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An unusually flexible expanded hexaamine cage and its CuII complexes: variable coordination modes and incomplete encapsulation

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An unusually flexible expanded hexaamine cage and its CuII complexes: variable coordination modes and incomplete encapsulation

Abstract
The bicyclic hexaamine "cage" ligand Me 8tricosaneN 6 (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 II the lability of the metal results in a dynamic equilibrium in solution between hexadentate- and pentadentate- coordinated complexes of Me 8tricosaneN 6. Both [Cu(Me 8tricosaneN 6)](ClO 4) 2 (6-coordinate) and [Cu(Me 8tricosaneN 6)](S 2O 6) (5-coordinate) have been characterized structurally. In weak acid (pH 1) a singly protonated complex [Cu(HMe 8tricosaneN 6)] 3+ 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 8tricosaneN 6)] 2+ at neutral pH comprises a five-coordinate, square pyramidal complex. Cyclic voltammetry of the square pyramidal [Cu(Me 8tricosaneN 6)] 2+ complex reveals a reversible Cu II/I 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 II complexes which are invariably hexadentate coordinated in neutral solution and cannot stabilize a Cu I form.

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Keywords
unusually, flexible, expanded, hexaamine, cage, its, CuII, complexes, variable, coordination, modes, incomplete, encapsulation, CMMB

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An Unusually Flexible Expanded Hexaamine Cage and Its Cu\textsuperscript{II} Complexes: Variable Coordination Modes and Incomplete Encapsulation

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Supporting Information

ABSTRACT: The bicyclic hexaamine "cage" ligand Me\textsubscript{5}tricosaneN\textsubscript{6} (1,5,9,13,20,20-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\textsuperscript{II} the lability of the metal results in a dynamic equilibrium in solution between hexadentate- and pentadentate-coordinated complexes of Me\textsubscript{5}tricosaneN\textsubscript{6}. Both [Cu(Me\textsubscript{5}tricosaneN\textsubscript{6})]([ClO\textsubscript{4}]\textsubscript{2} (6-coordinate) and [Cu(Me\textsubscript{5}tricosaneN\textsubscript{6})]([S\textsubscript{2}O\textsubscript{6}] (5-coordinate) have been characterized structurally. In weak acid (pH 1) a singly protonated complex [Cu(HMe\textsubscript{5}tricosaneN\textsubscript{6})]\textsuperscript{3+} has been isolated that finds the ligand binding as a pentadentate with the uncoordinated amine being protonated. Visual-NIR and electron paramagnetic resonance (EPR) spectroscopy show that the predominant solution structure of [Cu(Me\textsubscript{5}tricosaneN\textsubscript{6})]\textsuperscript{2+} at neutral pH comprises a five-coordinate, square pyramidal complex. Cyclic voltammetry of the square pyramidal [Cu(Me\textsubscript{5}tricosaneN\textsubscript{6})]\textsuperscript{2+} complex reveals a reversible Cu\textsuperscript{II/III} 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]icosane) Cu\textsuperscript{II} complexes which are invariably hexadentate coordinated in neutral solution and cannot stabilize a Cu\textsuperscript{II} form.

INTRODUCTION

The macrocyclic cage ligands sepulchrate (sep or 1,3,6,8,10-, 13,16,19-octaazabicyclo[6.6.6]icosane)\textsuperscript{1} and sarcophagine (sar or 3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane)\textsuperscript{2} 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\textsuperscript{3} and racemization.\textsuperscript{4} These properties have led to some important applications particularly in medicinal chemistry through the development of a functionalized ligand based on (NH\textsubscript{2})\textsubscript{2}sar (Chart 1) through complexation of \textsuperscript{64}Cu\textsuperscript{II} for diagnostic positron emission tomography (PET) imaging.\textsuperscript{5,6}

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,\textsuperscript{7–9} crown ethers,\textsuperscript{10} and cryptands\textsuperscript{11,12} 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.\textsuperscript{13–15}

