New Stereoselective Routes to Macrocyclic Ligands

Paul V. Bernhardt* and Philip C. Sharpe

Department of Chemistry, University of Queensland, Brisbane 4072, Australia

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Reaction of bis(ethane-1,2-diamine)copper(II) with acetaldehyde and nitromethane in methanol leads, stereoselectively, to the new macrocyclic complex (*trans*-5(*R*),7(*R*),12(*S*),14(*S*))-tetramethyl-6,13-dinitro-1,4,8,11-tetraazacyclotetradecane)copper(II) perchlorate α-$[CuL^1](ClO_4)_2$ in good yield. Reduction of the nitro groups affords the hexaamine (L^2), which was crystallized as $[H_4L^2](ClO_4)_4 \cdot 2H_2O$ and characterized by an X-ray crystal structure study (monoclinic $P2_1/n$, $a = 9.763(2)$ Å, $b = 12.1988(7)$ Å, $c = 13.036(2)$ Å, $\beta = 105.668(7)°$, $Z = 2$) and complexed with Cu^{II} to produce the complex β-$[Cu(H_2L^2)](ClO_4)_4 \cdot 2H_2O$, which has also been characterized by X-ray crystallography (monoclinic $P2_1/n$, $a = 9.717(4)$ Å , $b = 12.174(2)$ Å, $c = 13.036(5)$ Å, $\beta = 106.51(2)°$, $Z = 2$). Reaction of α-$[CuL^1]^{2+}$ with either basic hydrogen peroxide or dilute nitrous acid leads to mild reduction of the nitro groups to afford the ketoxime L^3 as its N-based isomeric Cu^{II} complexes, *trans*-**I** $[CuL^3](ClO_4)_2$ and *trans*-**II** $[Cu(L^3)Cl]Cl \cdot 7H_2O$, the latter of which has been characterized structurally: triclinic, $P\bar{1}$ $a = 10.8441(5)$ Å, $b = 11.6632(9)$ Å, $c = 11.8723(9)$ Å, $\alpha = 113.634(7)°$, $\beta = 95.744(5)$, $\gamma = 94.851(5)°$, $Z = 2$. Variations in the configurations of the coordinated amines in $[CuL^1]^{2+}$, $[CuL^2]^{2+}$, and $[CuL^3]^{2+}$ have a profound effect on the spectroscopy and electrochemistry of their complexes.

Introduction

Metal template directed reactions of coordinated acyclic ligands having cis-disposed primary amines with formaldehyde and a "carbon acid" bridging group have become established as a versatile route to C-substituted macrocyclic compounds.[1] The ring-closing agents that have been used are dominated by nitroalkanes and malonic esters leading to nitro- and carboxylate-appended macrocycles. Reduction of the nitro group generates a primary amine, which may participate in binding in a site perpendicular to the macrocyclic plane. Similar reactions may be achieved with primary amines,[2] amides, and sulfonamides[3] as the nucleophile, although the products of these reactions are typically unstable in the absence of the metal.

Nitromethane, a *tribasic* acid, is an effective "capping" agent when reacted with *three* facially coordinated primary amines and formaldehyde, leading to a nitro-substituted pseudo-adamantyl structure.[4] Nitroethane, a *dibasic* acid, in conjunction with formaldehyde, may link but *two* primary amino groups, with the resulting macrocycle bearing a nitro and a methyl group.[5] In principle, the linking of *two* cis-coordinated primary amines with a *tribasic* acid such as nitromethane should be possible, leaving one acidic hydrogen for further reaction. However, initial attempts involving the reaction of $[Cu(en)_2]^{2+}$ with formaldehyde and nitromethane have been unsuccessful. We have attributed this failure to a combination of poor stability of the bis-bidentate precursor and also reactivity of the desired product. In an effort to temper this reactivity, we attempted a similar cyclization of $[Cu(en)_2]^{2+}$ with nitromethane and acetaldehyde. Our hope was that greater steric crowding near the reactive apical secondary C-atom might inhibit unwanted side reactions of the target macrocycle. This goal has been realized, and the X-ray crystal structure of the product of this reaction $[CuL^1](ClO_4)_2$ has been communicated.[6] This complex represents the first successful use of nitromethane as the ring closure agent to produce a macromonocycle bearing a pendent secondary nitro group.

In metal-directed template reactions involving coordinated primary amines, the use of aldehydes other than formaldehyde has received little attention until recently. Propionaldehyde has been employed in the syntheses of new varieties of expanded macrocyclic hexaamine cages.[7,8] There was also a recent report of the use of benzaldehyde and nitroethane to effect cyclization of a tetraaminecopper(II) complex.[9] We have reported briefly the product $[CuL^1]^{2+}$ obtained from condensation of $[Cu(en)_2]^{2+}$ with nitromethane and acetaldehyde[6] and have found that this complex may undergo some unusual chemistry at its secondary nitro-substituted C-atoms.[10] We report herein the full details of the syntheses of these macrocycles and various related compounds. We reveal some unusual and unexpected reactions of the macrocyclic complex $[CuL^1]^{2+}$ leading to the stabilization of N-based configurational isomers not before seen in coordination compounds of this type.

Experimental Section

Safety Note. Perchlorate salts are potentially explosive. Although we have experienced no problems with the compounds reported herein,

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they should only be handled in small quantities and never be scraped from sintered glass frits nor be heated in the solid state. Nitromethane may become shock sensitive when bases or acids are added.

