

# An Unusually Flexible Expanded Hexamine Cage and Its Cu<sup>II</sup> Complexes: Variable Coordination Modes and Incomplete Encapsulation

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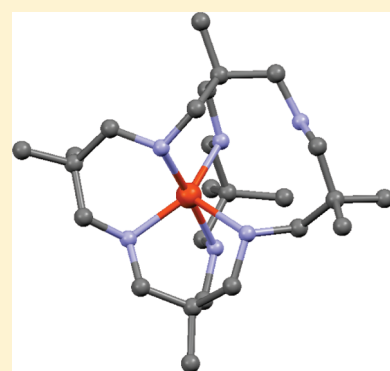
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**S** Supporting Information

**ABSTRACT:** The bicyclic hexamine “cage” ligand Me<sub>8</sub>tricosaneN<sub>6</sub> (1,5,5,9,13,13,20,20-octamethyl-3,7,11,15,18,22-hexaazabicyclo[7.7.7]tricosane) is capable of encapsulating octahedral metal ions, yet its expanded cavity allows the complexed metal to adopt a variety of geometries comprising either hexadentate or pentadentate coordination of the ligand. When complexed to Cu<sup>II</sup> the lability of the metal results in a dynamic equilibrium in solution between hexadentate- and pentadentate-coordinated complexes of Me<sub>8</sub>tricosaneN<sub>6</sub>. Both [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](ClO<sub>4</sub>)<sub>2</sub> (6-coordinate) and [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](S<sub>2</sub>O<sub>6</sub>) (5-coordinate) have been characterized structurally. In weak acid (pH 1) a singly protonated complex [Cu(HMe<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>3+</sup> has been isolated that finds the ligand binding as a pentadentate with the uncoordinated amine being protonated. vis-NIR and electron paramagnetic resonance (EPR) spectroscopy show that the predominant solution structure of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> at neutral pH comprises a five-coordinate, square pyramidal complex. Cyclic voltammetry of the square pyramidal [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> complex reveals a reversible Cu<sup>II/I</sup> couple. All of these structural, spectroscopic, and electrochemical features contrast with the smaller cavity and well studied “sarcophagine” (sar, 3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane) Cu<sup>II</sup> complexes which are invariably hexadentate coordinated in neutral solution and cannot stabilize a Cu<sup>I</sup> form.



## INTRODUCTION

The macrocyclic cage ligands sepulchrate (sep or 1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]icosane)<sup>1</sup> and sarcophagine (sar or 3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane)<sup>2</sup> and substituted analogues (Chart 1) occupy a pivotal place in coordination chemistry. Through systematic investigations of the transition metal coordination chemistry of sep and sar, unique physical properties of their complexes have emerged such as extreme resistance to dissociation<sup>3</sup> and racemization.<sup>4</sup> These properties have led to some important applications particularly in medicinal chemistry through the development of a functionalized ligand based on (NH<sub>2</sub>)<sub>2</sub>sar (Chart 1) through complexation of <sup>64</sup>Cu<sup>II</sup> for diagnostic positron emission tomography (PET) imaging.<sup>5,6</sup>

It has been well established that truly novel properties can arise through tuning the macrocyclic ring size, and these have led to many applications of macrocycles such as the expanded porphyrin family,<sup>7–9</sup> crown ethers,<sup>10</sup> and cryptands<sup>11,12</sup> whose ring size has been varied to suit the size of the guest ion or molecule. There are many other well studied families of organic hosts whose selectivity has been fine-tuned for guest binding by adjustment of the macrocyclic size and shape.<sup>13–15</sup>

A natural evolution of our research was to expand the macrocyclic ring size of sar by lengthening the three “straps” connecting each triamine “cap” of the ligand. This led to the

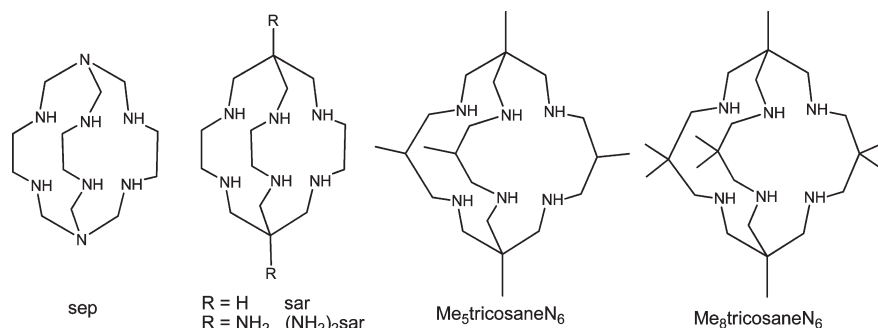
expanded macrobicyclic hexamine Me<sub>5</sub>tricosaneN<sub>6</sub> (1,5,9,13,20-pentamethyl-3,7,11,15,18,22-hexaazabicyclo[7.7.7]tricosane) whose complexes indeed exhibited remarkable structural, electronic, and spectroscopic properties<sup>16–20</sup> compared with the smaller cavity sar (and sep) cages. The Co<sup>III</sup> complex [Co(Me<sub>5</sub>tricosaneN<sub>6</sub>)]<sup>3+</sup> exhibits unusually long Co<sup>III</sup>–N bond lengths (2.010(4)–2.032(4) Å)<sup>16</sup> and a weak ligand field in comparison with [Co(sep)]<sup>3+</sup> (Co–N 1.96 Å).<sup>1</sup> In addition, the [Co(Me<sub>5</sub>tricosaneN<sub>6</sub>)]<sup>3+/2+</sup> redox couple<sup>16</sup> is found at a significantly more positive potential than [Co(sep)]<sup>3+/2+</sup>.<sup>4</sup> All of these features highlight the influence of the larger cavity of the Me<sub>5</sub>tricosaneN<sub>6</sub> ligand on the properties of the metal ion it encapsulates.

The octa-methylated analogue Me<sub>8</sub>tricosaneN<sub>6</sub> (1,5,5,9,13,13,20,20-octamethyl-3,7,11,15,18,22-hexaazabicyclo[7.7.7]tricosane, Chart 1), bears exactly the same ligand framework as Me<sub>5</sub>tricosaneN<sub>6</sub> yet the subtle addition of methyl groups on each strap alters its coordination chemistry markedly. Unusually high Co<sup>III/II</sup> redox potentials and optical properties have been reported for the Co complexes of Me<sub>8</sub>tricosaneN<sub>6</sub> and its triimine.<sup>21</sup> Oxidation of pink [Co(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> yields two different Co<sup>III</sup> complexes. One of these is an orange complex obtained from aqueous solution and

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Chart 1



has been characterized by X-ray crystallography, with an average  $\text{Co}^{\text{III}}-\text{N}$  distance of 1.99(1) Å,<sup>22</sup> intermediate between  $[\text{Co}(\text{Me}_5\text{tricosaneN}_6)]^{3+16}$  and  $[\text{Co}((\text{NH}_3)_2\text{sar})]^{5+23}$ . The second  $\text{Co}^{\text{III}}$  complex of  $\text{Me}_8\text{tricosaneN}_6$  was blue but gave identical NMR spectra to that of the orange compound in water. The structural basis of these unusual properties is still poorly understood and to date no systematic study of  $\text{Me}_8\text{tricosaneN}_6$  has revealed why its complexes exhibit such unusual properties compared with analogues from the sep and sar family.

Herein we report the synthesis and isolation of  $\text{Me}_5\text{tricosaneN}_6$  as its free base in addition to its copper(II) coordination chemistry. This study, in comparison with our previous investigations of the  $\text{Cu}^{\text{II}}$  coordination chemistry of  $\text{Me}_5\text{tricosaneN}_6$ <sup>19</sup> and  $(\text{NH}_2)_2\text{sar}$ ,<sup>24</sup> highlights the fact that  $\text{Me}_8\text{tricosaneN}_6$  is an atypical cage that, unlike sar and sep which demand a rigid and well-defined coordination environment, is extremely flexible and can accommodate a variety of coordination geometries and coordination numbers. This flexibility of coordination opens up a new area of cage ligand coordination chemistry whereby incompletely encapsulated complexes are the norm.

