A Functionalised Macrobicycle Complex Available for Surface Immobilisation and Protein Grafting

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The conversion of both the racemic and resolved forms of the Co(III) complex of an hydroxymethyl-substituted tripodal hexamine to macrobicycles via reaction with formaldehyde and nitromethane (and subsequent reduction of the product) has been conducted. The prospect is that it will provide cage complexes in which the hydroxyl substituent is sufficiently remote from the metal ion centre for its nucleophilicity to be largely unaffected. X-ray structure determinations have been used to characterise these new cage species as well as some complexes of the precursor hexamine and its mono-aminal. The electrochemistry and optical activity of the complexes have also been studied in detail.

Key Words: Macrocycle, Co(III), Cage, Hexamine, Electrochemistry

Introduction

The macrocyclic cage hexaamine “sarcophagine” (3,6,10,13,16,19-hexa-azabicyclo[6.6.6]icosane) and its substituted analogues (see 1 and 2 in Figure 1) are capable of complexing a variety of metal ions, rendering them not only inert to substitution but, amongst other things, imposing upon them a chiral environment.1-3 The remarkable properties of these caged metal ions have possible applications in biology,4-9 energy conversion10-12 and materials science.13,14 For this, it must be possible to covalently attach the cage to other (macro)molecules or surfaces, which then demands the presence of reactive functional groups suitable for such grafting. While the external amino groups of complexes such as [Co(1)]13 or [Co(2)]14 have been used successfully as such groups in reductive alkylation reactions,13-16 reactions at these sites are inhibited by their proximity to the cationic centres. This problem may be alleviated if the functional group that is to be employed as a linker is more remote from the metal than the amino groups of 1 or 2. In this paper we introduce the new disubstituted cages 3 and 4 where a synthetically useful hydroxymethyl group replaces the inert methyl group of the simpler analogue 1.

Our approach involves a combination of organic and transition metal template syntheses.17 Recently we have reported the hydroxymethyl substituted tripodal hexamine 5 isolated as its CoIII complex [Co(5)]18. The ligand 5 may be viewed as a precursor to 3 and 4 in that upon complexation with CoIII it provides a triplet of facially coordinated primary amino groups that may be ‘capped’ with formaldehyde and a tribasic acid such as MeNO2.1,2,19,20 The nitro-substituted cage is then easily reduced to the amine derivative without loss of the metal ion. The ligands 3 and 4 thus possess a hydroxyl group remote from the metal ion that may be activated for nucleophilic substitution reactions through e.g. the formation of reactive sulfonyl esters. The present work is an extension of our broader studies on the synthesis and properties of ligands functionalised with the synthetically useful hydroxymethyl group and we include herein description of some of the basic coordination chemistry of the new cage complexes derived from [Co(5)]18. The enantiomers of this complex, described herein, are precursors to the chiral cages [Co(3)]18 and [Co(4)]18. We also report the isolation of an unusual byproduct from the synthesis of 5, namely the aminal 6, which is incapable of coordinating as a hexadentate but which can bind as a quadridentate.

Experimental Section

Materials and equipment. Pentaerythritol tribromide was purchased from Tokyo Kasei (Japan) and other chemicals from Aldrich and used as received. The synthesis of (5) and purification by isolation of its CoIII complex, [Co(5)]Cl3·H2O has been described elsewhere.18 Ion exchange chromatography was conducted in glass columns under gravity flow flow
using either SP-Sephadex C-25 (Na+ form) or Dowex 50Wx2 (H+ form) ion-exchange resins.

Cyclic voltammetry employed a BAS100B/W potentiostat attached to a PAR Model 303 dropping mercury working electrode, a Pt counter and Ag/AgCl reference electrode. The supporting electrolyte was 0.1 M NaNO₃ and all solutions were purged with N₂ prior to measurement. IR spectra were recorded with a JASCO FT-IR 5300 with compounds dispersed as KBr discs. UV/vis absorption spectra were measured on a SCINCO S-2100 diode-array spectrophotometer and circular dichroism (CD) spectra on a Jasco 715 spectrometer. All solution measurements were made at 25 ± 1 °C. Elemental analyses were carried out with a Chemtronics TEA-3000 instrument.