Syntheses. The synthesis of $L^2 \cdot 6HCl$ has been reported.[11] All other reagents were obtained commercially and were used without further purification.

(a) (*trans*-5(*R*),7(*R*),12(*S*),14(*S*))-Tetramethyl-6,13-dinitro-1(*R*),4(*R*),8(*S*),11(*S*)-tetraazacyclotetradecanecopper(II) Perchlorate, α-[CuL^1](ClO$_4$)$_2$. To a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (25.0 g) in methanol (200 mL) was cautiously added with stirring a solution of ethane-1,2-diamine (13.5 mL) in methanol (25 mL). Acetaldehyde (25 mL) was added, and the solution darkened. The solution was brought to reflux, and a mixture of nitromethane (15 mL) and triethylamine (15 mL) was added gradually. The solution was stirred under reflux for 15 min and then at room temperature for 2 h. Refrigeration of the reaction mixture afforded a purple solid that was washed with three 5 mL portions of EtOH and air-dried. The crude product was recrystallized by dissolving in 25 mL water and then adding concentrated $HClO_4$ (10 mL). The pink product was collected by filtration (see Safety Note), and the filtrate was discarded. The solid was washed with EtOH and then diethyl ether, before being dried in a vacuum desiccator (yield 14.6 g, 23%). Anal. Calcd for $C_{14}H_{26}Cl_2CuN_6O_{12}$: C, 27.80; H, 4.33; N, 13.89. Found: C, 27.60; H, 5.07; N, 13.69. Electronic spectrum (H_2O): λ_{max} 519 nm (ϵ = 59.6 L mol^{-1} cm^{-1}); 259 nm (ϵ = 7200 L mol^{-1} cm^{-1}); (CH_3NO_2) λ_{max} 513 nm (ϵ = 156 L mol^{-1} cm^{-1}). IR (cm^{-1}): 1560 (s, NO_2) 3240, 3203 (N−H str).

(b) (*trans*-5,7,12,14-Tetramethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine) Tetrahydroperchlorate Dihydrate, [H$_4$L^2](ClO$_4$)$_4$·2H$_2$O. To a solution of $L^2 \cdot 6HCl$ (1.0 g) in water (20 mL) was added concentrated $HClO_4$ (*ca.* 2 mL). The solution was allowed to evaporate slowly at room temperature and afforded colorless crystals suitable for X-ray work. These were collected by filtration and air-dried (see Safety Note).

(c) (*trans*-6,13-Diammonio-5,7,12,14-tetramethyl-1,4,8,11-tetraazacyclotetradecane)copper(II) Perchlorate, β-[Cu(H$_2$L^2)](ClO$_4$)$_4$. To an aqueous solution of $Cu(NO_3)_2 \cdot 3H_2O$ (0.48 g) was added $L^2 \cdot 6HCl$ (1.0 g). The solution was stirred, and the pH was adjusted to 8 with dilute NaOH solution to ensure complete complexation. The purple solution was diluted to 1 L and applied to a Sephadex C-25 cation exchange column (Na^+ form). Elution was commenced with 0.05 M trisodium citrate solution. Four bands of approximately equal intensity eluted. The bands were reduced in volume, and the pH of the solutions was adjusted to ∼1 by the addition of concentrated $HClO_4$.

Bands 1 and 2 (β-[Cu(H$_2$L^2)](ClO$_4$)$_4$). Orange-red crystalline products precipitated from both bands upon slow evaporation of their solutions at room temperature. Spectroscopic measurements and X-ray diffraction showed that both bands were identical. Anal. Calcd for $C_{14}H_{36}Cl_4CuN_6O_{16}$: C, 22.43; H, 4.84; N, 11.21. Found: C, 21.42; H, 5.18; N, 10.65. Electronic spectrum (H_2O): λ_{max} 519 nm (ϵ = 133 L mol^{-1} cm^{-1}), 265 nm (ϵ 6620 L mol^{-1} cm^{-1}). X-ray-quality crystals of β-[Cu(H$_2$L^2)](ClO$_4$)$_4$·2H$_2$O formed from later crops. If crystals fail to form after several days, then addition of an excess of $LiClO_4$ will induce precipitation within several hours.

Bands 3 and 4. Orange powders were obtained from $NaClO_4$ solutions after standing for extended periods. Both bands exhibited infrared and electronic spectra identical to those obtained from bands 1 and 2.

A small amount of solid from each band was demetalated (Zn/HCl) and purified as the hexahydrochloride salt by passage over a Dowex 50WH2 column. The ^{1}H NMR spectra of the free ligands were identical, confirming that all four bands comprised copper complexes of L^2.

