorless solid, which was recrystallized from 2-propanol to give the disubstituted product as a colorless powder (0.50 g, 52%). The powder (0.43 g, 1.01 mmol) was dissolved in THF; *N*-methylhydroxylamine hydrochloride (0.51 g, 3.04 mmol) previously contradicted with NaOH (0.24 g, 3.04 mmol) in water was added, and the reaction mixture was refluxed for 1 day. The THF was evaporated to give a white precipitate, which was filtered and recrystallized from acetonitrile to give **5a** as a colorless powder (0.32 g, 71%). The total yield is 24%. Anal. Calcd for $C_{18}H_{34}N_{12}O_2$: C, 47.99; H, 7.61; N, 37.31. Found: C, 48.00; H, 7.70; N, 37.04. ^{1}H NMR (Figure S3−S4) (400 MHz; $CDCl_3$; rt) δ 3.6 (4 H, s, NCH_2), 3.5 (8 H, q, $J = 7.2$ Hz, CH_2CH_3), 3.3 (6 H, s, NMe), 1.2 (12 H, t, $J = 7.1$ Hz, CH_2CH_3). ^{13}C NMR (Figure S5) (400 MHz; $CDCl_3$, rt) δ 167.0, 165.5, 163.9, 41.3, 37.5, 13.4. Mp 149 °C.

6a (Figures S6−S8). The monosubstituted product was obtained as described above. The two consequent steps are similar to those undertaken for **5a**, where the monosubstituted product (1.0 g, 4.52 mmol) in THF to which triethylamine (0.63 mL, 4.55 mmol) was added was reacted with *N*,*N*′-dimethylethylenediamine (0.24 mL, 2.27 mmol) in THF and stirred overnight. The colorless powder obtained following filtration and evaporation was recrystallized from acetonitrile to give the disubstituted product as colorless crystals (0.67 g, 65%). The crystals (0.67 g, 1.48 mmol) in dichloromethane were refluxed overnight with *N*-methylhydroxylamine hydrochloride (0.74 g, 8.83 mmol) previously contradicted with NaOH (0.35 g, 8.83 mmol) in water, and evaporation of the dichloromethane and recrystallization from acetonitrile gave **6a** as a colorless powder (0.36 g, 51%). The total yield is 22%. Anal. Calcd for $C_{20}H_{38}N_{12}O_2$: C, 50.19; H, 8.00; N, 35.12. Found: C, 50.37; H, 8.14; N, 34.87. ^{1}H NMR (Figure S6−S7) (400 MHz; $CDCl_3$; rt) δ 3.7 (4 H, s, NCH_2CH_2N), 3.5 (8 H, q, $J = 6.8$ Hz, CH_2CH_3), 3.3 (6 H, s, NMe), 3.1 (6 H, s, NMe), 1.2 (12 H, t, $J = 7.0$ Hz, CH_2CH_3). ^{13}C NMR (Figure S8) (500 MHz; $CDCl_3$; rt) δ 167.9, 164.7, 163.6, 46.2, 41.3, 37.3, 35.1, 13.3; mp 99 °C.

7a (Figures S9−S18). 7a was synthesized similarly to **5a** and **6a** starting from cyanuric chloride (2.0 gr, 10.84 mmol) in THF previously mixed with DIPEA (1.88 mL, 10.79 mmol), at 0 °C where a color change to light yellow was observed, and diethyliminodiacetate (1.94 mL, 10.83 mmol) in THF. The product of the first step was recrystallized from 2-propanol (1.73 g, 47%). For the second step, the first product (1.5 g, 4.45 mmol) in THF mixed with DIPEA (0.78 mL, 4.48 mmol) was reacted with *N*,*N*′-dimethylethylenediamine (0.24 mL, 2.24 mmol) to give a colorless powder that was recrystallized from 2-propanol (0.84 g, 54%). This compound (0.84 g, 1.22 mmol) was further reacted in THF with *N*-methylhydroxylamine hydrochloride (0.61 g, 7.32 mmol) previously contradicted with NaOH (0.29 g, 7.32 mmol) in water. Refluxing the product in water following THF evaporation gave **6a** as a colorless powder that was recrystallized from 2-propanol (0.55 g, 63%) with a total yield of 16% for all three steps. Anal. Calcd for $C_{28}H_{46}N_{12}O_{10}$: C, 47.32; H, 6.52; N, 23.65. Found: C, 47.19; H, 6.53; N, 23.40. ^{1}H NMR (Figure S9−S10) (500 MHz; d_6-DMSO; 390 K) δ 4.4 (8 H, s, NCH_2CO), 4.2 (8 H, q, $J = 7.0$ Hz, CH_2CH_3), 3.7 (4 H, s, NH_2), 3.3 (6 H, s, NMe), 3.1 (6 H, s, NMe), 1.2 (12 H, t, $J = 7.0$ Hz, CH_2CH_3). ^{13}C NMR (Figure S11−S13) (500 MHz; d_8-THF; 280 K) δ 168.0, 167.9, 167.9, 167.8