## EXPERIMENTAL SECTION

**Reagents.** 1,1,1-tris(*p*-toluenesulfonyloxy)methyl)ethane was prepared according to a literature procedure.<sup>25</sup> The complex  $[\text{Co}(\text{tame})_2]\text{Cl}_3$  (tame = 1,1,1-tris(aminomethyl)ethane) was prepared as described.<sup>26</sup> An improved synthesis of the free ligand tame is described below.

**1,1,1-Tris((benzylamino)methyl)ethane.** 1,1,1-Tris(*p*-toluenesulfonyloxy)methyl)ethane (11.7 g, 20.0 mmol) was suspended in benzylamine (26 mL, 240 mmol) and heated to 180 °C for 2 h. The reaction mixture was then allowed to cool, resulting in precipitation of benzylammonium tosylate. Excess benzylamine was removed by vacuum distillation. After cooling, hexane (200 mL) was added to the remaining solid mass, and the mixture brought to reflux for 15 min. The reaction mixture was cooled to room temperature and then refrigerated overnight. The resulting suspension was filtered, and the solid washed with hexane. The combined filtrates were washed with water, then dried over magnesium sulfate and evaporated to give 1,1,1-tris((benzylamino)methyl)ethane as a colorless oil. (6.6 g, 85%). <sup>1</sup>H NMR spectrum ( $\text{CDCl}_3$ ):  $\delta$  0.88 (s, 3H,  $\text{CH}_3$ );  $\delta$  2.56 (s, 6H,  $\text{CH}_2\text{CH}_3$ );  $\delta$  3.75 (s, 6H,  $\text{CH}_2\text{Ph}$ );  $\delta$  7.1–7.4 (overlapping multiplet, 15H, ArH).

**1,1,1-Tris((benzylamino)methyl)ethane Trihydrochloride.** The triamine free base (6.6 g) was converted to the corresponding hydrochloride salt by dissolving the compound in methanol (50 mL) then adding conc. HCl (10 mL). The solvent was evaporated, and residual water removed as an azeotrope with ethanol on a rotary evaporator. The resulting solid was recrystallized from ethanol to give 1,1,1-tris((benzylamino)methyl)ethane  $\cdot$  3HCl as a colorless solid. (8.5 g, 100%).

<sup>1</sup>H NMR spectrum ( $\text{D}_2\text{O}$ ):  $\delta$  1.27 (s, 3H,  $\text{CH}_3$ );  $\delta$  3.22 (s, 6H,  $\text{CH}_2\text{CH}_3$ );  $\delta$  4.28 (s, 6H,  $\text{CH}_2\text{Ph}$ );  $\delta$  7.4–7.6 (overlapping multiplet, 15H, ArH).

**1,1,1-Tris((aminomethyl)ethane Trihydrochloride (tame  $\cdot$  3HCl).** 1,1,1-Tris((benzylamino)methyl)ethane  $\cdot$  3HCl (2.50 g, 5.0 mmol) was dissolved in methanol (150 mL) in a round bottomed flask and purged with nitrogen for 3 min. Palladium on carbon (10% (w/w); 0.53 g) was added followed by ammonium formate (4.73 g, 75 mmol), and then a reflux condenser with rubber septum was attached. The apparatus was evacuated and then filled with nitrogen. After this process was repeated a further two times, the reaction mixture was brought to reflux for 4 h. The reaction mixture was cooled and then filtered through a pad of Celite, which was washed with methanol. The combined filtrates were evaporated to give the product as a colorless solid (1.0 g, 88%). <sup>1</sup>H NMR spectrum ( $\text{D}_2\text{O}$ ):  $\delta$  1.25 (s, 3H,  $\text{CH}_3$ );  $\delta$  3.17 (s, 6H,  $\text{CH}_2$ ).

$[\text{Co}(\text{Me}_8\text{tricosaneN}_6)](\text{NO}_3)_2$ .  $[\text{Co}(\text{tame})_2]\text{Cl}_3$  (10.2 g; 0.0255 mol) and  $\text{NaClO}_4$  (46 g; 0.38 mol) were stirred with 250 mL of acetonitrile for 10 min. Paraformaldehyde (3.0 g; 0.10 mol) and isobutyraldehyde (71.9 g; 1.00 mol) were added to the solution, followed by 20 mL of triethylamine. The reaction mixture was stirred for 2 h at room temperature, during which time it changed color from orange to brown, and finally dark purple. Dilute HCl (1 M, 300 mL) was added to quench the reaction, and the resulting solution diluted to  $\sim$ 4 L with water and loaded onto a Dowex 50W X-2 cation exchange column (15  $\times$  6 cm resin bed). The dark red band was first washed with 700 mL of water, then 2 L of 1 M HCl. After these washings only the mixture of  $\text{Co}^{\text{III}}$  complexes formed in the reaction remained bound to the column. These were then eluted with 5 M HCl, and the eluate was evaporated to dryness using a rotary evaporator.

The resulting solid residue containing  $[\text{Co}(\text{Me}_8\text{tricosanetriamineN}_6)]\text{Cl}_3$  was dissolved in 400 mL of water and adsorbed onto a SP Sephadex C-25 cation exchange column (57  $\times$  9 cm resin bed) and eluted using 0.2 M  $\text{K}_2\text{SO}_4$ . The last pink band to elute was collected and adsorbed onto a Dowex 50W X-2 cation exchange column (7  $\times$  4.5 cm resin bed). The column was washed with 600 mL of water, followed by 2 L of 1 M HCl. Finally the column was eluted using 2 L of 5 M HCl to give a pink solution containing  $[\text{CoMe}_8\text{tricosanetriamineN}_6)]^{3+}$ , which was evaporated to dryness.

The resulting pink solid was dissolved in 30 mL of water, and the pH of the solution adjusted to  $\sim$ 10 with sat.  $\text{Na}_2\text{CO}_3$ . A solution containing  $\text{NaBH}_4$  (0.38 g; 9.9 mmol) dissolved in 40 mL of water (pH previously adjusted to  $\sim$ 10 with  $\text{Na}_2\text{CO}_3$ ) was then added with stirring. After 20 min the reaction was quenched by addition of 120 mL of sat.  $\text{NaHCO}_3$ . After a further 30 min stirring the solution was diluted to  $\sim$ 1.5 L with water and then adsorbed onto a SP Sephadex C-25 cation exchange column (55  $\times$  6 cm resin bed) and eluted using 0.2 M  $\text{NaNO}_3$ . A single light purple band was collected and evaporated on a hot plate at 40–50 °C to  $\sim$ 30 mL, resulting in a pink precipitate of  $[\text{Co}(\text{Me}_8\text{tricosaneN}_6)](\text{NO}_3)_2 \cdot \text{H}_2\text{O}$ , which was filtered off and dried in air. Yield 450 mg (3%). Anal. Calc. for  $\text{C}_{25}\text{H}_{56}\text{CoN}_8\text{O}_7$ :  $[\text{Co}(\text{Me}_8\text{tricosaneN}_6)](\text{NO}_3)_2$