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 hexaamine Me\textsubscript{5}tricosaneN\textsubscript{6} (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\textsuperscript{16–20} compared with the smaller cavity sar cages. The Co\textsuperscript{III} complex [Co(Me\textsubscript{5}tricosaneN\textsubscript{6})]\textsuperscript{3+} exhibits unusually long Co–N bond lengths (2.010(4) – 2.032(4) Å)\textsuperscript{16} and a weak ligand field in comparison with [Co(sep)]\textsuperscript{3+} (Co–N 1.96 Å).\textsuperscript{1} In addition, the [Co(Me\textsubscript{5}tricosaneN\textsubscript{6})]\textsuperscript{3+/2+} redox couple\textsuperscript{16} is found at a significantly more positive potential than [Co(sep)]\textsuperscript{3+/2+}.\textsuperscript{4} All of these features highlight the influence of the larger cavity of the Me\textsubscript{5}tricosaneN\textsubscript{6} ligand on the properties of the metal ion it encapsulates.

The octa-methylated analogue Me\textsubscript{8}tricosaneN\textsubscript{6} (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\textsubscript{5}tricosa- neN\textsubscript{6} yet the subtle addition of methyl groups on each strap alters its coordination chemistry markedly. Unusually high Co\textsuperscript{II/III} redox potentials and optical properties have been reported for the Co complexes of Me\textsubscript{5}tricosaneN\textsubscript{6} and its trimine.\textsuperscript{21} Oxidation of pink [Co(Me\textsubscript{5}tricosaneN\textsubscript{6})]\textsuperscript{2+} yields two different Co\textsuperscript{III} complexes. One of these is an orange complex obtained from aqueous solution and...
has been characterized by X-ray crystallography, with an average CoIII–N distance of 1.99(1) Å, intermediate between [Co-(Me5tricosaneN6)]3+16 and [Co((NH3)2)sar]3+. The second CoIII complex of Me8tricosaneN6 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 Me8tricosaneN6 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 Me8tricosaneN6 as its free base in addition to its copper(II) coordination chemistry. This study, in comparison with our previous investigations of the Cu2+ coordination chemistry of Me8tricosaneN6,19 and (NH2)2sar,24 highlights the fact that Me8tricosaneN6 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. The complex [Co(tame)3]Cl3 (tame = 1,1,1-tris(aminomethyl)ethane) was prepared as described.26 An improved synthesis of the free ligand tame is described below.

1,1,1-Tris((p-toluenesulfonyloxy)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 benzylamine (26 mL, 240 mmol) and heated to 180 °C for 10 min. Paraformaldehyde (3.0 g; 0.10 mol) and isobutyraldehyde (71.9 g) was added followed by ammonium formate (4.73 g, 75 mmol), and 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 about 4 L with water and loaded onto a Dowex 50W X-2 cation exchange column (15 × 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 CoIII 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 [Co(Me8tricosanetriimine-N6)]Cl3 was dissolved in 400 mL of water and adsorbed onto a SP Sephadex C-25 cation exchange column (57 × 9 cm resin bed) and eluted using 0.2 M KCl. The last pink band to elute was collected and adsorbed onto a Dowex 50W X-2 cation exchange column (7 × 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 [Co(Me8tricosanetriimineN6)]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 10 with sat. Na2CO3. A solution containing NaBH4 (0.38 g; 9.9 mmol) dissolved in 40 mL of water (pH previously adjusted to 10 with Na2CO3) was then added with stirring. After 20 min the reaction was quenched by addition of 120 mL of sat. NaHCO3. A single light purple band was collected and evaporated on a hot plate at 40–50 °C to ~30 mL, resulting in a pink precipitate of [Co(Me8tricosaneN6)](NO3)2·H2O, which was filtered off and dried in air. Yield 450 mg (3%). Anal. Calc. for C25H56CoN8O7: ([Co(Me8tricosaneN6)](NO3)2·H2O).
Anion exchange chromatography (Dowex 1-X8, Cl− form) of [Cu(Me8tricosaneN6)](NO3)2·H2O yielded the corresponding chloride salt, which was isolated after evaporation of the eluate. Anal. Calc. for C25H54N6Cl2O3: C 9.5. C25H58CoN6Cl2O3: (Co(Me8tricosaneN6)Cl2)ide salt, which was isolated after evaporation of the eluate. Anal. Calc. for C64.9; H 8.8; N 17.5; Co 9.2. Found C 64.7; H 9.2; N 17.4; Co 9.0.