(CO), 165.7, 165.7, 165.6, 165.5 (Ar^1), 163.3, 163.3, 163.3 (Ar^2), 163.0, 163.0, 163.0, 162.9 (Ar^3), 58.3, 58.3, 58.2, 58.2, 58.1 (CH_2CH_3), 47.2, 47.1, 47.0, 46.9, 46.8, 46.8 (NCH_2CO_2), 44.1, 44.0, 43.9, 43.8 ($NMeCH_2$), 163.3, 163.3, 163.3 (NMe), 163.1, 163.0, 163.0, 162.9 (NMe), 11.8, 11.8 (CH_2CH_3); mp 117 °C.

4b (Figures S19−S20). 4a (100 mg, 0.41 mmol) was reacted with $Ti(OiPr)_4$ (62 μL, 0.21 mmol) in THF for 3 h at rt. The orange solution was evaporated, and the product was crystallized from THF at −35 °C as fine needles (95 mg, 90%). λ_{max}(THF)/nm 378 (ϵ/M^{-1} cm^{-1} 6000) Anal. Calcd for $C_{18}H_{32}N_{12}O_4Ti$: C, 40.91; H, 6.10, N; 31.81. Found: C, 41.43; H, 6.36; N, 31.58. ^{1}H NMR (Figure S19) (400 MHz; $CDCl_3$; rt) 3.6 (8 H, q, J = 7.0 Hz, CH_2CH_3), 3.4 (12 H, s, NMe), 1.2 (12 H, t, J = 7.0 Hz, CH_2CH_3). ^{13}C NMR (Figure S20) (400 MHz; $CDCl_3$; rt) δ 164.1, 159.5, 42.1, 36.0, 13.2.

Crystal Data. 4b was crystallized from THF at −35 °C. The asymmetric unit contains one molecule of the complex and a half-molecule of THF solvent. $C_{18}H_{32}N_{12}O_4Ti\cdot0.5(C_4H_8O)$, M = 1129.02, monoclinic, a = 14.0304(9), b = 14.6037(9), c = 25.6883(16) Å, β = 92.9260(10)°, U = 5256.6(6) Å^3, T = 173(1) K, space group $I2/a$, Z = 4, μ(Mo Kα) = 0.380 cm^{-1}, 29915 reflections measured, 6265 unique (R_{int} = 0.0347). $R(F_o^2)$ for [$I > 2\sigma(I)$] = 0.0505, Rw for [$I > 2\sigma(I)$] = 0.1140.

7b (Figure S21). 7a (120 mg, 0.17 mmol) was added to $Ti(OiPr)_4$ (50 μL, 0.17 mmol) in THF, and the reaction was stirred overnight. The crude yellow product was crystallized from diethylether at rt (204 mg, 69%). λ_{max}(ether)/nm 320 (ϵ/M^{-1} cm^{-1} 11000). See Figure S21 for ^{1}H NMR of the crystals in d_8-THF measured at 400 MHz in air. Additional characterization by NMR was impeded by the complex hydrolytic instability.

Crystal Data. 7b was crystallized from diethylether at rt. The asymmetric unit contains half of the molecule and disorder. $(C_{34}H_{54}N_{12}O_{12}Ti)_2$, M = 870.79, triclinic, a = 10.580(3), b = 12.585(3), c = 18.065(4) Å, α = 89.161(5), β = 76.392(5), γ = 82.305(5)°, U = 2316.2(10) Å^3, T = 173(1) K, space group $P1^-$, Z = 2, μ(Mo Kα) = 0.251 cm^{-1}, 27170 reflections measured, 10718 unique (R_{int} = 0.1459). $R(F_o^2)$ for [$I > 2\sigma(I)$] = 0.1618, Rw for [$I > 2\sigma(I)$] = 0.4253.

Acknowledgment. We thank Dr. Roy Shenhar for fruitful discussions, Dr. Roy Hoffman and Yair Ozeri for NMR advice, and Dr. Shmuel Cohen for crystallography.

Supporting Information Available: Spectra for **4a**,**b** **5a**, **6a**, and **7a**,**b** and crystallographic data for **4b** and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800966S