

Bis-hydroxyaminotriazines: highly stable hydroxylamine-based ligands for iron(III) cations

Jenny Gun, Irina Ekelchik, Ovadia Lev, Rimma Shelkov and Artem Melman*

Supporting Information

General Information. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254), flash chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230-400 Mesh ASTM). Unless mentioned specifically, ^1H and ^{13}C NMR spectra were recorded on Bruker AMX-300 and DRX-400 spectrometer in deuterated chloroform (CDCl_3) using the residual solvent peaks for calibration at rt. Elementary analyses were performed by the microanalytical laboratory of the Hebrew University of Jerusalem, Jerusalem. Unless otherwise stated, all reagents used are commercially available. Glassware was oven-dried before use and solvents were purified by conventional methods. High resolution mass-spectra were recorded at Technion, Haifa.

General procedure for preparation of ligands 2a-c, 2e, 2g-h. To a solution of 2,4,6-trichloro-1,3,5-triazine (18.4 g, 100 mmol) in ethyl acetate (300 mL) was dropwise added at $-2\text{ }^\circ\text{C}$ under vigorous stirring a solution of a corresponding secondary amine $\text{R}^1\text{R}^2\text{NH}$ (200 mmol) in THF (100 ml). The reaction was continued 15 min after completing the addition, filtered, the filtrate was evaporated to afford crystalline 2,6-dichloro-4- R^1 , R^2N -1,3,5-triazines that are purified by recrystallization from isopropanol. To a suspension of resultant recrystallized 2,6-dichloro-4- R^1 , R^2N -1,3,5-triazines (30 mmol) in dioxane at $0\text{ }^\circ\text{C}$ (90 ml) was added a solution of R^3NHOR^4 hydrochloride (120 mmol) and NaOH (5.4 g, 108 mmol) in water (20 mL).

The reaction mixture was stirred for 14 h, diluted with water and the precipitated BHT ligands **2a-c**, **2e**, **2g-h** were collected by filtration and recrystallized from isopropanol.

2,6-Bis-[hydroxy(methyl)amino]-4-morpholino-1,3,5-triazine (2a) Yield 40%. M. p. 198-199 °C. ¹H NMR (300 MHz, D₂O): 3.27(s, 2H); 3.42 (s, 6H); 3.67 (t, *J*=4.5 Hz, 4H); 3.84 (t, *J*=4.5 Hz, 4H). ¹³C NMR (CDCl₃, 75 MHz): 36.8, 44.0, 66.6, 175.7, 177.2. Calcd. for C₉H₁₆N₆O₃: C, 42.18; H, 6.28; N, 32.79. Found: C, 42.34; H, 6.28; N, 33.04 .

2,6-Bis-[hydroxy(methyl)amino]-4-dicyclohexylamino-1,3,5-triazine (2b) Yield 46%. M. p. 202-203 °C. ¹H NMR (300 MHz): 1.11 (br. app. quint, 2H); 1.28 (br. app. q., 4 H); 1.57 (br. app. t, 6H); 1.80 (br. app. d, 4H); 1.97 (br. s, 4H); 3.36 (s, 6H); 3.9 (very br. s, 2H); 9.62 (br. s, 2H). ¹³C NMR (CDCl₃, 75 MHz): 25.7; 26.3; 37.3; 55.6; 161.9. NCH proton of cyclohexyl rings are not observed in ¹H NMR but can be indirectly seen in ¹³C non-decoupled NMR providing doublet for NCH carbon of cyclohexyl ring. Reasons for this behavior will be reported elsewhere. Calcd. for C₁₇H₃₀N₆O₂: C, 58.26; H, 8.63; N, 23.98. Found: C, 58.31; H, 8.70; N, 24.28.

2,6-Bis-[hydroxy(methyl)amino]-4-bis(*N*-ethoxycarbonylmethyl)amino-1,3,5-triazine (2c). Yield 87%. M.p. 131-132 °C. ¹H NMR (300 MHz): 1.27 (t, *J*=7.1 Hz, 6H); 3.34 (s, 6H); 4.20 (q, *J*=7.1 Hz, 4H); 4.32 (s, 4H). ¹³C NMR (CDCl₃, 75 MHz): 14.1, 36.8, 49.9, 61.1, 161.8, 163.6, 169.8. Calcd. for C₁₃H₂₂N₆O₆: C, 43.57; H, 6.19; N, 23.45. Found: C, 43.52; H, 6.29; N, 23.47.