(d) (*trans*-5,7,12,14-Tetramethyl-1,4,8,11-tetraazacyclotetradecane-6,13-dione dioxime)copper(II) Chloride, Method 1: *trans*-II [Cu(L^3)Cl]Cl·3H$_2$O. A solution of α-[CuL^1](ClO$_4$)$_2$ (4.0 g) in water (100 mL) was chilled in an ice bath, K_2CO_3 (16 g) was then added, and the solution was stirred for 15 min at 0 °C. Hydrogen peroxide (26 mL, 30%) was added dropwise with stirring. After the addition was complete, the mixture was brought to room temperature and neutralized with HCl. The solution was diluted to 2 L and charged onto a Sephadex C-25 column. The major blue band eluted with 0.4 M NaCl and crystallized upon evaporation of the eluate. Anal. Calcd for $C_{14}H_{36}Cl_2CuN_6O_5$: C, 33.43; H, 7.22; N, 16.71. Found: C, 32.95; H, 7.17; N, 16.37. Electronic spectrum (H_2O): λ_{max} 556 nm (ϵ = 191 L mol^{-1} cm^{-1}), 271 nm (ϵ = 6530 L mol^{-1} cm^{-1}). Slow evaporation of a solution of the product containing added $NaBF_4$ gives X-ray-quality crystals of *trans*-**II** [Cu(L^3)Cl]BF$_4$·H$_2$O. The single-crystal X-ray structural analysis of this complex has been communicated.[10]

Method 2. A solution of α-[CuL^1](ClO$_4$)$_2$ (4.0 g) in 400 mL water was made weakly acidic (pH 5) with HCl solution then cooled to 0 °C in an ice bath. An aqueous solution of $NaNO_2$ (7.5 g in 200 mL) was added dropwise over 30 min with stirring. The solution was removed from the ice bath and stirred at room temperature for a further 2 h. The solution was diluted to 5 L and applied to a Sephadex C-25 cation exchange column (10 × 75 cm). Five purple/blue bands (in addition to free Cu^{2+}) eluted with 0.05 M trisodium citrate solution: band 1, λ_{max} 563 nm (minor, discarded); band 2, λ_{max} 556 nm (minor, discarded); band 3, λ_{max} 568 nm; band 4, λ_{max} 577 nm (minor, discarded); band 5, λ_{max} 591 nm (major). Only the third and fifth bands were present in sufficient quantities to allow isolation of solid products. These major bands were isolated by dilution of their citrate solutions and reapplication on a small Sephadex C-25 column as described below.

Band 3 (*trans*-**I** [CuL^3](ClO$_4$)$_2$·2H$_2$O) eluted from the column with 0.2 M $NaClO_4$ solution, and upon evaporation to ca. 20 mL precipitated as a purple powder. The product was collected by filtration (see Safety Note) and washed with ethanol. Anal. Calcd for $C_{14}H_{30}Cl_2CuN_6O_{10} \cdot 2H_2O$: C, 27.44; H, 5.59; N, 13.71. Found: C, 27.71; H, 5.35; N, 13.64. Electronic spectrum (H_2O): λ_{max} 549 nm (ϵ = 189 L mol^{-1} cm^{-1}), 271 nm (ϵ = 6860 L mol^{-1} cm^{-1}).

Band 5 (*trans*-**II** [Cu(L^3)Cl]Cl·3H$_2$O) eluted with 0.4 M NaCl solution. Concentration of the blue solution results in precipitation of a compound that is spectroscopically identical to that obtained from Method 1. X-ray-quality crystals of *trans*-**II** [Cu(L^3)Cl]Cl·7H$_2$O were obtained from the filtrate. Alternatively, refluxing an aqueous solution of *trans*-**I** [CuL^3](ClO$_4$)$_2$·2H$_2$O in the presence of a small amount of NaCl results in conversion to the N-based isomer *trans*-**II** [Cu(L^3)Cl]Cl.

(e) (*trans*-5,7,12,14-Tetramethyl-1,4,8,11-tetraazacyclotetradecane-6,13-dione Dioxime) L^3. A solution of either *trans*-**I** [CuL^3](ClO$_4$)$_2$ or *trans*-**II** [Cu(L^3)Cl]Cl (ca. 0.1 g) in D_2O (3 mL) was treated with excess $Na_2S \cdot H_2O$ (ca. 0.5 g) in a well-ventilated fume hood. After stirring at room temperature for ca. 15 min, the solution was filtered. NMR spectroscopy of the residue indicated that the metal-free ligand remained intact. ^{1}H NMR (D_2O): δ ∼1.2 (overlapping doub., CH_3), 2.4−2.8 (mult., CH_2), 3.5 (quart., CH), 4.3 ppm (quart., CH). ^{13}C NMR: δ 18.4, 21.8, 43.9, 45.6, 47.5, 48.2, 162.3 ppm.

Physical Methods. Nuclear magnetic resonance spectra were measured at 200 (^{1}H) and 50.3 MHz (^{13}C) on a Bruker AC200 spectrometer. Spectra were referenced with tetradeuterated sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) (^{1}H) or with 1,4-dioxane (^{13}C). Electrochemical measurements were carried out with a BAS 100B/W potentiostat, using Pt auxiliary and Ag−AgCl reference electrodes. For cyclic voltammetry experiments, a glassy carbon working electrode was used, whereas for differential pulse polarography measurements an EG&G PARC model 303 dropping mercury working electrode was employed. All electrochemical solutions contained ca. 5 mM complex in aqueous 0.1 M $NaClO_4$ and were purged with nitrogen before measurement. Electronic spectra were measured with a Beckman DU 7500 UV−vis spectrometer. Infrared spectra of compounds dispersed in KBr disks were measured using a Perkin-Elmer 1600 Series FT-IR spectrometer. EPR spectra of all Cu^{II} complexes were measured on a Bruker ER200 D spectrometer as frozen 1 mM solutions (1:2 DMF/water, 77 K). Spin Hamiltonian parameters were obtained by spectral simulation.[12] Potentiometric titrations of an aqueous solution (0.1 M NEt_4ClO_4) of L^2 were carried out at 298 K with a Metroohm 665 Dosimat and an Orion model 720A pH meter,