Table 1. Crystal Data

|  | Me <sub>8</sub> tricosaneN <sub>6</sub>        | [Cu(Me <sub>8</sub> tricosaneN <sub>6</sub> )]<br>(NO <sub>3</sub> ) <sub>2</sub> · 2H <sub>2</sub> O | [Cu(Me <sub>8</sub> tricosane)]<br>(S <sub>2</sub> O <sub>6</sub> )            | [Cu(HMe <sub>8</sub> tricosaneN <sub>6</sub> )]<br>(NO <sub>3</sub> ) <sub>3</sub> · H <sub>2</sub> O |
|--|--|---|--|---|
| formula  | C <sub>25</sub> H <sub>54</sub> N <sub>6</sub> | C <sub>25</sub> H <sub>58</sub> CuN <sub>8</sub> O <sub>8</sub>                                       | C <sub>25</sub> H <sub>54</sub> CuN <sub>6</sub> O <sub>6</sub> S <sub>2</sub> | C <sub>25</sub> H <sub>57</sub> CuN <sub>9</sub> O <sub>10</sub>                                      |
| Fw   | 438.74   | 662.33  | 666.40   | 707.34  |
| cryst. syst.                                   | triclinic                                      | tetragonal  | monoclinic   | monoclinic  |
| space group                                    | <i>P</i> $\bar{1}$ (No. 2)                     | <i>P</i> 4 <sub>2</sub> / <i>n</i> (No. 86)   | <i>P</i> 2 <sub>1</sub> / <i>c</i> (No. 14)                                    | <i>P</i> 2 <sub>1</sub> / <i>n</i> (No. 14, variant)  |
| <i>a</i> /Å                                    | 10.2473(1)                                     | 10.8480(8)  | 10.527(1)  | 18.996(1)   |
| <i>b</i> /Å                                    | 11.4242(2)                                     |   | 15.585(2)  | 10.7350(6)  |
| <i>c</i> /Å                                    | 12.9246(2)                                     | 28.720(3)   | 19.257(3)  | 19.297(1)   |
| $\alpha$ /deg                                  | 96.516(1)                                      |   |  |   |
| $\beta$ /deg                                   | 112.770(1)                                     |   | 90.68(1)   | 119.174(9)  |
| $\gamma$ /deg                                  | 100.383(1)                                     |   |  |   |
| <i>V</i> /Å <sup>3</sup>                       | 1343.98(4)                                     | 3379.8(5)   | 3159.1(7)  | 3435.8(4)   |
| <i>Z</i>                                       | 2  | 4   | 4  | 4   |
| <i>T</i> /K                                    | 200(2)   | 293(2)  | 200(2)   | 293(2)  |
| $\lambda$ /Å                                   | 0.71073  | 0.71073   | 0.71073  | 0.71073   |
| $\mu$ /cm <sup>−1</sup>                        | 0.065  | 0.701   | 0.86   | 0.699   |
| $\rho_{\text{calc}}$                           | 1.084  | 1.302   | 1.393  | 1.367   |
| <i>R</i> (obs data) <sup>a</sup>               | 0.0402   | 0.0689  | 0.038  | 0.0412  |
| <i>wR</i> <sub>2</sub> (all data) <sup>b</sup> | 0.1138   | 0.1867  | 0.035  | 0.0902  |

<sup>a</sup>  $R(F_o) = \sum ||F_o| - |F_c|| / \sum |F_o|$ . <sup>b</sup>  $R_w(F_o^2) = [\sum w(F_o^2 - F_c^2) / \sum wF_o^2]^{1/2}$ .

·H<sub>2</sub>O): C 46.9; H 8.8; N 17.5; Co 9.2. Found C 46.7; H 9.2; N 17.4; Co 9.3.

Anion exchange chromatography (Dowex 1-X8, Cl<sup>−</sup> form) of [Co(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub> · H<sub>2</sub>O yielded the corresponding chloride salt, which was isolated after evaporation of the eluate. Anal. Calc. for C<sub>25</sub>H<sub>60</sub>CoN<sub>6</sub>Cl<sub>2</sub>O<sub>3</sub>: ([Co(Me<sub>8</sub>tricosaneN<sub>6</sub>)]Cl<sub>2</sub> · 3H<sub>2</sub>O): C 48.2; H 9.7; N 13.5; Cl 11.4; Co 9.5. Found C 49.0; H 9.6; N 13.3; Cl 11.9; Co 9.5.

Me<sub>8</sub>tricosaneN<sub>6</sub>. [Co(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub> (1.14 g, 1.83 mmol) was dissolved in 500 mL of water. The solution was then adsorbed onto a column of Dowex 50W X-2 cation exchange resin (7.5 × 4.5 cm resin bed, H<sup>+</sup> form), and the column washed with 0.5 M HCl (500 mL) and then 1 M HCl (1 L) which resulted in complex dissociation and elution of pink Co<sub>aq</sub><sup>2+</sup>. A faint white band of the free ligand was apparent on the top of the light brown column, and this eluted with 5 M HCl (1.5 L). The eluate was evaporated to dryness, and the resulting colorless powder redissolved in approximately 20 mL of water. Sufficient saturated NaOH solution was then added to adjust the pH to ~12, resulting in a brown precipitate which was isolated by filtration and dried in air. The precipitate was recrystallized using a minimum amount (250 mL) of hot MeCN to yield pure Me<sub>8</sub>tricosaneN<sub>6</sub>. Yield 640 mg (80%).

Anal. Calc. for C<sub>25</sub>H<sub>56</sub>N<sub>6</sub>O (Me<sub>8</sub>tricosaneN<sub>6</sub> · H<sub>2</sub>O): C 65.7; H 12.4; N 18.4. Found C 64.9; H 12.6; N 18.0. <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>):  $\delta$  0.70 (s, 6H, cap CH<sub>3</sub>);  $\delta$  0.89 (s, 18H, strap CH<sub>3</sub>);  $\delta$  2.35 (s, 12H, strap CH<sub>2</sub>);  $\delta$  2.52 (s, 12H, cap CH<sub>2</sub>). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>):  $\delta$  25.31 (cap CH<sub>3</sub>);  $\delta$  25.62 (strap CH<sub>3</sub>);  $\delta$  35.18 (strap quaternary C);  $\delta$  38.66 (cap quaternary C);  $\delta$  61.73 (cap CH<sub>2</sub>);  $\delta$  62.66 (strap CH<sub>2</sub>).

[Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub>. Me<sub>8</sub>tricosaneN<sub>6</sub> (100 mg, 0.23 mmol) was dissolved in 10 mL of ethanol with gentle heating. To this was added a solution of 56 mg of Cu(NO<sub>3</sub>)<sub>2</sub> · 2.5H<sub>2</sub>O (0.24 mmol) in 6 mL of ethanol resulting in an immediate color change to dark blue. The solution was heated at ~50 °C for 15 min and then allowed to evaporate to near dryness, resulting in dark blue crystals of the desired compound which were suitable for X-ray work. The perchlorate salt was obtained by addition of sat. NaClO<sub>4</sub> to a concentrated solution of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](ClO<sub>4</sub>)<sub>2</sub>. Anal. Calc. for C<sub>25</sub>H<sub>60</sub>CuN<sub>6</sub>Cl<sub>2</sub>O<sub>11</sub>:

[Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](ClO<sub>4</sub>)<sub>2</sub> · 3H<sub>2</sub>O: C 39.8; H 8.0; N 11.1; Cl 9.4. Found C 39.6; H 7.5; N 10.5; Cl 9.3. The CF<sub>3</sub>SO<sub>3</sub><sup>−</sup>, PF<sub>6</sub><sup>−</sup> and S<sub>2</sub>O<sub>6</sub><sup>2−</sup> salts were obtained similarly by addition of the sodium salt of the respective anion. The dithionate salt was obtained as X-ray quality crystals from dilute ammonia solution.

[Cu(HMe<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>3</sub>. [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub> (5 mg) was dissolved in DMF/H<sub>2</sub>O (1:2) (1 mL). Dilute nitric acid was added dropwise to pH 1 which led to a color change from blue to purple. Slow evaporation of the solution at room temperature afforded purple crystals of the complex suitable for X-ray work.

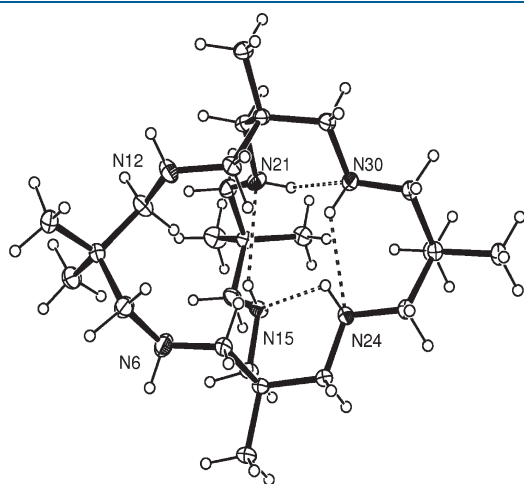
**Physical Methods.** Positive ion electrospray ionization (ESI) mass spectra were obtained using a Waters VG Quattro mass spectrometer and aqueous solutions containing either Me<sub>8</sub>tricosaneN<sub>6</sub> or its copper(II) complex. The absorption spectrum of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> was recorded using a Varian Cary 500 UV–vis–NIR spectrophotometer and quartz cuvettes. Cyclic voltammetry was performed on a BAS100B/W potentiostat employing a glassy carbon working electrode, Pt auxiliary electrode, and Ag/AgCl reference electrode. The supporting electrolyte was 0.1 NaNO<sub>3</sub>, and all solutions were purged with Ar before measurement. Elemental analysis was performed by the Microanalytical Unit at the Australian National University. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Unity-300 (300 MHz <sup>1</sup>H, 75 MHz <sup>13</sup>C) spectrometer in either D<sub>2</sub>O or CDCl<sub>3</sub>. Electron paramagnetic resonance (EPR) spectra were measured with a Bruker ER200 instrument at X-band frequency (~9.3 GHz) as 2 mM DMF/H<sub>2</sub>O 1:2 frozen solutions at 140 K. Spin Hamiltonian parameters were determined by spectral simulation with the program EPR50F.<sup>27</sup>