2,6-Bis-[hydroxy(methyl)amino]-4-(*N*-methyl, *N*-ethoxycarbonyl)amino-1,3,5-triazine (2e) Yield 86%. M.p. 122-124 °C. ¹H NMR (300 MHz): 1.27 (t, *J*=7.1 Hz, 6H); 3.34 (s, 6H); 3.21 (s, 3H); 3.43 (s, 3H); 3.52 (s, 3H); 4.20 (q, *J*=7.1 Hz, 2H); 4.24 (s, 2H). ¹³C NMR (CDCl₃, 75 MHz): 14.2, 36.0, 36.8, 51.0, 61.0, 161.7, 163.6,

169.8. Calcd. for C₁₀H₁₈N₆O₄: C, 41.95; H, 6.34; N, 29.36. Found: C, 41.72; H, 6.23; N, 29.70.

2,6-Bis-(hydroxyamino)-4-dicyclohexylamino-1,3,5-triazine (2g) Yield 80%. M.p. 217-218 °C decomp. ¹H NMR (300 MHz): 1.1 (br. app. quint, 2H); 1.32 (br. app. q., 4 H); 1.58 (br. app. d., 6H); 1.69 (br. app. d, 2H); 1.85 (app.d, 4H); 2.04 (br. s, 4H); 3.7 (br. s). ¹³C NMR (CDCl₃, 75 MHz): 24.9, 25.7, 29.9, 55.6, 159.5, 161.9. Calcd. for C₁₅H₂₆N₆O₂: C, 55.88; H, 8.13; N, 26.08. Found: C, 56.14; H, 8.28.

2,6-Bis-(benzyloxyamino)-4-dicyclohexylamino-1,3,5-triazine (2h). Yield 68%. M. p. 217-218 °C. ¹H NMR (CDCl₃, 400 MHz): 1.1 (br. app. q, 2H); 1.32 (br. app. q., 4 H); 1.58 (br. s, 8H); 1.78 (br. app. d, 4H); 2.1 (very br. s, 2H); 4.94(s, 4H); 7.35 (br. app.q, 6H); 7.43 (d, *J*=6.8 Hz, 4H); 7.53 (br. s, 2H). ¹³C NMR (CDCl₃, 75 MHz): 25.5, 26.3, 30.4, 55.5, 78.1, 128.1, 128.3, 128.8, 136.3, 164.8, 167.9. Calcd. for C₂₉H₃₈N₆O₂: C, 69.29; H, 7.62; N, 16.72. Found: C, 69.24; H, 7.79; N, 16.42.