**Syntheses**

trans-[Co(6+H)(ClO₄)₂] and cis-[Co(6+H)(en)]Cl₂(H₂O): Pentaaerythritol tribromide (5.0 g, 15.4 mmol) was gradually added to ethane-1,2-diamine (en) (18.0 g, 300 mmol) and the mixture heated at 120 °C for 72 h. The bulk was gradually added to ethane-1,2-diamine (en) (18.0 g, 300 mmol) and the mixture heated at 120 °C. Elemental analyses were carried out with a Chemtronics TEA-3000 instrument.

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**λ**

λ

Δ

ε

max (M–1 cm–1)) 488 (+0.42), 440 (+0.60), 340 (+0.070); and Δ- [Co(5)]³⁺, αmin/max (nm) (Δε (M−1 cm−1)) 488 (−0.42), 440 (+0.60), 340 (−0.070).

[Racemic (Co5)Cl₂·H₂O: Racemic (Co5)Cl₂·H₂O (1.0 g) was dissolved in water (100 mL) and formaldehyde (6.3 g), nitromethane (1.3 g), and NaClO₄ (1.0 g) were added. After standing at room temperature for 3 d the reaction was quenched by addition of HCl (2 mol L⁻¹, 30 mL) and heated at 60 °C for 2 h. The mixture was diluted to 1 L and absorbed onto a column of SP-Sephadex C-25 (Na+ form, 7 cm × 120 cm), washed with water (200 mL) and eluted with sodium citrate (0.15 mol L⁻¹). An orange fraction was collected, and applied onto a Dowex 50Wx2 column and eluted with HCl (3 mol L⁻¹) after prior washing with water (100 mL) and HCl (0.5 mol L⁻¹, 500 mL), respectively, then evaporated to dryness under reduced pressure. The compound was dissolved in a minimal amount of water and vapour diffusion of ethanol applied to produce the crystals suitable for the X-ray work. (Yield, 1.2 g). Anal. Calc. for Co₃H₆Cl₂Co₅O₅·5·C₅H₁₂O₅: C, 32.65; H, 6.58; N, 17.77. Found: C, 32.5; H, 6.7; N, 18.0%. Visible spectrum, αmax (nm) (log εmax (M⁻¹ cm⁻¹)) 474 (2.08), 342 (2.00). IR spectrum (KBr disc) 1555, 1343 cm⁻¹ (NO₂).

Δ and Δ- [Co(3)]³⁺[Cl₆PF₆]: Δ and Δ- [Co(3)]³⁺ were each obtained directly via the same synthesis for the racemate (previous synthesis) but using either optically pure Δ- or Δ- [Co(5)]³⁺[ClO₄]₂ as the precursor. Following chromatography, as described above, addition of NH₄PF₆ to a concentrated aqueous solution of the chloride salt provided orange crystals suitable for a structure determination. (Yield, 0.57 g for Δ-isomer and 0.56 g for Δ-isomer). Anal. Calc. for Co₃H₆Cl₂Co₅O₅·5·C₅H₁₂O₅: C, 28.40; H, 5.24; N, 15.46. Found: C, 28.2; H, 5.3; N, 15.6%. CD spectra of Δ- [Co(3)]³⁺, αmin/max (nm) (Δε (M−1 cm−1)) 473 (−2.14), 343 (−0.18); and Δ- [Co(3)]³⁺, αmin/max (nm) (Δε (M−1 cm−1)) 473 (+2.14), 343 (+0.18).