Me8tricosaneN6: [Cu(Me8tricosaneN6)](NO3)2 (1.14 g, 1.83 mmol) was dissolved in DMF/H2O (1:2) (1 mL). Dilute nitric acid (~9.3 GHz) as 2 mM DMF/H2O 1:2 frozen solutions at 140 K. Spin Hamiltonian parameters were determined by spectral simulation with the program EPR50F.27

Crystallography. For Me8tricosaneN6 the X-ray data were collected using 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.28 For [Cu(Me8tricosaneN6)](S2O6) and texsan in the case of Me8tricosaneN6. The absorption spectrum of [Cu(Me8tricosaneN6)]2+ 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 NaNO3, and all solutions were purged with Ar before measurement. Elemental analysis was performed by the Microanalytical Unit at the Australian National University. 1H and 13C NMR spectra were recorded on a Varian Unity-300 (300 MHz 1H, 75 MHz 13C) spectrometer in either D2O or CDCl3. Electron paramagnetic resonance (EPR) spectra were measured with a Bruker ER200 instrument at X-band frequency (~9.3 GHz) as 2 mM DMF/H2O 1:2 frozen solutions at 140 K. Spin Hamiltonian parameters were determined by spectral simulation with the program EPR50F.27

<table>
<thead>
<tr>
<th>Table 1. Crystal Data</th>
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<td>R(∑obs data)</td>
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\[R(F_o) = \frac{\sum|F_o| - |F_c|}{\sum|F_o|}, \quad wR(F_o^2) = \frac{\sum w(F_o^2 - F_c^2)^2}{\sum w F_o^2}^{1/2}.\]
(NO₃)₃·H₂O crystallographic data were acquired at 293 K on an Oxford Diffraction Gemini CCD diffractometer and operating within the range 2 < 2θ < 50 Å. Data reduction and empirical absorption corrections (multiscan) were performed with Oxford Diffraction CrystAlisPro 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. Structures were solved by direct methods with SHELXS and refined by full-matrix least-squares analysis with SHELXL-97 (Table 1). All non-H atoms were refined with anisotropic thermal parameters. In all structures graphite-monochromated Mo Kα radiation (0.71073 Å) was used. Molecular structure diagrams in Figures 2–4 were produced with ORTEP3, while space filling and packing diagrams were produced with Mercury (vers 2.4) and disorder in the structure of [Cu(Me₈tricosaneN₆)](NO₃)₂·2H₂O (Supporting Information Figure S2) was shown with PLUTON. 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 Me₈tricosaneN₆ there was 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 Me₈tricosaneN₆ (Scheme 1) proceeds via a metal directed template reaction using [Co(tame)₂][NO₃]₃ (tame = 1,1,1-tris-(aminomethyl)ethane) as the precursor. The triamine tame is well-known and also is the precursor for the related cage ligand Me₅tricosaneN₆. 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. After hydrolysis, distillation at high temperatures (>200 °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. 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 LiAlH₄, of 1,1,1-tris(azidomethyl)ethane. 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. 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 LiAlH₄, of 1,1,1-tris(azidomethyl)ethane. 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.
Synthesis and Characterization of Me₈tricosaneN₆. The synthesis of Me₈tricosaneN₆ (Scheme 1) proceeds via a metal template reaction of [Co(tame)₂]³⁺ with formaldehyde and isobutyraldehyde (2-methylpropanal), yielding the structurally characterized Co³⁺ tri-imine complex [Co(Me₈tricosanetriimineN₆)]Cl₃.²¹ 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 polyamines. Separation and characterization of all Co³⁺ complexes formed in the formaldehyde/isobutyraldehyde condensation reaction has not been achieved, but ¹³C NMR indicates that there are many species and they are typically asymmetric. Unreacted [Co(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 Co³⁺ cages¹,² which proceed in quantitative yields. Reduction of [Co(Me₈tricosanetriimineN₆)]³⁺ affords two N-based diastereomeric Co²⁺ complexes of Me₈tricosaneN₆;²¹ one pink and one violet which are both remarkably air stable unlike all other Co²⁺ hexaamines.

