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

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Ethylene-bridged bis(hydroxylamino-1,3,5-triazine) compounds, that may serve as tetradeutate ligands, were synthesized in three steps from 2,4,6-trichloro-1,3,5-triazine. These compounds demonstrate different rotation restrictions around the CAr-N bonds due to their distinctive electronic structure as apparent from their resonative contributors. A dinuclear complex Ti2(µ-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 sp2 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 amionoalkoxo donors in addition to a coordinative triazine nitrogen.

Scheme 1

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donor, for Ti(IV) metal (Scheme 2).\(^{14}\) We reported formation of homoleptic [ONO]_2Ti-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,\(^{15-20}\) and the promising results observed with Ti(IV) complexes,\(^{18,19,27-34}\) prompt us to investigate our aminoxalkoxo 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 \([2−1] \) 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).

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 1H NMR, and the structure and properties of a resulting Ti(IV) complex is compared to those of the homoleptic complexes of tridentate triazine ligands.
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-3h$^{14}$ 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. 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 at room temperature in THF. Single crystals demonstrating restricted rotation (a) and in 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 $d_5$-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 NC$_2$H$_4$CO$_2$Et group as particularly revealed by HSQW 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 $d_5$-THF at 280 K demonstrating restricted rotation (a) and in $d_5$-DMSO at 390 K demonstrating free rotation (b).](Image)
restricted rotation around the CAr–N bonds, due to the highly contributing resonative structure where the amino substituents on the triazine rings are of sp² 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 ∆Gq for rotation of 36.5–38.5 ± 1.3 kJ mol⁻¹, we conclude that the rotation around the CAr–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 CAr–NCH₂ 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 ∆Gq calculated based on coalescence of the two NMe and the two NCH₂ signals for rotation around the CAr–N(Me)CH₂CH₂ bond is 69.0 ± 1.3 kJ mol⁻¹, whereas the ∆Gq calculated based on coalescence of NCH₂CO₂ signals for rotation around the CAr–N(CH₂CO₂Et)₂ bond is 78.7 ± 1.3 kJ mol⁻¹. Clearly, the compounds 5a and 6a demonstrate lower ∆Gq values of 61.9 (2.1 and 64.9 (2.1 kJ mol⁻¹, respectively, for rotation around the CAr–N(Me/H)CH₂CH₂ 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 C₁-symmetrical dinuclear species, of the formula Ti₂(µ-L)₂(OiPr)₄ (L = bis(triazine)), where the two Ti(IV) centers are of a highly distorted octahedral configuration.
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, 36 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 following THF evaporation gave N,N′-dimethylhydroxylamine hydrochloride (0.61 g, 7.32 mmol) previously contradicted with NaOH (0.50 g, 8.83 mmol) in water. The total yield is 5%. The second step was recrystallized from 2-propanol (0.84 g, 54%). This powder that was recrystallized from 2-propanol (0.84 g, 54%) was redissolved in THF mixed with dipeA (0.78 mL, 4.48 mmol) was reacted with N,N′-dimethylhydroxylamine (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,N′-dimethylhydroxylamine 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 (0.32 g, 71%). The total yield is 24%. Anal. Calcld for C16H16N12O2: C, 47.99; H, 7.61; N, 37.31. Found: C, 48.00; H, 7.70; N, 37.04. 1H NMR (Figure S3–S5) (500 MHz; CDCl3; rt) δ 3.5 (8 H, q, J = 7.0 Hz, CH2CH3). 13C NMR (Figure S8) (500 MHz; CDCl3; rt) δ 167.1, 164.7, 163.6, 46.2, 41.3, 37.3, 35.3, 13.3; 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 with N,N′-dimethylethylenediamine 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. Calcld for C21H22N12O2: C, 50.19; H, 8.00; N, 35.12. Found: C, 50.37; H, 8.14; N, 34.87. 1H NMR (Figure S6–S7) (400 MHz; CDCl3; rt) δ 3.7 (4 H, s, NMe), 3.5 (8 H, q, J = 7.2 Hz, CH2CH3). 3.3 (6 H, s, NMe), 1.2 (12 H, t, J = 7.1 Hz, CH2CH3). 13C NMR (Figure S5) (400 MHz; CDCl3; rt) δ 167.0, 165.5, 163.9, 41.3, 37.5, 13.4. 1.49 °C. 7a (Figures S9–S10). 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 diethylimidocacetate (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,N′-dimethylhydroxylamine 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. Calcld for C28H46N12O10: C, 47.32; H, 6.52; N, 23.65. Found: C, 48.00; H, 7.70; N, 37.04. 1H NMR (Figure S3–S4) (500 MHz; CDCl3; rt) δ 1.9 (7.1 Hz, CH2CH3). 13C NMR (Figure S6) (500 MHz; CDCl3; rt) δ 167.9, 164.7, 163.6, 41.3, 37.3, 35.3, 13.3; mp 146 °C.