[Co(4+H)(S₂O₆)²⁺]: Racemic [Co(3)]³⁺[Cl₆PF₆] (2.0 g) was dissolved in water (100 mL) and Zn powder (5.0 g) was added. HCl (3 mol L⁻¹, 200 mL) was added dropwise over 1 h while the reaction mixture was kept under a nitrogen atmosphere. The reaction mixture was monitored periodically by taking small aliquots and passing them over a small SP-Sephadex column with sodium citrate (0.1 mol L⁻¹) as eluent until the only one band was seen. The suspension was filtered to remove unreacted Zn powder and the filtrate remove the chiral anion. After washing with water (200 mL) and dilute HCl (0.5 mol L⁻¹) the optically pure cation eluted with HCl (3 mol L⁻¹). This was evaporated to dryness under reduced pressure. The yield was quantitative. Each fraction was redissolved in a minimum volume of water, then excess NaClO₄ was added to each solution. Vapour diffusion of ethanol into each solution produced orange crystals of the mixed chloride-perchlorate salt suitable for X-ray work. Crystals from the first eluted fraction were used for crystallography. Anal. Calc. for Co₃H₆Cl₂Co₅O₅·5·C₅H₁₂O₅: C, 28.40; H, 5.24; N, 15.46. Found: C, 28.2; H, 5.3; N, 15.6%. CD spectra of Δ- [Co(3)]³⁺, αmin/max (nm) (Δε (M−1 cm−1)) 473 (−2.14), 343 (−0.18); and Δ- [Co(3)]³⁺, αmin/max (nm) (Δε (M−1 cm−1)) 473 (+2.14), 343 (+0.18).
reoxidised by addition of H2O2 (30%, 5 mL) and heating at 60 °C for 1 h. The yellowish orange solution was diluted to 1 L with water and absorbed onto a Dowex 50W×2 column, then eluted with HCl (3 mol L−1) after prior washing with water (200 mL) and HCl (0.5 mol L−1). Trace amounts of pink Coaq4+2 eluted first well ahead of the dominant orange fraction of the desired product. The eluate was evaporated to dryness under reduced pressure and redissolved in a minimum amount of water. Ethanol (300 mL) was added to give a yellow precipitate, which was filtered and washed with ethanol, then dried under vacuum. The yield was almost quantitative (1.9 g). The chloride salt was dissolved in a minimum amount of water and lithium dithionate was added. Slow evaporation at room temperature afforded crystals of [Co(4+H)(S2O6)2] but these were found to be twinned and unsuitable for X-ray work. Anal. Calc. for C14H40Cl4CoN8O5.5 C12H29Cl4CoN6O9 C11H30Cl3CoN6O5 C15H36Cl3CoN7O4.5 C15H33Cl2CoF6N7O3P

**Results and Discussion**

**Ligand Synthesis and Isolation of an Unusual Byproduct.** We have recently reported the synthesis of the functionalised tripodal ligand 5 as is CoIII complex, along with its Ni5S5 analogue. Although the yield of the target hexamine 5 is good, other products are formed, as shown here. The purification of polyamines is a process commonly rendered difficult by their involatility and resistance to crystallisation. A solution to this problem is to separate the various polyamine reaction products as either their CoIII or CuII complexes. The former approach is preferred when characterisation is the aim through the use of NMR techniques while the latter is more convenient when isolation of the purified metal free ligand is the target; CuII complexes being labile and easily demetallated through reduction or precipitation.

<table>
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<th>Table 1. Crystal Data</th>
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<td><strong>R(Fo)²</strong></td>
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*variant of Pnma; \( R(F_o) = \frac{\sum|F_o|-|F_e|}{\sum|F_o|} \); \( wR(F_o)² = (\sum w(F_o)² - F_e²)/\sum w(F_o)²) \)
with sulfide. Interestingly, where CuII complexation has been performed in oxygenated MeOH, this has sometimes led to the unanticipated formation of aminal (methylene-diamine) derivatives of the polyamines.24 Here, we have found a similar instance of this type of chemistry through the identification of compound 6 where formaldehyde has bridged a pair of secondary amines. Given that no formaldehyde was present during the initial organic chemistry, we must conclude that the source of formaldehyde was a CoIII-mediated oxidation of MeOH to CH2O (driven by the presence of dioxygen). The ligand 6 was isolated as two different CoIII complexes; cis-[Co(6+H)(en)]4+ and trans-[Co(6+H)Cl2]4+. The crystal structures of each complex cation are shown in Figures 2 and 3 respectively.

In cis-[Co(6)(en)]4+ the ligand binds as a quadridentate, one primary amine is protonated while the aminal N-atom closer to the protonated amine is neither protonated nor coordinated. The chelating co-ligand ethane-1,2-diamine enforces a folded cis configuration of the quadridentate coordinated ligand. The primary and secondary amine N-donors form Co-N bonds of similar length but the bond to the coordinated tertiary amine (N(2)) is much longer, as expected on the basis of steric effects. Although formally unprotonated, N(5) is engaged in a strong intramolecular H-bond donated by the adjacent ethane-1,2-diamine ligand.

The trans-dichloro complex trans-[Co(6+H)Cl2]4+ was also isolated from the same synthesis. The geometry of the complex ion is shown in Figure 3. Again one primary amine is protonated and its adjacent tertiary amine remains unprotonated and also uncoordinated. A weak intramolecular H-bond is present in this case from the secondary amine N(3) to the free tertiary amine. Again, the coordinated tertiary amine (N(2)) forms the weakest bond of the four amine donors.