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Table 1. Crystal Data

	$[H_4L^2](ClO_4)_4\cdot 2H_2O$	$[Cu(H_2L^2)](ClO_4)_4\cdot 2H_2O$	$[Cu(L^3)Cl]Cl\cdot 7H_2O$
space group	$P2_1/n$ (No. 14)[a]	$P2_1/n$ (No. 14)[a]	$P\bar{1}$ (No. 2)
formula	$C_{14}H_{42}Cl_4N_6O_{18}$	$C_{14}H_{40}Cl_4CuN_6O_{18}$	$C_{14}H_{44}Cl_2CuN_6O_9$
a, Å	9.763(2)	9.717(4)	10.8441(5)
b, Å	12.1988(7)	12.174(2)	11.6632(9)
c, Å	13.036(2)	13.062(5)	11.8723(9)
α, deg			113.634(7)
β, deg	105.668(7)	106.51(2)	95.744(5)
γ, deg			94.851(5)
V, Å^3	1494.9(4)	1481.5(9)	1355.9(2)
ρ_{calcd}, g cm^{-3}	1.609	1.762	1.408
fw	724.34	785.86	574.99
Z	2	2	2
μ, cm^{-1}	4.82	11.85	10.52
temp, °C	23	23	23
λ, Å	0.710 73	0.710 73	0.710 73
N	2617	2604	4753
N_o ($F_o > 2\sigma$)	1863	2059	3827
$2\theta_{max}$, deg	50	50	50
data, restraints, parameters	2617, 0, 217	2604, 0, 217	4753, 0, 289
goodness of fit	1.135	1.040	1.101
residual extrema, e Å^{-3}	0.5, −0.6	0.4, −0.3	0.5, −0.4
$R(F_o)$,[b] $wR_2(F_o2)$[c]	0.0572, 0.1597[d]	0.0303, 0.0798[e]	0.0331, 0.0871[f]

[a] Variant of $P2_1/c$. [b] $R(F_o) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [c] $wR_2(F_o^2) = (\Sigma w(F_o^2 - F_c^2)/\Sigma wF_o2)^{1/2}$. [d] $w^{-1} = (\sigma^2(F_o^2) + (0.0798P)^2 + 2.97P)$ where $P = {}^1/_3\max(F_o^2, 0) + {}^2/_3F_c^2$. [e] $w^{-1} = (\sigma^2(F_o^2) + (0.0431P)^2 + 1.43P)$. [f] $w^{-1} = (\sigma^2(F_o^2) + (0.0495P)^2 + 0.60P)$.

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

	$[H_4L^2](ClO_4)_4\cdot 2H_2O$	$[Cu(H_2L^2)](ClO_4)_4\cdot 2H_2O$	$[Cu(L^3)Cl]Cl\cdot 7H_2O$
Cu−N(1)		1.984(2)	2.016(2)
Cu−N(2)		2.044(2)	2.038(2)
Cu−N(4)			2.027(2)
Cu−N(5)			2.026(2)
Cu−Cl(1)			2.5413(2)
C(2)−N(3)	1.503(5)	1.508(3)	1.276(3)
N(3)−O(1)			1.407(3)
Cu−N(2)−C(3)		116.3(2)	113.6(2)
C(3)−N(2)−C(4)	116.2(3)	113.3(2)	112.8(2)
C(1)−C(2)−C(3)	116.7(3)	117.1(2)	120.6(2)

using NEt_4OH as the base. Data were analyzed with the program TITFIT.[13] Molecular mechanics calculations were performed with MOMEC[14] using a published force field.[15] Additional parameters were included to model the ketoxime groups: C═N(OH), $k_r = 6.50$ mdyn Å^{-1}, $r_o = 1.26$ Å; N−O(H), $k = 6.50$ mdyn Å^{-1}, $r_o = 1.38$ Å; C═N−O, $k_\theta = 0.97$ mdyn rad^{-1}, $\theta_o = 2.094$ rad. Other parameters, e.g. C−C(═N), H−O(N), etc. were adapted from the original force field.[15]

X-ray Crystal Structure Analyses. Cell constants were determined by a least-squares fit to the setting parameters of 25 independent reflections measured on an Enraf-Nonius CAD4 four-circle diffractometer employing graphite-monochromated Mo Kα radiation and operating in the $\omega-2\theta$ scan mode. Data reduction and empirical absorption corrections (ψ scans) were applied with the XTAL package.[16]

The structures of β-$[Cu(H_2L^2)](ClO_4)_4\cdot 2H_2O$ and *trans*-**II** $[Cu(L^3)Cl]Cl\cdot 7H_2O$ were solved by heavy atom methods, and the structure of $[H_4L^2](ClO_4)_4\cdot 2H_2O$ was solved by direct methods with SHELXS86[17] and refined by full-matrix least-squares analysis with SHELXL97.[18] All non-H atoms were refined with anisotropic thermal parameters, whereas H atoms were included at estimated positions and allowed to ride on their respective C, N, or O atom. For the structure of $[H_4L^2](ClO_4)_4\cdot 2H_2O$, the sites of amine protonation were initially located from difference maps, and then the H atoms were restrained at these positions. Crystal data are assembled in Table 1, and the atomic nomenclature is defined in Figures 1−3 drawn with the program PLATON.[19] Selected bond lengths and angles are assembled in Table 2.