<p>| TABLE 2. Selected Bond Lengths (Å) and Angles (deg) for 7b |</p>
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<td>2.356(9)</td>
<td>N(8)–C(16)</td>
<td>1.300(14)</td>
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<td>N(4)–O(1)</td>
<td>1.342(10)</td>
<td>C(16)–N(11)</td>
<td>1.387(14)</td>
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<td>1.349(13)</td>
<td>C(12)–C(27)</td>
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<td>O(1)–Ti–N(1)</td>
<td>74.7(3)</td>
<td>N(8)–C(16)–N(11)</td>
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(CO), 165.7, 165.7, 165.6, 165.5 (Ar1), 163.3, 163.3, 163.3 (Ar2),
163.0, 163.0, 162.9 (Ar3), 58.3, 58.3, 58.2, 58.2, 58.1
(CH2CH3), 47.2, 47.1, 47.0, 46.9, 46.8, 46.8 (NCH2CO2), 44.1, 44.0,
43.9, 43.8 (NMeCH2), 163.3, 163.3, 163.3 (NMe), 163.1, 163.0,
163.0, 162.9 (NMe), 11.8, 11.8 (CH2CH3); 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%).

λmax(THF)/nm 378 (ε/M −1 cm−1 16000) Anal. Calcd for C18H32N12O4Ti: C, 40.91; H, 6.10,
N; 31.81. Found: C, 41.43; H, 6.36; N, 31.58. 1H NMR (Figure
S19) (400 MHz; CDCl3; rt) δ 3.6 (8 H, q, J = 7.0 Hz, CH2CH3), 3.4
(12 H, s, NMe), 1.2 (12 H, t, J = 7.0 Hz, CH2CH3). 13C NMR
(Figure S20) (400 MHz; CDCl3; 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. C18H32N12O4Ti · 0.5(C4H8O), M = 1129.02, monoclinic,
a = 14.0304(9), b = 14.6037(9), c = 25.6883(16) Å, β = 92.1260(10)°, U = 5256.6(6) Å3, T = 173(1) K, space group I2/a, Z = 2, µ(Mo Kα) = 0.251 cm−1, 27170 reflections measured, 10718 unique (Rint = 0.1459). R(F2) for [I > 2σ(I)] = 0.1618, Rw for [I > 2σ(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, 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.
JOC800966S

The crude yellow product was crystallized from diethylether at rt
(204 mg, 69%). λmax(ether)/nm 320 (ε/M −1 cm−1 11000). See Figure
S21 for 1H NMR of the crystals in d8-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.
(C34H54N12O12Ti)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) Å3, T = 173(1) K, space group P1 −
, Z = 2, µ(Mo Kα) = 0.251 cm−1, 27170 reflections measured, 10718
unique (Rint = 0.1459). R(F2) for [I > 2σ(I)] = 0.1618, Rw for [I > 2σ(I)] = 0.4253.