**Crystallography.** For Me<sub>8</sub>tricosaneN<sub>6</sub> the X-ray data were collected with a Nonius KappaCCD diffractometer at 200 K using the COLLECT software (Nonius B.V.) while both data reduction and cell refinement were accomplished using DENZO/SCALEPACK.<sup>28</sup> For [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](S<sub>2</sub>O<sub>6</sub>) data were collected on a Rigaku AFC6S while data reduction was carried out with the teXsan package (Rigaku/MS). The structures were solved with SIR92<sup>29</sup> and refined by full-matrix least-squares analysis using the program CRYSTALS<sup>30</sup> in the case of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](S<sub>2</sub>O<sub>6</sub>) and teXsan in the case of Me<sub>8</sub>tricosaneN<sub>6</sub>. For [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub> · 2H<sub>2</sub>O and [Cu(HMe<sub>8</sub>tricosaneN<sub>6</sub>)]



( $\text{NO}_3$ ) $_3$ · $\text{H}_2\text{O}$  crystallographic data were acquired at 293 K on an Oxford Diffraction Gemini CCD diffractometer and operating within the range  $2 < 2\theta < 50^\circ$ . Data reduction and empirical absorption corrections (multiscan) were performed with Oxford Diffraction CrysAlisPro software (Oxford Diffraction, vers. 171.33.42). Structures were solved by direct methods with SHELXS and refined by full-matrix least-squares analysis with SHELXL-97<sup>31</sup> (Table 1). All non-H atoms were refined with anisotropic thermal parameters. In all structures graphite-monochromated Mo-K $\alpha$  radiation (0.71073 Å) was used.

Molecular structure diagrams in Figures 2–4 were produced with ORTEP3,<sup>32</sup> while space filling and packing diagrams were produced with Mercury (vers 2.4) and disorder in the structure of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)](\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  (Supporting Information Figure S2) was shown with PLUTON.<sup>33</sup> This comprised complete rotational disorder of the complex cation about a crystallographic 2-fold axis with only the metal atom occupying this axis. Because of the proximity of the two disordered components, the ligand C- and N-atoms were refined isotropically (each at half occupancy). Restraints on the C–N and C–C bonds were applied early in refinement but were lifted for the final stages until convergence. The disordered nitrate anions were restrained to be trigonal planar. In the structure of  $\text{Me}_8\text{tricosaneN}_6$  there was



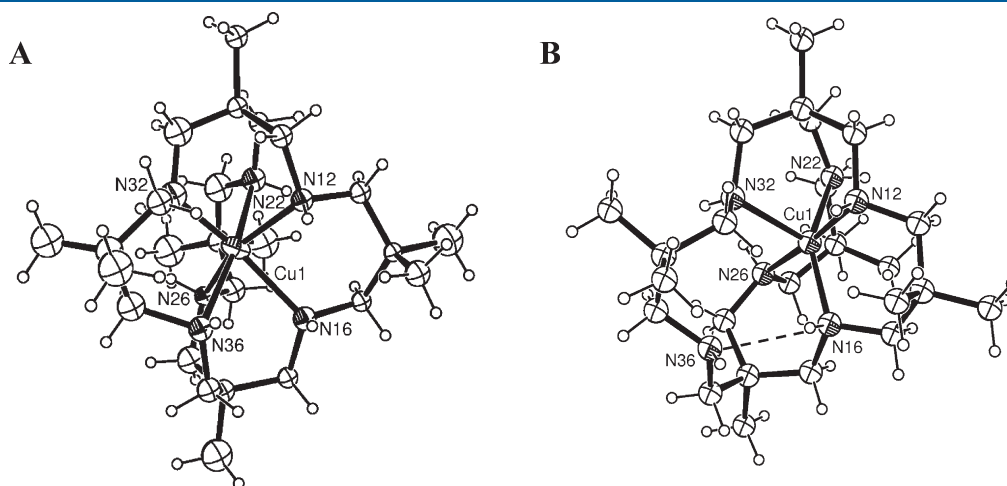
**Figure 1.** ORTEP view of the free ligand  $\text{Me}_8\text{tricosaneN}_6$ . Only one of the two contributors to NH disorder is shown (30% probability ellipsoids).

disorder in the sites of the amine protons attached to atoms N15, N21, N24, and N30.

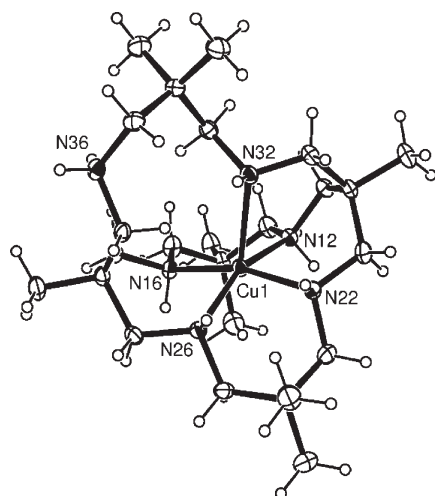
## RESULTS AND DISCUSSION

**Improved Synthesis of 1,1,1-Tris(aminomethyl)ethane (tame).** The synthesis of  $\text{Me}_8\text{tricosaneN}_6$  (Scheme 1) proceeds via a metal directed template reaction using  $[\text{Co}(\text{tame})_2]^{3+}$  (tame = 1,1,1-tris-(aminomethyl)ethane) as the precursor. The triamine tame is well-known<sup>25,34–36</sup> and also is the precursor for the related cage ligand  $\text{Me}_5\text{tricosaneN}_6$ .<sup>16</sup> Most synthetic routes toward tame utilize 1,1,1-tris(hydroxymethyl)ethane as its tris-(benzenesulfonate) or tris(tosylate) ester. In one of the earliest reported procedures, the tris(benzenesulfonate) ester was reacted with potassium phthalimide in xylene to obtain the corresponding tris(phthalamido) derivative, which was then subjected to hydrolysis with aqueous KOH for 2–3 days.<sup>25</sup> After hydrolysis, distillation at high temperatures ( $>200^\circ\text{C}$ ) was required to obtain impure tame ligand. Geue and Searle later reported an improved version of this procedure, in which potassium phthalimide was reacted with the tris(benzenesulfonate) ester of 1,1,1-tris(hydroxymethyl)ethane in dimethylformamide (DMF), instead of xylene, and the subsequent alkaline hydrolysis was performed in a high pressure autoclave.<sup>35</sup> Subsequent separation of the protonated tame ligand from various other polyamine byproducts requires cation exchange column chromatography. Although this procedure is able to be performed on a relatively large scale, the chromatographic purification procedure is laborious and the need to perform the hydrolysis under conditions of high temperature and pressure is an added drawback. A commonly used alternative method for obtaining tame relies on the preparation, and subsequent reduction with  $\text{LiAlH}_4$ , of 1,1,1-tris(azidomethyl)ethane.<sup>34,36</sup> However, owing to the potential explosive hazards of organic azides, this method is not recommended for large scale preparations.

The new method we report herein avoids both hazardous triazide intermediates and cation exchange column chromatography, affording tame as its hydrochloride salt in good yield. A further advantage is that the method is readily able to be scaled up. When large-scale reactions are being performed the ammonium formate is best added gradually as a methanolic solution rather than as a single quantity of solid reagent.



**Figure 2.** ORTEP views (from the same aspect) of (A) six-coordinate  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)](\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  and (B) five-coordinate  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)](\text{S}_2\text{O}_6)$ . 30% probability ellipsoids are shown, and anions have been omitted for clarity. Note the same configuration of the coordinated N-donors is present in both complexes while a H-bond to N36 in B replaces the coordinate bond in A.