Optical Resolution of \([\text{Co(5)}]^{3+}\). Chromatographic resolution of \([\text{Co(5)}]^{3+}\) with the chiral antimony tartrate anion was readily achieved in a manner similar to that employed by us for related hexaamine CoIII complexes.25 Separation is achieved by differential ion paring between the two enantiomers and the chiral anion; the stronger diasteromeric ion pair eluting more rapidly due to its diminished affinity for the cation exchange resin. The absolute configuration of the enantiomer more rapidly eluted by Na2[Sb2(R,R-tart)2] was established as \(\Lambda\) by X-ray crystallography. The coordination geometry, coordinate bond lengths and conformation determined from the crystal structure of L-[Co(5)](ClO4)Cl2 (Figure 5) match those of racemic \([\text{Co(5)}]^{3+}\)Cl·H2O reported recently.18 As in the racemate structure, N-H…Cl (2.33-2.37 Å; 154-173º) and N-H…O H-bonding interactions are many, but it is notable that those involving the chloride ions fall in a particularly narrow range.

The acyclic \([\text{Co(5)}]^{3+}\) complex is readily converted to the macrobicyclic cage compound \([\text{Co(3)}]^{4+}\), a new member of

![Figure 2](image-url) ORTEP view of the cis-[Co(6)(en)]4+ cation (30% ellipsoids). Selected bond lengths (Å): Co(1)-N(1) 1.971(4), Co(1)-N(2) 2.055(4), Co(1)-N(3) 1.974(4), Co(1)-N(4) 1.954(4), Co(1)-N(7) 1.985(4), Co(1)-N(8) 1.966(4). The intramolecular H-bond (N(8)-H…N(5) 2.08 Å, 144.7º) is also shown.

![Figure 3](image-url) ORTEP view of the trans-[Co(6+H)Cl2]4+ cation. Selected bond lengths (Å): Co(1)-N(1) 1.984(3), Co(1)-N(2) 2.029(3), Co(1)-N(3) 1.966(3), Co(1)-N(4) 1.964(3), Co(1)-Cl(1) 2.245(1), Co(1)-Cl(2) 2.267(1). The intramolecular H-bond (N(3)-H…N(5) 2.44 Å, 116.1º) is shown.

![Figure 4](image-url) ORTEP view of L-[Co(5)]4+ (30% ellipsoids). Selected bond lengths (Å): Co(1)-N(1) 1.973(2), Co(1)-N(2) 1.979(2), Co(1)-N(3) 1.969(2), Co(1)-N(4) 1.976(2), Co(1)-N(5) 1.955(2), Co(1)-N(6) 1.971(2).
the extended sarcophagine family, using well-established methods. The structure of the nitro-substituted cage complex [Co(3)Cl3·1½H2O]3+ was determined. The nitro-cap is apparent in Figure 5. Structurally characterised CoIII complexes from the sar family abound in the literature, and most exhibit the same lel3 conformation seen here (with the -CH2-CH2-groups of all five-membered chelate rings aligned with the 3-fold axis of the complex.

The Co-N bond lengths in this conformation are similar to those of the acyclic parent [Co(5)]3+. All six secondary amines participate in strong H-bonding interactions with the chloride ions [H...Cl 2.27-2.42 Å, N-H...Cl 160-175º], as do the water and hydroxyl protons.

Optically pure Λ-[Co(3)]3+ was synthesised under identical synthetic conditions using the previously resolved precursor Λ-[Co(5)]3+. The absolute configuration of the cage complex was confirmed crystallographically from the mixed salt Λ-[Co(3)](PF6)Cl2. The bond lengths and angles within the complex cation and its conformation do not differ significantly from those of the racemate, so no figure is shown of the structure. Once again, all six secondary amines participate in strong H-bonding interactions with chloride ions [H...Cl 2.17-2.33 Å, N-H...Cl 161-173º], but not with the hexafluorophosphate anion. The hydroxyl proton of the ligand donates a weak hydrogen bond to a chloride ion [O(1)-H(1A)···Cl(1) 2.66 Å, 140º].

Electronic Absorption and Circular Dichroism Spectroscopy. The electronic spectra of all complexes matched those of the sarcophagine analogues. Although the effective ligand fields are C3 for [Co(5)]3+ and D1h for the cages only two broad d-d maxima were observed in the electronic absorption spectra (T1g ← 1A1g and T2g ← 1A1g (Ox)). CD spectroscopy may reveal splitting of the first spin-allowed d-d transition as the two component (1A2 ← 1A1 and 1E ← 1A1) usually have opposite sign. CD spectroscopy is also sensitive to the conformation of the five-membered chelate rings where conversions from the so-called lel3 to obj3 conformation are accompanied by inversion of CD maxima.