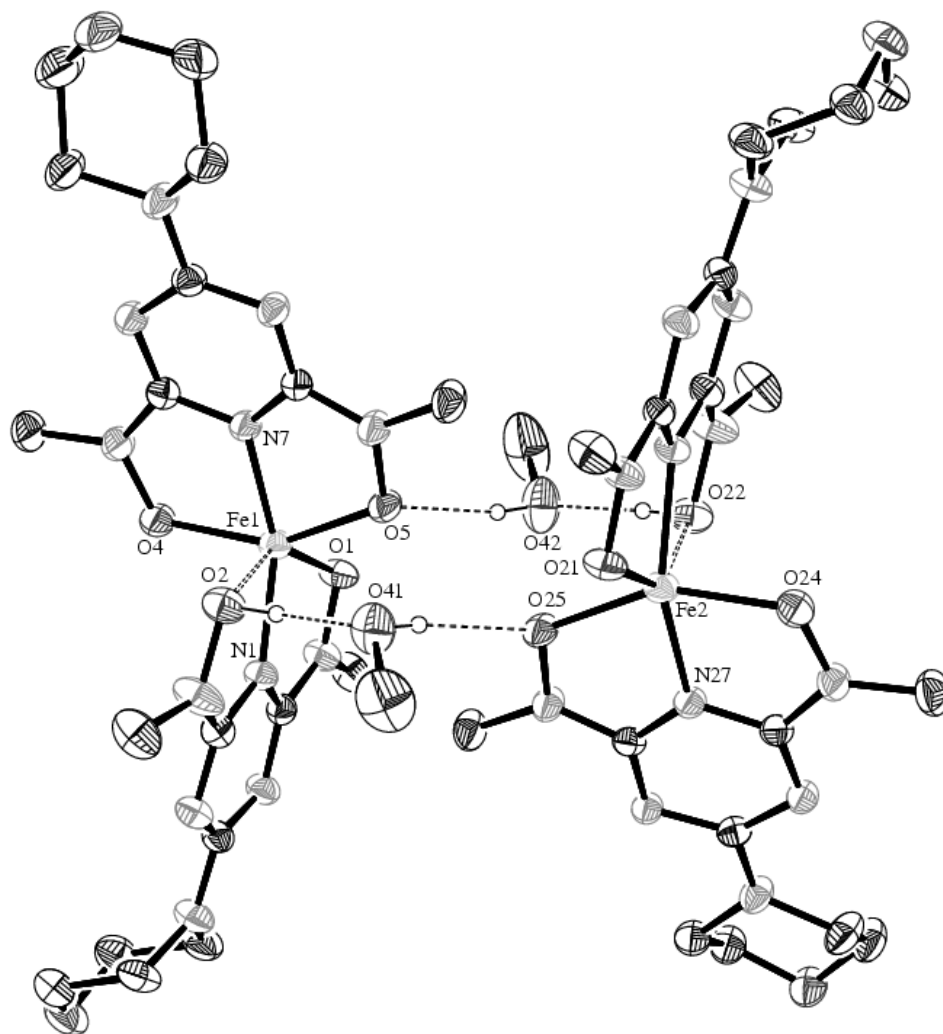
General procedure for preparation of ligands 2d, f. A suspension of BHT ligands **2c** or **2e** (0.1 mmol) in ethanol (2 mL) and 2M aq. NaOH (2 mmol, 1 mL) was stirred for 16 h. The reaction mixture was acidified to pH 3 with 5% aq. HCl and evaporated to dryness. The residue was dissolved in boiling chloroform, the chloroform solution was evaporated, residue is triturated with ether, and the resultant crystals were isolated by filtration.

2,6-Bis[hydroxy(methyl)amino]-4-bis(hydroxycarbonylmethyl)amino-1,3,5-triazine (2f). Yield 42%. M. p. 210-212 °C decomp. ¹H NMR (300 MHz, D₂O): 3.42 (s, 6H); 4.25 (s, 4H). ¹³C NMR (75 MHz, D₂O): 37.5, 51.3, 162.7, 167.1, 173.8. Calcd. for C₉H₁₄N₆O₆xH₂O: C, 33.75; H, 5.04; N, 26.24. Found: C, 33.34; H, 5.00; N, 26.43.

2,6-Bis[hydroxy(methyl)amino]-4-(*N*-methyl, *N*-hydroxycarbonylmethyl)amino-1,3,5-triazine (2h). Yields 14%. M. p. 178-182 °C decomp. ¹H NMR (300 MHz, D₂O): 3.22 (s, 3H); 3.38 (s, 3H); 3.47 (s, 3H); 4.35 (s, 2H). ¹³C NMR (75 MHz, D₂O): 35.9, 37.0, 37.1, 51.4, 163.4, 167.9, 173.8. Calcd. HRMS (ESI) for C₈H₁₄N₆O₄H⁺ 259.1149, found 259.1146.

Preparation of 2:1 dimeric 2a-iron(III) complex.

To a solution of 2a (256 mg, 1 mmol) in 1:1 mixture of MeOH and THF (200 mL) was added a solution of iron acetate (0.5 mmol, 87 mg) in methanol (50 ml). The dark violet reaction mixture was evaporated to dryness, the residue was dissolved in dichloromethane (100 ml), filtered, evaporated again, dissolved in dichloromethane (10 mL), and diluted with hexane (10 mL) to precipitate title compound (220 mg, 77%). Resultant black-violet crystals have M. p. 220 °C (decomp). As in cases of other paramagnetic Fe(III) complexes, no ¹H and ¹³C NMR signals in solutions of the complex in different deuterated solvents can be observed. IR (film, cm⁻¹): 595, 759, 944, 1020, 1113, 1170, 1208, 1275, 1443, 1531 br, 1626, 2856, 2918, 2965, 3300-3700 br. Calcd. for C₁₈H₂₉N₁₂FeO₆: C, 38.24; H, 5.17; N, 29.73. Found: C, 38.55; H, 5.21; N, 29.83. Crystals for X-rays were prepared from water/methanol.



Full size ORTEP drawing of molecular structure of 2:1 dimeric **2a**-iron(III) complex with two molecules of MeOH.