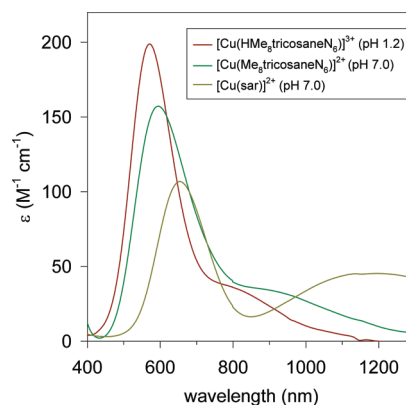


**Figure 3.** ORTEP view of five-coordinate  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)](\text{NO}_3)_3 \cdot \text{H}_2\text{O}$ . 30% probability ellipsoids are shown, and anions and water molecules have been omitted for clarity.

**Synthesis and Characterization of  $\text{Me}_8\text{tricosaneN}_6$ .** The synthesis of  $\text{Me}_8\text{tricosaneN}_6$  (Scheme 1) proceeds via a metal template reaction of  $[\text{Co}(\text{tame})_2]^{3+}$  with formaldehyde and isobutyraldehyde (2-methylpropanal), yielding the structurally characterized  $\text{Co}^{\text{III}}$  tri-imine complex  $[\text{Co}(\text{Me}_8\text{tricosanetriimineN}_6)]\text{Cl}_3$ .<sup>21</sup> This is the lowest yielding step (ca. 10%) of the reaction sequence as the mixed aldehyde reaction has many other possible outcomes including methylene-linked amines (aminals) and other polyimines. Separation and characterization of all  $\text{Co}^{\text{III}}$  complexes formed in the formaldehyde/isobutyraldehyde condensation reaction has not been achieved, but  $^{13}\text{C}$  NMR indicates that there are many species and they are typically asymmetric. Unreacted  $[\text{Co}(\text{tame})_2]^{3+}$  is typically recovered as about 10% of all Co complexes after column chromatography. The inherently low yield of this reaction is in contrast to the metal directed Mannich reactions leading to the sar and sep  $\text{Co}^{\text{III}}$  cages<sup>1,2</sup> which proceed in quantitative yields. Reduction of  $[\text{Co}(\text{Me}_8\text{tricosanetriimineN}_6)]^{3+}$  affords two N-based diastereomeric  $\text{Co}^{\text{II}}$  complexes of  $\text{Me}_8\text{tricosaneN}_6$ ;<sup>21</sup> one pink and one violet which are both remarkably air stable unlike all other  $\text{Co}^{\text{II}}$  hexaamines.

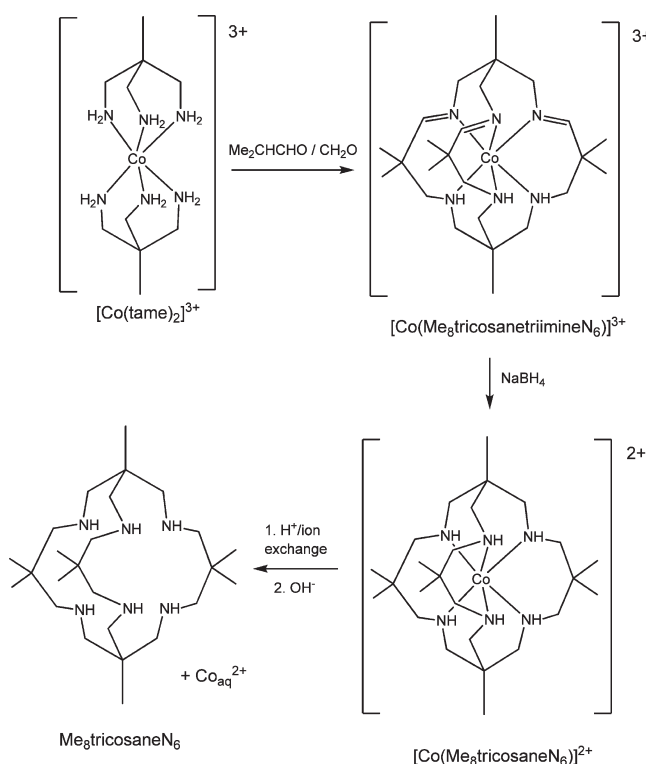
The cobalt(II) complexes of smaller cavity ligands (e.g.,  $[\text{Co}(\text{sep})]^{2+}$  and  $[\text{Co}(\text{sar})]^{2+}$ ) are exceptionally resistant to dissociation in acidic solution. For example, divalent  $[\text{Co}((\text{NH}_3)_2\text{-sar})]^{4+}$  shows no detectable loss of the metal ion in strongly acidic solution at 20 °C after several days.<sup>2</sup> Procedures for preparing the metal-free hexaamine cage ligands sar and  $(\text{NH}_2)_2\text{sar}$  require forcing conditions, such as high temperatures in concentrated HBr (in a sealed tube) or reaction with hot aqueous cyanide to remove the metal from its cage.<sup>3</sup> In contrast,  $[\text{Co}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  dissociates rapidly in dilute acid (1 M HCl), and the liberated  $\text{Co}_{\text{aq}}^{2+}$  ions separate readily from the protonated free ligand and on a cation exchange column. This resembles the behavior of  $[\text{Co}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$ , which undergoes rapid and essentially quantitative demetalation after being treated with 5 M HCl for 1 h at 70 °C.<sup>16</sup>

The positive ion ESI mass spectrum of  $\text{Me}_8\text{tricosaneN}_6$  in water only contained signals ( $m/z$  439), assigned to  $(\text{Me}_8\text{tricosaneN}_6 + \text{H})^+$ . Only four resonances were evident in the  $^1\text{H}$  NMR spectrum of  $\text{Me}_8\text{tricosaneN}_6$  in  $\text{CDCl}_3$ , and six  $^{13}\text{C}$  NMR peaks, consistent



**Figure 4.** vis-NIR spectra of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (pH 1.2 and 7.0) and  $[\text{Cu}(\text{sar})]^{2+}$  (pH 7.0).

**Scheme 1**



with the ligand exhibiting effective  $D_{3h}$  symmetry in solution. Complete assignment of all NMR signals was achieved from a gHMBC spectrum of the compound (Supporting Information, Figure S1), which enabled the proton and carbon resonances arising from the two different types of methylene groups in the caps and straps to be identified.

Single crystals of  $\text{Me}_8\text{tricosaneN}_6$  suitable for X-ray crystallography were obtained from evaporation of an acetonitrile solution of the free ligand. Figure 1 shows the asymmetric conformation of the ligand. A feature is an array of four intramolecular H-bonds ( $\text{N}-\text{H} \cdots \text{N}$ ) that link two of the three straps and orient the four N-atoms in an approximately planar array ready for metal coordination. The third strap is in a completely different conformation, and in this state neither of its N-donors are organized for metal binding. The conformation

Table 2. Selected Bond Lengths (Å) and Angles (deg)

|            | [Cu(Me <sub>8</sub> tricosaneN <sub>6</sub> )] <sup>2+</sup><br>(6-coord., NO <sub>3</sub> <sup>−</sup> salt) | [Cu(Me <sub>8</sub> tricosaneN <sub>6</sub> )] <sup>2+</sup><br>(5-coord., S <sub>2</sub> O <sub>6</sub> <sup>2−</sup> salt) | [Cu(HMe <sub>8</sub> tricosaneN <sub>6</sub> )] <sup>3+</sup><br>(5-coord., NO <sub>3</sub> <sup>−</sup> salt) |
|------------|---|--|--|
| Cu–N12     | 2.06(1)   | 2.037(3)   | 2.051(2)   |
| Cu–N22     | 2.43(1)   | 2.038(3)   | 2.037(2)   |
| Cu–N32     | 2.00(1)   | 2.338(3)   | 2.406(2)   |
| Cu–N16     | 2.27(1)   | 2.034(3)   | 2.039(2)   |
| Cu–N26     | 2.037(9)  | 2.030(3)   | 2.093(2)   |
| Cu–N36     | 2.54(1)   |  |  |
| N12–Cu–N22 | 80.6(5)   | 88.5(1)  | 88.34(9)   |
| N12–Cu–N32 | 94.2(5)   | 80.0(1)  | 90.71(8)   |
| N12–Cu–N16 | 79.7(5)   | 90.6(1)  | 96.00(8)   |
| N12–Cu–N26 | 152.2(5)  | 174.9(1)   | 159.10(9)  |
| N12–Cu–N36 | 108.1(3)  |  |  |
| N22–Cu–N16 | 111.3(4)  | 147.2(1)   | 164.77(9)  |
| $\tau^a$   |   | 0.46   | 0.09   |