Some interesting features emerge from the data. Firstly, the mixed ligand complex cis-[Co(6+H)(en)]4+ exhibited

**Figure 5.** View of the racemic [Co(3)]3+ cation (30% probability ellipsoids). Selected bond lengths (Å): Co(1)-N(1) 1.974(2), Co(1)-N(2) 1.959(2), Co(1)-N(3) 1.972(2), Co(1)-N(4) 1.976(2), Co(1)-N(5) 1.979(2), Co(1)-N(6) 1.975(2).

**Figure 6.** Circular dichroism spectra of (1) Λ-[Co(5)]3+, (2) Δ-[Co(5)]3+, (3) Λ-[Co(3)]3+ (from complex (1)), (4) Δ-[Co(3)]3+ (from complex (2)), (5) Λ-[Co(4+H)]4+ (from complex (3)) and (6) Δ-[Co(4+H)]4+ (from complex (4)).

### Table 2. CD Maxima of Selected Hexaamine CoIII Complexes

<table>
<thead>
<tr>
<th>Complex</th>
<th>λmin/m (Δε (M⁻¹ cm⁻¹))</th>
<th>Reference</th>
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<tr>
<td>Λ-[Co(2)]3+</td>
<td>476 (+2.68), 362 (+0.17)</td>
<td>24</td>
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<tr>
<td>Δ-[Co(2+2H)]4+</td>
<td>491 (+2.04), 353 (+0.37)</td>
<td>24</td>
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<tr>
<td>Λ-[Co(3)]3+</td>
<td>473 (−2.14), 343 (−0.18)</td>
<td>This work</td>
</tr>
<tr>
<td>Δ-[Co(4)]4+</td>
<td>467 (−2.37), 362 (−0.13)</td>
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</tr>
<tr>
<td>Λ-[Co(5)]3+</td>
<td>488 (+0.42), 440 (−0.60), 340 (+0.070)</td>
<td>This work</td>
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most positive redox couple (−185 mV vs Ag/AgCl, pH 6) which is likely to be a composite effect of the extra positive charge on the free protonated primary amine and the coordinated tertiary amine which both favour reduction to the divalent oxidation state. The electrochemistry of [Co(5)]^{3+} has been reported previously\(^1\) but the data are included here for comparison. The Co^{III} redox potential is −517 mV vs Ag/AgCl. The electron withdrawing influence of the nitro group in [Co(3)]^{3+} is apparent in the anodically shifted Co^{III} redox potential (−360 mV vs Ag/AgCl). Replacement of the nitro group with a primary amine in [Co(4)]^{3+} lowers the redox potential to −513 mV vs Ag/AgCl.

The nitro group in [Co(3)]^{3+} is also electroactive. Continuing the sweep to low potential (Figure 8) reveals an irreversible multi-electron nitro group reduction and the reversibility of the Co response is lost. This feature has been discussed previously.\(^{27}\)

The voltammetry of the amino-substituted analogue [Co(4)]^{3+} was pH dependent (Figure 9). At pH 5 and higher, the Co^{III} couple is constant at −513 mV vs Ag/AgCl while at pH 3 this couple shifts to at −353 mV vs Ag/AgCl. This may be explained by protonation of the Co^{III} form at lower pH (i.e. [Co(4+H)]^{4+} which leads to an anodic shift in the Co(III/II) redox couple. At pH 4, two reversible responses are seen of approximately equal magnitude thus we can estimate the pK\(_{a}\) of the pendant amine as around 4. More accurate determination of this protonation constant must await potentiometric titrations.

**Conclusions**

The Co^{III} complexes of the new sarcophagine analogues 3 and 4 show closely similar spectral and electrochemical properties to those of simpler cage species. Given that the hydroxy substituent does not influence the bound metal characteristics, our hope is that the reverse also will apply. Thus, it should be possible to perform substitution reactions at the hydroxyl site without the deleterious steric and electronic effects that have hampered cage complex derivatisation reactions in the past. Here, we have also shown that the optically pure forms of the Co^{III} complexes of 3 and 4 are easily obtained, raising prospects for their use as chiral components of more elaborate systems. This work is currently under way.
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References