Results

The template reaction leading to $[CuL^1]^{2+}$ is stereospecific, despite there being six stereogenic C atoms and four stereogenic N atoms in the coordinated ligand. Neglecting for the moment the configurations of the methyl-substituted C-atoms, two possible centrosymmetric *trans*-**III**[20] N-based geometric isomers exist for the tetradentate-coordinated ligand; referred to as α and β,[21] where the pendent nitro or amino group is axial or equatorial, respectively (Chart 2). In this case, the observed[6] isomer was α-$[CuL^1]^{2+}$. By contrast, the analogous metal template reaction involving nitroethane and formaldehyde as

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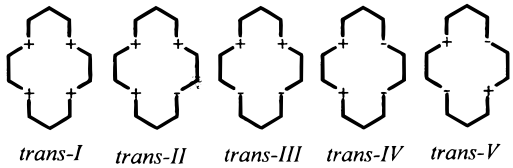
(20) The five possible N-based isomers of coordinated fourteen-membered macrocycles. The + sign indicates that the attached H atom is above the macrocyclic plane, whereas the − sign implies that the H atom is below the plane.



(21) Curtis, N. F.; Gainsford, G. J.; Siriwardena, A.; Weatherburn, D. C. *Aust. J. Chem.* **1993**, *46*, 755.

Chart 1

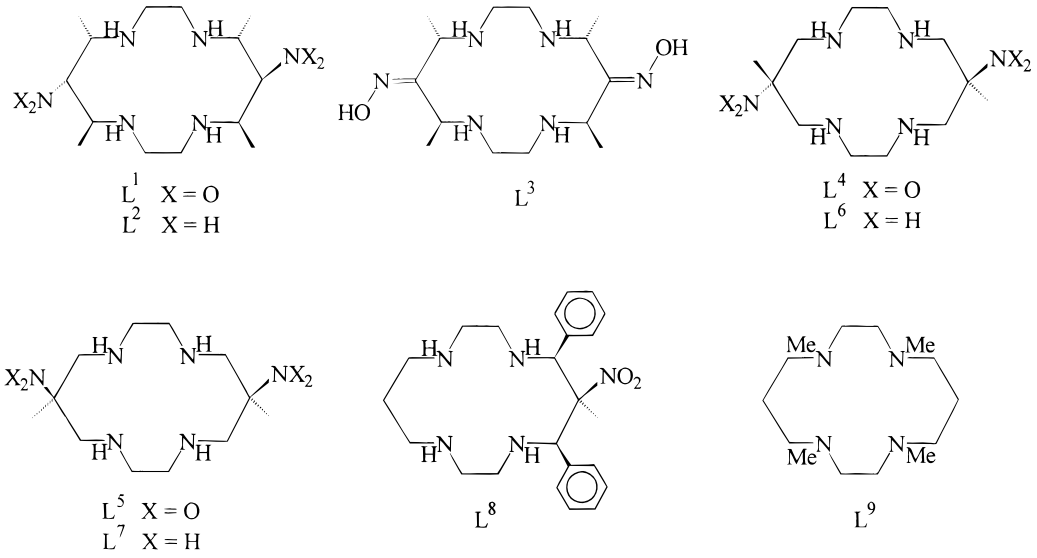
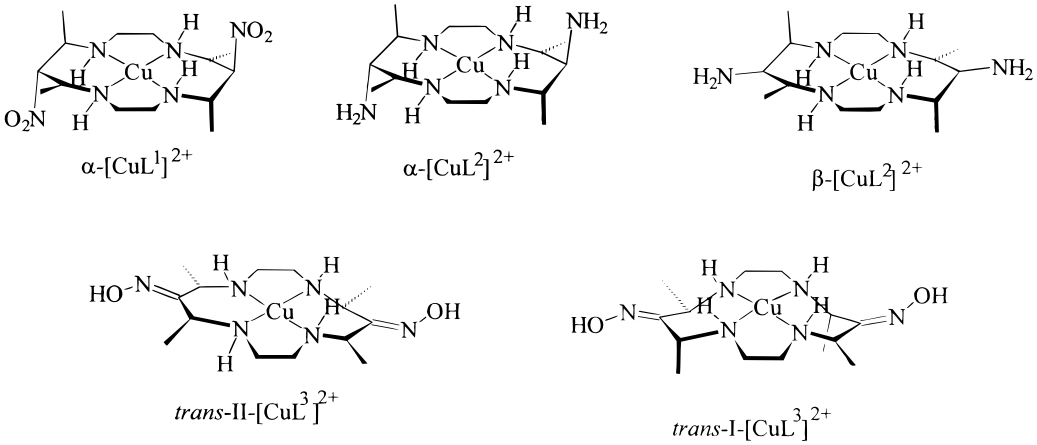


Chart 2



cyclization reagents leads to two dinitro-substituted C-based isomers (*trans*-L^4 and *cis*-L^5).[22] However, in this case we have only identified the trans isomer of L^1 and but one of the many possible diastereomers based on the configurations of the four C-methyl groups. This stereoselectivity has been verified by reduction and demetalation of α-$[CuL^1]^{2+}$ to produce L^2, which is present in only one isomeric form as shown by NMR spectroscopy.[6]