The cobalt(II) complexes of smaller cavity ligands (e.g., [Co(sep)]²⁺ and [Co(sar)]²⁺) are exceptionally resistant to dissociation in acidic solution. For example, divalent [Co((NH₃)₂-sar)]⁴⁺ shows no detectable loss of the metal ion in strongly acidic solution at 20 °C after several days.² Procedures for preparing the metal-free hexaamine cage ligands sar and (NH₂)₂sar 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.³ In contrast, [Co(Me₈tricosaneN₆)]²⁺ dissociates rapidly in dilute acid (1 M HCl), and the liberated Co₃⁺ ions separate readily from the protonated free ligand on a cation exchange column. This resembles the behavior of [Co(Me₅tricosaneN₆)]²⁺, which undergoes rapid and essentially quantitative demetalation after being treated with 5 M HCl for 1 h at 70 °C.¹⁶

The positive ion ESI mass spectrum of Me₈tricosaneN₆ in water only contained signals (m/z 439), assigned to Me₈tricosaneN₆ + H⁺. Only four resonances were evident in the ¹H NMR spectrum of Me₈tricosaneN₆ in CDCl₃, and six ¹³C NMR peaks, consistent with the ligand exhibiting effective D₃ₕ 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 Me₈tricosaneN₆ 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 (N–H···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

Figure 3. ORTEP view of five-coordinate [Cu(HMe₈tricosaneN₆)](NO₃)₃·H₂O. 30% probability ellipsoids are shown, and anions and water molecules have been omitted for clarity.

Figure 4. vis–NIR spectra of [Cu(Me₈tricosaneN₆)]²⁺ (pH 1.2 and 7.0) and [Cu(sar)]²⁺ (pH 7.0).

Scheme 1
of Me₈tricosaneN₆ is quite similar to that of diprotonated (H₂Me₈tricosaneN₆)(CF₃SO₃)₂.²⁰

Structural Characterization of Cu⁺ Complexes of Me₈tricosaneN₆. Dark blue solutions of [Cu(Me₈tricosaneN₆)]²⁺ formed rapidly by mixing free ligand and a Cu⁺ 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 (amine). 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⁺ complexes because of the Jahn—Teller effect.³⁷,³⁸ 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⁺,NiII,N₇⁺, and ZnII structures of Me₈tricosaneN₆ reported to date where disorder of the cation has been a feature.

The mode of coordination in [Cu(Me₈tricosaneN₆)](NO₃)₂ 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 RRRSSS configuration.) The SSSRSS diastereomer possesses D₃ symmetry, and this isomer was identified in [Co(Me₈tricosaneN₆)](NO₃)₂.¹¹ In the same paper a different N-based isomeric form (SSRSS) was found for [Co(Me₈tricosaneN₆)][ZnCl₄]. The observation of three different N-based isomers from the few extant structures of crystallographically characterized hexadentate complexes of Me₈tricosaneN₆ 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 N₆ coordinated complexes currently in the Cambridge Structural Database. Complexes from the [M(Me₈tricosaneN₆)]³⁺ family presently fall into two categories: pseudo-octahedral D₃ SSSRSS isomers (NiII, CuII, CuI, ZnII, PtIV)₁₆,₁₈,₁₉,₃⁹ and C₃h SSSRRR trigonal prismatic forms (CdII, HgII).²⁰

Crystallization of [Cu(Me₈tricosaneN₆)]²⁺ as its S₂O₆²⁻ 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 (for N12, figure 2A). Yet another mode of coordination is seen in the structure of [Cu(Me₈tricosaneN₆)](S₂O₆) where a vector were drawn between Cu and the sixth uncoordinated N bond (to N6). The structure of [Cu(Me₈tricosaneN₆)](S₂O₆) where a vector were drawn between Cu and the sixth uncoordinated N bond (to N6).

<table>
<thead>
<tr>
<th>Table 2. Selected Bond Lengths (Å) and Angles (deg)</th>
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<th>[Cu(Me₈tricosaneN₆)]²⁺</th>
<th>[Cu(HMe₈tricosaneN₆)]³⁺</th>
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<td>(5-coord., S₂O₆²⁻ salt)</td>
<td>(5-coord., NO₃⁻ salt)</td>
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<td>Cu—N36</td>
<td>2.54(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N12—Cu—N22</td>
<td>80.6(5)</td>
<td>88.5(1)</td>
<td>88.34(9)</td>
</tr>
<tr>
<td>N12—Cu—N32</td>
<td>94.2(5)</td>
<td>80.0(1)</td>
<td>90.71(8)</td>
</tr>
<tr>
<td>N12—Cu—N16</td>
<td>79.7(5)</td>
<td>90.6(1)</td>
<td>96.00(8)</td>
</tr>
<tr>
<td>N12—Cu—N26</td>
<td>152.2(5)</td>
<td>174.9(1)</td>
<td>159.10(9)</td>
</tr>
<tr>
<td>N12—Cu—N36</td>
<td>108.1(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N22—Cu—N16</td>
<td>111.3(4)</td>
<td>147.2(1)</td>
<td>164.77(9)</td>
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</table>