<sup>a</sup>  $\tau = \alpha - \beta / 60$  where  $\alpha$  and  $\beta$  are the two largest coordinate angles.

of Me<sub>8</sub>tricosaneN<sub>6</sub> is quite similar to that of diprotonated (H<sub>2</sub>Me<sub>8</sub>tricosaneN<sub>6</sub>)(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub>.<sup>20</sup>

**Structural Characterization of Cu<sup>II</sup> Complexes of Me<sub>8</sub>tricosaneN<sub>6</sub>.** Dark blue solutions of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> formed rapidly by mixing free ligand and a Cu<sup>II</sup> salt in methanol or ethanol. The complex could then be isolated as a variety of salts (e.g., nitrate, perchlorate, triflate, dithionate, or hexafluorophosphate) by addition of an excess of the sodium salt of the appropriate anion. Two subtly different complexes were crystallized from aqueous ethanol (nitrate) and dilute aqueous ammonia (dithionate). Both were characterized crystallographically.

The structure of the nitrate salt (Figure 2A) finds the cage coordinated as a hexadentate. One pair of *trans* Cu–N bonds (to N22 and N36) are longer than the remaining four coordinate bonds as expected for axially elongated six-coordinate Cu<sup>II</sup> complexes because of the Jahn–Teller effect.<sup>37,38</sup> The structure is in fact disordered with the Cu ion occupying a 2-fold axis that passes through no other atoms (Supporting Information, Figure S2). These two orientations of the cation evidently may pack equally well as each other. This is reminiscent of the Cu<sup>II</sup>,<sup>19</sup> Ni<sup>II</sup>, and Zn<sup>II</sup> structures<sup>18</sup> of Me<sub>5</sub>tricosaneN<sub>6</sub> reported to date where disorder of the cation has been a feature.

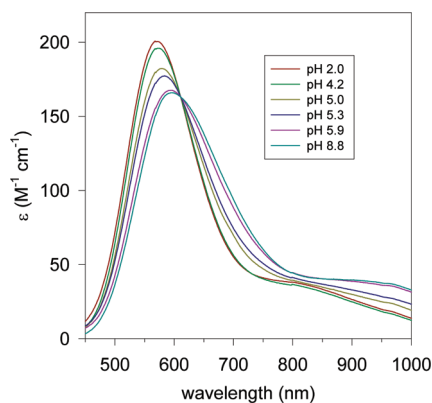
The mode of coordination in [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub> is asymmetric. This is best described by the absolute configuration of the six chirotopic N-donors; in this case SSSRSS (for N12, N22, N32, N16, N26, and N36, respectively) as drawn in Figure 2. (The structure is of a racemate so this relative configuration naturally includes the enantiomeric RRRSRR configuration) The SSSSSS diastereomer possesses D<sub>3</sub> symmetry, and this isomer was identified in [Co(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub>.<sup>21</sup> In the same paper a different N-based isomeric form (SRSRSS) was found for [Co(Me<sub>8</sub>tricosaneN<sub>6</sub>)] [ZnCl<sub>4</sub>]. The observation of three different N-based isomers from the few extant structures of crystallographically characterized hexadentate complexes of Me<sub>8</sub>tricosaneN<sub>6</sub> is testimony to the cavity of the ligand being exceptionally flexible, which is in stark contrast to the sep and sar family where a single N-based isomeric form (SSSSSS/RRRRRR) has been identified in each of the 136 crystal structures of N<sub>6</sub> coordinated complexes currently in the Cambridge Structural Database. Complexes from the [M(Me<sub>5</sub>tricosaneN<sub>6</sub>)]<sup>n+</sup> family presently fall into two categories: pseudo-

octahedral D<sub>3</sub> SSSSSS isomers (Ni<sup>II</sup>, Co<sup>III</sup>, Cu<sup>II</sup>, Zn<sup>II</sup>, Pt<sup>IV</sup>)<sup>16,18,19,39</sup> and C<sub>3h</sub> SSSRRR trigonal prismatic forms (Cd<sup>II</sup>, Hg<sup>II</sup>).<sup>20</sup>

Crystallization of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> as its S<sub>2</sub>O<sub>6</sub><sup>2−</sup> salt from weakly basic solution (dilute ammonia) afforded crystals suitable for X-ray studies, and the structure of the complex cation is shown in Figure 2B. Yet another mode of coordination is seen where the ligand is bound as a pentadentate, and the noncoordinated secondary amine (N36) accepts an intramolecular H-bond (N16–H···N36 2.34 Å). The five-coordinate geometry of the Cu ion falls between that of square pyramidal and trigonal bipyramidal. This degree of distortion may be quantified by the parameter  $\tau$  (see Table 2 for definition).<sup>40</sup> For an ideal square pyramid  $\tau = 0$  while for an ideal trigonal bipyramid  $\tau = 1$ . In the case of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](S<sub>2</sub>O<sub>6</sub>) we obtain a value  $\tau = 0.46$ . There is extensive H-bonding between the complex cation and the dithionate anion (Supporting Information, Figure S3).

In solution there should be little impediment to conversion between the six-coordinate and five-coordinate forms of the cation [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> defined in Figure 2 as they share the same configuration of their coordinated N-donors. Hexadentate coordinated [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>2</sub>·2H<sub>2</sub>O exhibits an SSSRSS (RRRSRR) configuration while [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](S<sub>2</sub>O<sub>6</sub>) is SSSRS (RRRSR), that is, they share the same N-based configuration of their five common coordinated amines. Moreover, if a vector were drawn between Cu and the sixth uncoordinated amine (N36) in Figure 2B then this amine would retain the same absolute (S) configuration as the hexadentate form in Figure 2A. On this basis we assume that the five- and six-coordinate cations in Figure 2 are interconvertible in solution, and H-bonding with the anions and packing forces dictate which solid state structure is observed. In the structure of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)](S<sub>2</sub>O<sub>6</sub>) the dithionate anion forms a number of H-bonds with the cation (Supporting Information, Figure S3), and these are sufficient to favor the 5-coordinate geometry.

A solution of [Cu(Me<sub>8</sub>tricosaneN<sub>6</sub>)]<sup>2+</sup> was acidified to pH 1 with dilute nitric acid which afforded a color change from blue to purple indicative of a change in coordination mode. Slow evaporation of this solution led to isolation of X-ray quality crystals of the monoprotonated complex [Cu(HMe<sub>8</sub>tricosaneN<sub>6</sub>)](NO<sub>3</sub>)<sub>3</sub>·H<sub>2</sub>O, and the structure of the complex cation is

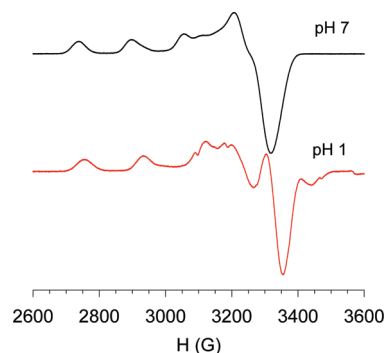


**Figure 5.** Spectrophotometric (vis–NIR) pH titration of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  in water ( $0.1 \text{ M KNO}_3$ ). The pH values are shown in the legend.

shown in Figure 3. The ligand is coordinated in a pentadentate mode with one amine protonated. There is a change in the N-based isomeric form relative to 5-coordinate  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)](\text{S}_2\text{O}_6)$  upon protonation (SSRS to SSRRR for N12, N22, N32, N16, and N26, respectively). As a result of the two N-inversions (at N32 and N26), the coordinate angles and geometry both change. The five coordinate geometry of  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)](\text{NO}_3)_3 \cdot \text{H}_2\text{O}$  is close to (axially elongated) square pyramidal ( $\tau = 0.09$ ).<sup>40</sup> The axial elongation is again typical of Jahn–Teller distorted 5-coordinate  $\text{Cu}^{\text{II}}$  complexes where the axial bond (Cu–N32) is at least  $0.3 \text{ \AA}$  longer than the four remaining Cu–N bonds in the equatorial plane.<sup>37,41</sup>

**Electrospray Ionization Mass Spectrometry.** The positive ion ESI mass spectra of various salts of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  resembled strongly those obtained previously for metal ion complexes of other cage ligands.<sup>42</sup> In each case the mass spectrum showed ions of high abundance at  $m/z$  251.1, which are attributable to the divalent cation. The only other ions present were generally of much lower abundance, and attributable to ion pairs formed either in the gas phase or solution. For example, the mass spectrum of the triflate salt showed ions at  $m/z$  650.6 from  $([\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+} + \text{CF}_3\text{SO}_3^-)^+$ , while for the hexafluorophosphate salt the corresponding ions arising from  $([\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+} + \text{PF}_6^-)^+$  were present at  $m/z$  646.6.