The crystal structure of $[H_4L^2](ClO_4)_4 \cdot 2H_2O$ finds the ligand on a center of symmetry (Figure 1). The two pendent amines are *trans* to each other, and the absolute configuration of the four methyl-substituted C atoms is *R*[C(1)]*R*[C(3)]*S*[C(1′)]-*S*[(C(3′)], in accord with the structure of the dinitro precursor α-$[CuL^1](ClO_4)_2$.[6] In this conformation, there is an alternating axial and equatorial arrangement of the methyl groups. The sites of protonation comprise a pair of centrosymmetrically related secondary amines and the two pendent primary amines. Intramolecular H-bonding is identified between the protonated (donor) and nonprotonated (acceptor) macrocyclic amines. We have previously identified similar structures in closely related protonated macrocyclic amines.[23,24] There are also a large number of intermolecular H-bonding interactions formed between the protonated amines, water molecules and perchlorate anions. Potentiometric titration identified five protonation constants for L^2: pK_a values 11.1(1), 10.3(1), 5.5(1), 5.2(1), and 3.5(1). These values are comparable with those determined for the related hexaamine macrocycles L^6 and L^7.[25,26] The sixth protonation constants of L^2, L^6, and L^7 are all too low to be determined potentiometrically.

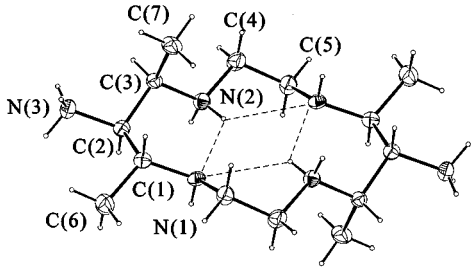


Figure 1. View of the $[H_4L^2]^{4+}$ cation (30% probability ellipsoids shown).

Complexation of the potentially hexadentate macrocycle L^2 with Cu^{II} yielded acid-stable purple solutions immediately upon

(22) Bernhardt, P. V.; Comba, P.; Hambley, T. W.; Lawrance, G. A.; Várnagy, K. *J. Chem. Soc., Dalton Trans.* **1992**, 355.
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(24) Bernhardt, P. V.; Hambley, T. W.; Lawrance, G. A. *Aust. J. Chem.* **1990**, *43*, 699.
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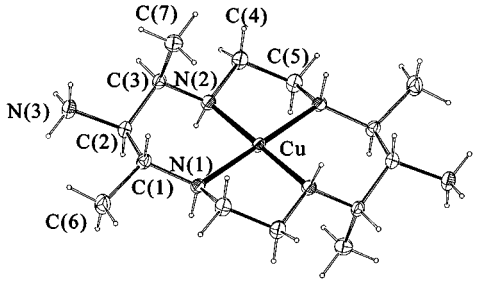

Figure 2. View of the $[Cu(H_2L^2)]^{4+}$ cation (30% probability ellipsoids shown).

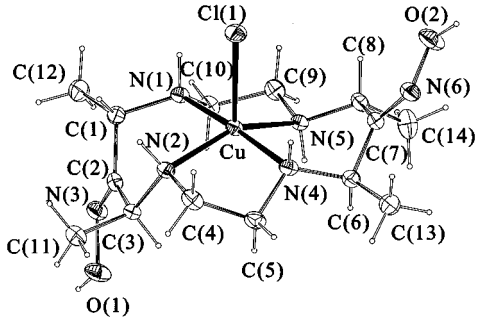

Figure 3. View of the $[Cu(L^3)Cl]^+$ cation (30% probability ellipsoids shown).

mixing the ligand hydrochloride and a Cu^{II} salt in aqueous solution. We have recently reported[11] the hexadentate-coordinated Co^{III} complex of L^2 where both pendent amines coordinate in trans coordination sites, but in this case the preference of Cu^{II} for square-planar or tetragonally elongated coordination geometries precludes coordination by the pendent amines. The X-ray crystal structure of $[Cu(H_2L^2)](ClO_4)_4 \cdot 2H_2O$ comprises a centrosymmetric cation with anions and water molecules on general sites (Figure 2). The configuration of the N-donors is defined as *trans*-**III** β. The complex is isomorphous with the protonated free ligand $[H_4L^2](ClO_4)_4 \cdot 2H_2O$ (Table 1) where the metal ion replaces the two protons formerly situated in the macrocyclic cavity without significant disruption of the crystal lattice. A square-planar coordination environment is defined for β-$[Cu(H_2L^2)](ClO_4)_4 \cdot 2H_2O$, with no intermolecular contacts closer than ca. 2.8 Å being made with the cation. This geometry is uncommon in the coordination chemistry of Cu^{II} with N-donor ligands where tetragonally elongated six-coordinate or distorted square-pyramidal complexes are the norm. The Cu−N bond lengths are significantly different (Table 2), resulting in a rhombic distortion of the CuN_4 plane. The structure may be compared with that of the dinitro precursor α-$[CuL^1](ClO_4)_2$, where a square-planar geometry was also found,[6] but no rhombic distortion of the CuN_4 plane was identified. There is significant distortion of some angles within the macrocyclic ring. Most notably, the apical, ideally tetrahedral, C(1)−C(2)−C(3) angle is expanded. Similar angles are found in the structures of the protonated metal free ligand and the dinitro precursor α-$[CuL^1]^{2+}$ (118.1(5)°).[6] By comparison, the analogous C−C−C angles identified in the structures of α-$[CuL^6(OH_2)_2]^{2+}$ and β-$[Cu(H_2L^6)(OClO_3)_2]^{2+}$ are 112.3(2) and 112.9(5)°, respectively.[27] This distortion is clearly due to the steric influence of the four C-methyl substituents.