were determined from X-ray diffraction and are shown in Table 2. The selected bond lengths and angles are taken from the Cambridge Structural Database, and are presented in the Supporting Information (Table S1). 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 (for N12, figure 2A). Yet another mode of coordination is seen in the structure of [Cu(Me₈tricosaneN₆)](S₂O₆) where a vector were drawn between Cu and the sixth uncoordinated N bond (to N6).

A solution of [Cu(Me₈tricosaneN₆)]²⁺ 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(HMe₈tricosane-N₆)](NO₃)₃·H₂O, and the structure of the complex cation is...
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 \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) upon protonation (SSSRS to SSSRR 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 \( [\text{Cu}((\text{HMe8tricosaneN6)}][\text{NO3})_3 \cdot \text{H2O} \) is close to (axially elongated) square pyramidal \((\tau = 0.09)\). The axial elongation is again typical of Jahn–Teller distorted 5-coordinate CuII complexes.

**Electrospray Ionization Mass Spectrometry.** The positive ion ESI mass spectra of various salts of \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) resembled strongly those obtained previously for metal ion complexes of other cage ligands. 

In each case the mass spectrum showed ions of high abundance at \( m/z \) 251, 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 \( ([\text{Cu(Me8tricosaneN6)}]^{2+} + \text{CF3SO3})^- \), while for the hexafluorophosphate salt the corresponding ions arising from \( ([\text{Cu(Me8tricosaneN6)}]^{2+} + \text{PF6})^- \) were present at \( m/z \) 646.6.

**Electronic Spectroscopy.** The electronic absorption spectra of \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) and \( [\text{Cu(sar)}]^{2+} \) in water (pH 7) are compared in Figure 4. Although both complexes are blue, the spectrum of the larger cavity \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) 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 \( [\text{Cu(sar)}]^{2+} \) exhibited a pronounced NIR absorption band at 1189 nm which is characteristic of a CuIIN6 complex in a trigonally twisted (and tetragonally elongated) smaller N6 cage. The band at 279 nm is a shoulder at about 900 nm and a more intense charge transfer band at 604 nm. This pronounced shift suggests inclusion of solvent molecules in the coordination sphere (H2O or MeCN) and supports the view that the cage is only partially coordinated to the metal.

A solution of \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) 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 \( [\text{Cu}((\text{HMe8tricosaneN6)}][\text{NO3})_3 \cdot \text{H2O} \) (Figure 3) the visible spectrum measured at pH 1 may be assigned to this same five-coordinate structure.

A spectrophotometric pH titration on \( [\text{Cu(Me8tricosaneN6)}]^{2+}/[\text{Cu(Me8tricosaneN6)}]^{3+} \) 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 SPECFIT43 gave a pKa for the protonation reaction of 5.2(1). This value is typical of a noncoordinated amine in proximity to a dipositively charged metal.19,42

The spectral changes (both in wavelength and peak intensity) are consistent with the solid state structures shown in Figure 2B for \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) (distorted square pyramidal) and \( [\text{Cu(Me8tricosaneN6)}]^{3+} \) in Figure 3 (square pyramidal).

**Electron Paramagnetic Spectroscopy.** EPR spectroscopy was also undertaken to further characterize the solution structures of \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) and \( [\text{Cu(Me8tricosaneN6)}]^{3+} \) (Figure 6) as the spin Hamiltonian (\( g \) and \( A \)) values of CuII complexes are very sensitive to both coordination number and geometry.45 Clearly both spectra are very similar, and each is consistent with an axially symmetric CuII ion (\( g_z > g_x \)). The \( g \) and \( A \) values are actually very similar to those reported for \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) and distinct from the trigonally twisted (and tetragonally elongated) smaller N6 cage complex \( [\text{Cu}((\text{NH2})_2\text{sar})]^{2+} \) (see Table 3) where \( g_x = g_y = g_z \) and \( A_x = A_y > A_z \). The EPR spectrum of the protonated complex \( [\text{Cu}((\text{HMe8tricosaneN6)}]^{3+} \) (Figure 6B) was only slightly different to that of \( [\text{Cu}((\text{HMe8tricosaneN6)}]^{3+} \) (Figure 6A); the main change being a decrease in \( g_x \) (from 2.240 to 2.205) and in \( A_z \) (Table 3).