**Electronic Spectroscopy.** The electronic absorption spectra of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  and  $[\text{Cu}(\text{sar})]^{2+}$  in water (pH 7) are compared in Figure 4. Although both complexes are blue, the spectrum of the larger cavity  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  complex showed a broad d–d band in the visible region at 604 nm, a shoulder at about 900 nm and a more intense charge transfer band at 279 nm. By comparison, the electronic spectrum of  $[\text{Cu}(\text{sar})]^{2+}$  exhibits a pronounced NIR absorption band at 1189 nm which is characteristic of a  $\text{Cu}^{\text{II}}\text{N}_6$  complex in a tetragonally elongated ligand field ( $d_{x^2-y^2}$  ground state).<sup>19,24,37,38</sup> The absence of a prominent NIR absorption band for  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  suggests that this complex may not be six-coordinate in solution, or at least that any 6-coordinate form is a minor component of an equilibrium mixture. When the spectrum of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  was measured in acetonitrile the visible maximum shifted to 641 nm. This pronounced shift suggests inclusion of solvent molecules in the coordination sphere ( $\text{H}_2\text{O}$  or MeCN) and supports the view that the cage is only partially coordinated to the metal.



**Figure 6.** X-band EPR spectra of (A)  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (pH 7) and (B)  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  (pH 1). Both solutions contained  $2 \text{ mM}$  complex in DMF/water (1:2), and spectra were acquired at  $140 \text{ K}$ . The spectral frequency was  $9.337 \text{ GHz}$ .

A solution of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  acidified to pH 1.2 with nitric acid became immediately purple ( $\lambda_{\text{max}}$  570 nm, Figure 4). These are the same conditions used to prepare the structurally characterized protonated complex shown in Figure 3. Given that the structure of the compound crystallized at pH 1 has been established as five-coordinate  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  (Figure 3) the visible spectrum measured at pH 1 may be assigned to this same five-coordinate structure.

A spectrophotometric pH titration on  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}/[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  was carried out comprising spectra acquired at 19 different pH values. A selection of these data are presented in Figure 5, which shows the gradual spectral changes between pH 6 and 4. Global analysis of the entire set of 19 spectra with SPECFIT<sup>43</sup> gave a  $\text{pK}_a$  for the protonation reaction of 5.2(1). This value is typical of a noncoordinated amine in proximity to a dipositively charged metal.<sup>41,44</sup> The spectral changes (both in wavelength and peak intensity) are consistent with the solid state structures shown in Figure 2B for  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (distorted square pyramidal) and  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  in Figure 3 (square pyramidal).

**Electron Paramagnetic Spectroscopy.** EPR spectroscopy was also undertaken to further characterize the solution structures of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  and  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  (Figure 6) as the spin Hamiltonian ( $g$  and  $A$ ) values of  $\text{Cu}^{\text{II}}$  complexes are very sensitive to both coordination number and geometry.<sup>45</sup> Clearly both spectra are very similar, and each is consistent with an axially symmetric  $\text{Cu}^{\text{II}}$  ion ( $g_z > g_y = g_x$ ;  $A_z > A_y = A_x$ ). The spin Hamiltonian parameters were obtained by spectral simulation<sup>27</sup> (Supporting Information, Figure S4). The  $g$  and  $A$  values are actually very similar to those reported<sup>19</sup> for  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  and distinct from the trigonally twisted (and tetragonally elongated) smaller  $\text{N}_6$  cage complex  $[\text{Cu}((\text{NH}_2)_2\text{sar})]^{2+}$  (see Table 3) where  $g_z > g_y > g_x$  and  $A_z > A_y > A_x$ .<sup>24</sup> The EPR spectrum of the protonated complex  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  (Figure 6B) was only slightly different to that of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (Figure 6A); the main change being a decrease in  $g_z$  (from 2.240 to 2.205) and increase in  $A_z$  (Table 3).

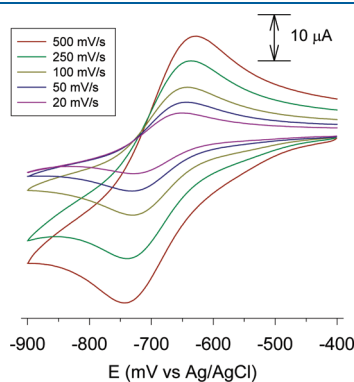
The spin Hamiltonian parameters for  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$ ,  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$ , and  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  (published previously, Table 3)<sup>19</sup> are quite similar and suggest a common solution structure. Given that  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  is undoubtedly five-coordinate and its square pyramidal structure is shown in Figure 3, by implication  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  and



$[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  are also dominantly five-coordinate in solution. The somewhat larger  $A_z$  and smaller  $g_z$  values found for  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  are consistent with a structure closer to ideal square pyramidal (essentially coplanar equatorial N-donors) relative to five-coordinate  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  where a solid state structure intermediate of square pyramidal and trigonal bipyramidal was found (Figure 2B).

Recently it has been shown that  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  (as its  $\text{CF}_3\text{SO}_3^-$  salt) is also capable of adopting a pentadentate coordinated structure, even without ligand protonation, although in that case the  $\text{CF}_3\text{SO}_3^-$  anion was found to be coordinated in the solid state.<sup>46</sup> Previously  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  was crystallized and structurally characterized in a six-coordinate form,<sup>19</sup> so it also appears that five and six-coordinate  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  complexes are also in facile equilibrium in solution, which parallels the behavior of the new  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  complexes reported herein.

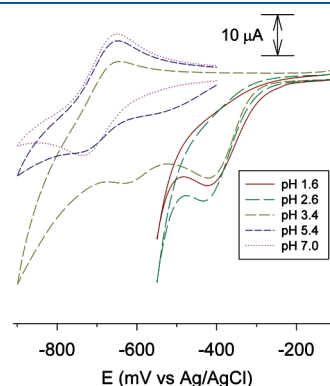
**Electrochemistry.** Previous cyclic voltammetry studies of the small cavity cage complex  $[\text{Cu}(\text{sar})]^{2+}$  demonstrated that it undergoes an irreversible reduction in aqueous solution at all scan rates.<sup>47</sup> This may be attributed to the  $\text{Cu}^{\text{I}}$  ion being incompatible with the preferred hexadentate binding mode of the cage. No structurally characterized six-coordinate  $\text{Cu}^{\text{I}}$  complexes are known, and  $\text{Cu}^{\text{I}}$  complexes with coordination numbers greater than 4 are very rare. The cyclic voltammogram of a neutral, aqueous solution of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  shows a facile and quasi-reversible  $\text{Cu}^{\text{II/I}}$  couple at  $-690$  mV vs Ag/AgCl with the anodic/cathodic peak current ratio ( $i_{\text{pa}}/i_{\text{pc}}$ ) being essentially unity at all sweep rates from 20 to  $1000 \text{ mV s}^{-1}$ . Representative voltammograms are shown in Figure 7 recorded at pH 7. The peak separation ( $\Delta E$ ) increased only slightly from 65 mV (at a  $20 \text{ mV s}^{-1}$  sweep rate) to 98 mV ( $1000 \text{ mV s}^{-1}$  sweep rate) indicative of fast heterogeneous electron transfer. For comparison the electrochemical data for  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+19}$  and the smaller cavity cage  $[\text{Cu}(\text{NH}_2)_2\text{sar}]^{2+}$  are included in Table 3.