Axial coordination of water molecules or anions (Cu−O ∼ 2.5 Å) is usually observed in the solid-state structures of tetraazamacrocyclic Cu^{II} complexes, and the colors of these tetragonally elongated six-coordinate complexes are typically pink or purple. By contrast, the axially disposed methyl groups in α-$[CuL^1](ClO_4)_2$ and β-$[Cu(H_2L^2)](ClO_4)_4 \cdot 2H_2O$ block the approach of counterions or water molecules perpendicular to the macrocyclic plane, and their solid-state color is distinctly orange. However, their color in solution changes to purple, which indicates that solvation of the axial coordination sites does occur upon dissolution.

The spectroscopic properties of bands 3 and 4 from the chromatographic purification of the Cu^{II}/L^2 reaction were identical with those exhibited by the crystallographically characterized β-$[Cu(H_2L^2)](ClO_4)_4$ (bands 1 and 2). It is likely that bands 3 and 4 both comprise the N-based diastereomer α-$[Cu(H_2L^2]^{4+}$, but slow isomerization in solution to give β-$[Cu(H_2L^2)]^{4+}$ occurs. Splitting of each of the putative isomers α- and β-$[Cu(H_2L^2)]^{4+}$ into two bands may be attributed to acid−base (pendent amines) or ion pair equilibria on the chromatography column.

The reactivity of the secondary nitro groups in α-$[CuL^1]^{2+}$ was demonstrated by two mild reductions (Methods 1 and 2 in Experimental Section) resulting in quantitative conversion of the nitro groups into their corresponding ketoximes, L^3. In Method 1 (involving K_2CO_3 and H_2O_2) one dominant product was obtained, and an X-ray crystal structure analysis of this complex, *trans*-**II** $[Cu(L^3)Cl](BF_4) \cdot H_2O$, has been communicated.[10] We have found that the same product may be obtained by reacting α-$[CuL^1]^{2+}$ with $NaNO_2$ at pH 5, and this has been crystallized as its chloride salt *trans*-**II** $[Cu(L^3)Cl]Cl \cdot 7H_2O$. The structure of the complex cation (Figure 3) is identical to that of the BF_4^- salt, with the most distinctive feature being the unusual *trans*-**II** (*RRRS*) configuration of N-donors. This configuration results in a dramatic change in the conformation of the coordinated macrocycle compared with the parent complex α-$[CuL^1]^{2+}$ (*trans*-**III**). Most importantly, the four methyl groups all effectively become equatorial, compared with their alternating axial and equatorial arrangement in α-$[CuL^1]^{2+}$ or β-$[Cu(H_2L^2)]^{4+}$. This conformational change allows coordination by a chloro ligand in the site perpendicular to the macrocyclic plane to give a distorted square-pyramidal coordination geometry. In going from the precursor α-$[CuL^1]^{2+}$ to *trans*-**II** $[CuL^3]^{2+}$ the central C atoms in the six-membered chelate rings change from tetrahedral to trigonal planar, and the apical C(1)−C(2)−C(3) is widened accordingly.

A purple complex of L^3 was also isolated from the reaction between α-$[CuL^1]^{2+}$ and $NaNO_2$, but no X-ray-quality crystals were obtained. The solid-state color of this complex is quite distinct from those of the orange centrosymmetric parent α-$[CuL^1](ClO_4)_2$ and the blue square-pyramidal *trans*-**II** $[Cu(L^3)Cl]Cl \cdot 7H_2O$. These color differences were also apparent during column chromatography, which indicates that the *trans*-**I** $[CuL^3]^{2+}$ and *trans*-**II** $[CuL^3]^{2+}$ complexes are genuinely isomeric and not simply the same complex crystallized with different anions. This purple complex of L^3 is rapidly converted to the blue *trans*-**II** $[CuL^3]^{2+}$ when the compound is refluxed in the presence of chloride ions (a competing ligand). Therefore, the blue *trans*-**II** $[CuL^3]^{2+}$ isomer must be more stable, which has frustrated attempts to produce X-ray-quality crystals of the purple isomer. It is probable that the blue and purple isomers are related by a single inverted N-donor. It is unlikely that the purple complex is the centrosymmetric *trans*-**III** isomer, as its visible electronic maximum (549 nm) is well removed from those observed for *trans*-**III** α-$[CuL^1]^{2+}$ and *trans*-**III** β-$[CuL^2]^{2+}$ (ca. 519 nm) but close to that found for the distorted *trans*-**II** $[CuL^3]^{2+}$ (556 nm). On this basis the purple complex is

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Table 3. Physical Properties of Tetraaminecopper(II) Complexes