The spin Hamiltonian parameters for \( [\text{Cu(Me8tricosaneN6)}]^{2+}, [\text{Cu}((\text{HMe8tricosaneN6)}]^{3+}, \) and \( [\text{Cu(Me8tricosaneN6)}]^{3+} \) (published previously, Table 3) are quite similar and suggest a common solution structure. Given that \( [\text{Cu}((\text{HMe8tricosaneN6)}]^{3+} \) is undoubtedly five-coordinate and its square pyramidal structure is shown in Figure 3, by implication \( [\text{Cu(Me8tricosaneN6)}]^{2+} \) and
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aqueous NaNO3, pH 7) are also dominantly five-coordinate in solution. The somewhat larger \( A_g \) and smaller \( g_z \) values found for \([\text{Cu(HMe}_8\text{tricosaneN}_6\text{)}]^2^+\) are consistent with a structure closer to ideal square pyramidal (essentially coplanar equatorial N-donors) relative to five-coordinate \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^2^+\) where a solid state structure intermediate of square pyramidal and trigonal bipyramidal was found (Figure 2B).

Recently it has been shown that \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) (as its CF3SO3– salt) is also capable of adopting a pentadentate coordinated structure, even without ligand protonation, although in that case the CF3SO3– anion was found to be coordinated in the solid state.\(^{46}\) Previously \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) was crystallized and structurally characterized in a six-coordinate form,\(^ {19}\) so it also appears that five and six-coordinate \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) complexes are also in facile equilibrium in solution, which parallels the behavior of the new \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) complexes reported herein.

Electrochemistry. Previous cyclic voltammetry studies of the small cavity cage complex \([\text{Cu(sar)}]^2^+\) demonstrated that it undergoes an irreversible reduction in aqueous solution at all scan rates.\(^{47}\) This may be attributed to the CuI ion being incompatible with the preferred hexadentate binding mode of the cage. No structurally characterized six-coordinate Cu complexes are known, and Cu complexes with coordination numbers greater than 4 are very rare. The cyclic voltammogram of a neutral, aqueous solution of \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) shows a facile and quasi-reversible \( \text{Cu}^{2^+}/\text{Cu}^{+} \) couple at \(-690 \text{ mV vs Ag/AgCl} \) with the anodic/cathodic peak current ratio \( (i_{pa}/i_{pc}) \) being essentially unity at all sweep rates from 20 to 1000 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 mV s\(^{-1}\) sweep rate) to 98 mV (1000 mV s\(^{-1}\) sweep rate) indicative of fast heterogeneous electron transfer. For comparison the electrochemical data for \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) and the smaller cavity cage \([\text{Cu(NH}_3)_2\text{sat})^{2^+}\) are included in Table 3.