**Figure 7.** Cyclic voltammetry of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (0.1 M aqueous  $\text{NaNO}_3$ , pH 7) at different sweep rates (20 to  $500 \text{ mV s}^{-1}$ ).

The voltammetry of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  is strongly pH dependent. Bearing in mind the  $\text{pK}_a$  of 5.2(1) determined spectrophotometrically for  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  the results reflect the electrochemistry of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  and its conjugate acid  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$ . As the pH is lowered (Figure 8), an irreversible cathodic peak emerges at  $-420$  mV which is due to reduction of  $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$  followed by rapid acid catalyzed dissociation liberating  $\text{Cu}_{\text{aq}}^{+}$  from the cage. Below  $\sim \text{pH } 4$  a cathodic  $\text{H}^+$  reduction wave (ca.  $-650$  mV vs Ag/AgCl) becomes dominant and obscures all other signals to lower potential. At pH values between 7 and 10 the voltammetry is unchanged.

**Structural Aspects and Crystal Packing.** Apart from the greater degree of conformational flexibility seen in complexes from the  $[\text{M}(\text{Me}_5\text{tricosaneN}_6)]^{n+}$  and  $[\text{M}(\text{Me}_8\text{tricosaneN}_6)]^{n+}$  family, the disorder also seen commonly in the limited set of crystal structures from these expanded cages appears to be a consequence of their more “spherical” shape relative to the  $[\text{M}(\text{sar})]^{n+}$  and  $[\text{M}(\text{sep})]^{n+}$  analogues. This is illustrated in Figure 9 where three “representative” crystal structures of complexes (two  $\text{Co}^{\text{III}}$  and one  $\text{Co}^{\text{II}}$ ) from each family are shown in space filling representation. The  $[\text{M}((\text{NH}_3)_2\text{sar})]^{n+}$  complex cation (Figure 9A) has an elongated, ellipsoidal shape with the three ethylenediamine chelates resulting in a narrow equatorial “belt” encircling the metal. In contrast the  $[\text{M}(\text{Me}_5\text{tricosaneN}_6)]^{n+}$  (Figure 9B) and  $[\text{M}(\text{Me}_8\text{tricosaneN}_6)]^{n+}$  (Figure 9C) cations, with six-membered chelate rings and methyl groups attached to the central C-atom define a more oblate shape. To aid comparisons, all three complexes bear an isosteric substituent ( $-\text{NH}_3^+$  or  $-\text{CH}_3$ ) on the apical cap C-atoms, so are essentially the same vertical length as drawn. Apart from their more isotropic shape, the NH groups in  $[\text{M}(\text{Me}_5\text{tricosaneN}_6)]^{n+}$  and  $[\text{M}(\text{Me}_8\text{tricosaneN}_6)]^{n+}$  are more obscured (blue N atoms) by the adjacent methyl groups rendering them less accessible to H-bond acceptors in the crystal lattice. We believe that these features are responsible for the disorder we have seen so far in many complexes from the  $\text{Me}_5\text{tricosaneN}_6$  and  $\text{Me}_8\text{tricosaneN}_6$  family.

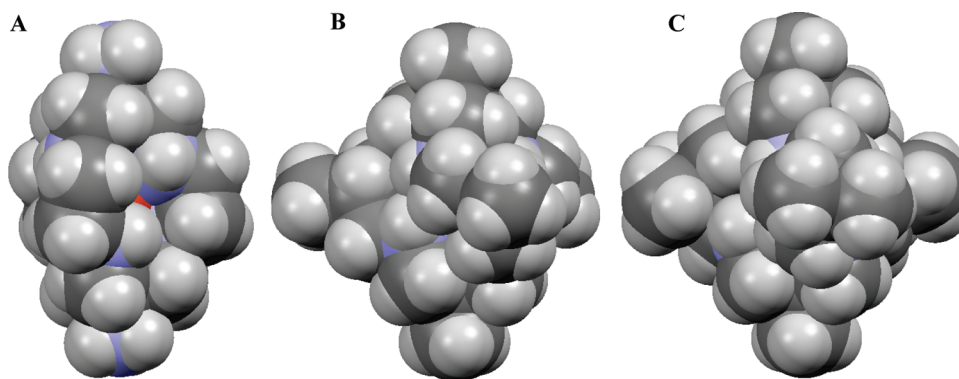


**Figure 8.** Cyclic voltammetry of 1 mM  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (0.1 M aqueous  $\text{NaNO}_3$ ,  $100 \text{ mV s}^{-1}$  sweep rate) at different pH values.

**Table 3.** EPR Spin Hamiltonian Parameters, Optical Spectroscopy, and Electrochemical Data for  $\text{Cu}^{\text{II}}$  Complexes in This Work

|   | $g_z (A_z, \text{G})$ | $g_y (A_y, \text{G})$ | $g_x (A_x)$ | $\lambda_{\text{max}} (\text{nm})$ | $E_{\text{Cu(II/I)}} (\text{mV vs Ag/AgCl})$ |
|---|-----------------------|-----------------------|-------------|------------------------------------|--|
| $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  | 2.240 (159)           | 2.052 (20)            | 2.052 (20)  | 604, 900(sh)                       | $-690$                                       |
| $[\text{Cu}(\text{HMe}_8\text{tricosaneN}_6)]^{3+}$ | 2.205 (177)           | 2.050 (24)            | 2.050 (24)  | 570                                | $-420$ (cathodic peak, irrev.)               |
| $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  | 2.250 (160)           | 2.060 (—)             | 2.060 (—)   | 616                                | $-760$                                       |
| $[\text{Cu}(\text{NH}_2)_2\text{sar}]^{2+}$         | 2.220 (130)           | 2.12 (55)             | 2.07 (15)   | 658, 1177                          | $-750$ (cathodic peak, irrev.)               |





**Figure 9.** Space filling representations of the complex cations (A)  $[\text{Co}((\text{NH}_3)_2\text{sar})]^{5+}$  (bis(antimonyl tartrate) chloride salt),<sup>23</sup> (B)  $[\text{Co}(\text{Me}_8\text{tricosaneN}_6)]^{3+}$  ( $\text{PF}_6^-$  salt),<sup>16</sup> and (C)  $[\text{Co}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (nitrate salt).<sup>21</sup> Coordinates taken from Cambridge Structural Database and displayed in Mercury (vers 2.4).

## CONCLUSIONS

We have shown that the ligand  $\text{Me}_8\text{tricosaneN}_6$  is unique among the hexaamine cage family in being able to accommodate a number of different coordination modes in this case to the same metal  $\text{Cu}^{\text{II}}$ . The larger and flexible cavity offered by  $\text{Me}_8\text{tricosaneN}_6$  is in contrast to ligands from the sar family which bind all six-coordinate transition metals tightly and in most cases irreversibly. Fortunately, we have been able to isolate and structurally characterize two distinct forms of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$ ; one six-coordinate and the other five-coordinate. In solution all evidence (EPR, electrochemistry, and optical spectroscopy) leads to the conclusion that  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  (at neutral or basic pH) is predominantly in a five-coordinate form resembling that shown in Figure 2B, that is, only five of the six N-donors are bound to the metal at any given time. Given the remarkably similar spectroscopy of  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  and  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  (Table 3), we believe it is likely that  $[\text{Cu}(\text{Me}_5\text{tricosaneN}_6)]^{2+}$  too is five-coordinate in solution and can also equilibrate between 6- and 5-coordinate forms rapidly. Further studies of this remarkable new addition to the hexaamine cage family are underway.

## ASSOCIATED CONTENT

**S Supporting Information.** Crystal structure data in CIF format, 2D NMR spectra of  $\text{Me}_8\text{tricosaneN}_6$ , views of the disordered  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)]^{2+}$  cation, packing diagram for  $[\text{Cu}(\text{Me}_8\text{tricosaneN}_6)](\text{S}_2\text{O}_6) \cdot \text{H}_2\text{O}$ , and simulated and experimental EPR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

<sup>†</sup>Deceased, 29th December 2008.

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