The voltammetry of \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) is strongly pH dependent. Bearing in mind the pK\(_a\) of 5.2(1) determined spectrophotometrically for \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) the results reflect the electrochemistry of \([\text{Cu(HMe}_8\text{tricosaneN}_6\text{)}]^{2^+}\) and its conjugate acid \([\text{Cu(HMe}_8\text{tricosaneN}_6\text{)}]^{3^+}\). As the pH is lowered (Figure 8), an irreversible cathodic peak emerges at \(-420 \text{ mV} \) which is due to reduction of \([\text{Cu(HMe}_8\text{tricosaneN}_6\text{)}]^{3^+}\) followed by rapid acid catalyzed dissociation liberating Cu\(_{aq}\) from the cage. Below \(-p\text{H} 4\) a cathodic H+ reduction wave (ca. \(-650 \text{ mV vs Ag/AgCl} \) 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 \([\text{M(Me}_8\text{tricosaneN}_6\text{)}]^{n^+}\) and \([\text{M(Me}_8\text{tricosaneN}_6\text{)}]^{n^+}\) 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 \([\text{M(sar)}]^{n^+}\) and \([\text{M(sep)}]^{n^+}\) analogues. This is illustrated in Figure 9 where three “representative” crystal structures of complexes (two Cu\(^{III}\) and one Cu\(^{II}\)) from each family are shown in space filling representation. The \([\text{M((NH}_3)_2\text{sat})]^{n^+}\) 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 \([\text{M(Me}_8\text{tricosaneN}_6\text{)}]^{n^+}\) (Figure 9B) and \([\text{M(Me}_8\text{tricosaneN}_6\text{)}]^{n^+}\) (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 \([\text{M(Me}_8\text{tricosaneN}_6\text{)}]^{n^+}\) \((\text{M} = \text{Co})\) (Figure 9B) and \([\text{M(Me}_8\text{tricosaneN}_6\text{)}]^{n^+}\) (Figure 9C) cations, with six-membered chelate rings and methyl groups attached to the central C-atom define a more oblate shape. In the crystal lattice. We believe that these features are responsible for the disorder we have seen so far in many complexes from the \(\text{Me}_8\text{tricosaneN}_6\) and \(\text{Me}_8\text{tricosaneN}_6\) family.

**Table 3.** EPR Spin Hamiltonian Parameters, Optical Spectroscopy, and Electrochemical Data for CuII Complexes in This Work

<table>
<thead>
<tr>
<th>Complex</th>
<th>( g_x ) (A(_\gamma))</th>
<th>( g_y ) (A(_\gamma))</th>
<th>( g_z ) (A(_\gamma))</th>
<th>( \lambda_{max} ) (nm)</th>
<th>( E_{\text{Cu}^{II}/\text{Cu}^{+}} ) (mV vs Ag/AgCl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+})</td>
<td>2.240 (159)</td>
<td>2.052 (20)</td>
<td>2.052 (20)</td>
<td>604, 900(sh)</td>
<td>(-690)</td>
</tr>
<tr>
<td>([\text{Cu(HMe}_8\text{tricosaneN}_6\text{)}]^{2^+})</td>
<td>2.205 (177)</td>
<td>2.050 (24)</td>
<td>2.050 (24)</td>
<td>570</td>
<td>(-420) (cathodic peak, irrev.)</td>
</tr>
<tr>
<td>([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+})</td>
<td>2.250 (160)</td>
<td>2.060 (–)</td>
<td>2.060 (–)</td>
<td>616</td>
<td>(-760)</td>
</tr>
<tr>
<td>([\text{Cu(NH}_3)_2\text{sat})^{2^+})</td>
<td>2.220 (130)</td>
<td>2.12 (55)</td>
<td>2.07 (15)</td>
<td>658, 1177</td>
<td>(-750) (cathodic peak, irrev.)</td>
</tr>
</tbody>
</table>

![Figure 7. Cyclic voltammetry of \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) (0.1 M aqueous NaNO3, pH 7) at different sweep rates (20 to 500 mV s\(^{-1}\)).](image1)

![Figure 8. Cyclic voltammetry of 1 mM \([\text{Cu(Me}_8\text{tricosaneN}_6\text{)}]^{2^+}\) (0.1 M aqueous NaNO3, pH 7) at different sweep rates (20 to 500 mV s\(^{-1}\)).](image2)
Figure 9. Space filling representations of the complex cations (A) \([\text{Co}((\text{NH}_3)_2\text{sar})]^{3+}\) (bis(antimonyl tartrate) chloride salt), (B) \([\text{Co}([\text{Me}_8\text{tricosaneN}_6])]^{2+}\) (PF6− salt), and (C) \([\text{Co}([\text{Me}_6\text{tricosaneN}_6])]^{2+}\) (nitrate salt). 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 CuII. 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, spectroscopy, 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 \([\text{Cu}([\text{Me}_6\text{tricosaneN}_6])]^{2+}\) (Table 3), we believe it is likely that \([\text{Cu}([\text{Me}_8\text{tricosaneN}_6])]^{2+}\) 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

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 \([\text{Cu}([\text{Me}_8\text{tricosaneN}_6])](\text{S}_2\text{O}_6)^{-}\)-\(\text{H}_2\text{O}\), 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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## REFERENCES