	Cu−N (Å)	λ_{max} (nm)	$E_{1/2}$ (V *vs* Ag/AgCl)	$g_{\|\|}$	$A_{\|\|}$ (G)	$g_{\perp}$	$A_{\perp}$ (G)
α-$[CuL^1]^{2+}$	2.004(3), 2.014(5)[a]	519	−0.48 (Cu), −0.86 (−NO_2)	2.195	198.0	2.040	30.0
β-$[Cu(H_2L^2)]^{4+}$	1.984(2), 2.043(2)	519	−0.67	2.195	197.0	2.045	28.0
trans-**II** $[CuL^3]^{2+}$	2.021(4)−2.047(4)	556	−0.67	2.198	185.0	2.058	24.8
trans-**I** $[CuL^3]^{2+}$	−	549	−0.75	2.200	189.0	2.055	25.0
α-$[CuL^6]^{2+}$	2.016(2), 2.013(4)[b]	501[b]	−0.74[b]	2.186[c]	207.0	2.049	39.0
β-$[CuL^6]^{2+}$	2.011(2), 1.997(4)[b]	518[b]	−0.77[b]	2.198[d]	200.0	2.053	35.0

[a] Reference 6. [b] Reference 26. [c] Lawrance, G. A.; Skelton, B. W.; White, A. H.; Comba, P. *Aust. J. Chem.* **1986**, *39*, 1101. [d] Comba, P.; Curtis, N. F.; Lawrance, G. A.; Sargeson, A. M.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1986**, *25*, 4260.

assigned as *trans*-**I** $[CuL^3]^{2+}$, where all amine H atoms are on the same side of the macrocyclic plane. Other N-based isomers such as *trans*-**V** and *trans*-**IV** $[CuL^3]^{2+}$ cannot be ruled out, but no examples are known for either of these configurations in the complexes of tetradentate coordinated planar macrocycles.[28] Support for the assignment that *trans*-**I** $[CuL^3]^{2+}$ and *trans*-**II** $[CuL^3]^{2+}$ are indeed N-based isomeric complexes of the same ligand was provided by NMR spectroscopy of the free ligands following demetalation. The two spectra were identical, and moreover they indicate that the integrity of the oxime is maintained even in the absence of the metal. The proton-decoupled ^{13}C NMR spectrum of L^3 yielded seven resonances consistent with the centrosymmetric free ligand. Moreover, the chemical shift of the oxime carbon (δ(C═N) 162.3 ppm) indicates that hydrolysis to the ketone (δ(C═O) ∼210 ppm) does not occur to any significant extent under these conditions.

The frozen solution EPR spectra of α-$[CuL^1]^{2+}$, β-$[CuL^2]^{2+}$, *trans*-**II** $[CuL^3]^{2+}$, and *trans*-**I** $[CuL^3]^{2+}$ yielded spin Hamiltonian parameters (Table 3) consistent with tetragonally elongated octahedral or square-pyramidal geometries ($d_{x^2-y^2}$ ground state). The spectra of α-$[CuL^1]^{2+}$ and β-$[CuL^2]^{2+}$ are not significantly different. The spectra of *trans*-**I** $[CuL^3]^{2+}$ and *trans*-**II** $[CuL^3]^{2+}$ show significant reductions in $A_{||}$ and an increase in $g_{||}$. The molecular *g* values and hyperfine constants are related to the energies of the d−d electronic transitions.[29] The weaker ligand field observed in the visible electronic spectra of the *trans*-**II** and *trans*-**I** $[CuL^3]^{2+}$ isomers (relative to α-$[CuL^1]^{2+}$) is consistent with larger $g_{||}$ and smaller $A_{||}$ values. This is indicative of a less planar $Cu^{II}N_4$ chromophore in solution than those found in the complexes of L^1 or L^2.[30]

Electrochemistry of the macrocyclic complexes reported in this work revealed metal centered reductions of varying degrees of reversibility. The $Cu^{II/I}$ redox couples for *trans*-**I** and *trans*-**II** $[CuL^3]^{2+}$ (Table 3) were totally reversible at all scan rates between 10 and 1000 mV s^{-1}, indicating that their monovalent complexes are stable in aqueous solution on the voltammetric time scale (>10 s) and that electron transfer is rapid (Figure 4). By contrast, the two centrosymmetric complexes α-$[CuL^1]^{2+}$ and β-$[CuL^2]^{2+}$ give irreversible responses.

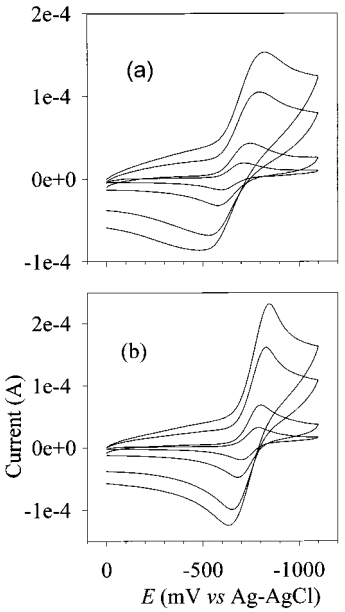

Figure 4. Cyclic voltammograms of (a) *trans*-**II** $[CuL^3]^{2+}$ and (b) *trans*-**I** $[CuL^3]^{2+}$; scan rates 20, 100, 500, and 1000 mV s^{-1}, glassy carbon working electrode, 0.1 M $NaClO_4$.

Discussion

Metal Template Reaction. In the synthesis of α-$[CuL^1](ClO_4)_2$, the intermediate ethylimines resulting from condensation between the coordinated primary amines and acetaldehyde are sufficiently stable for the cyclization reaction to proceed. However, attempts to use propionaldehyde instead of acetaldehyde under the same conditions failed. Aromatic aldehydes have recently been used for metal template reactions of this type employing strictly anhydrous conditions,[9] and the Cu^{II} complex of an acyclic benzylimine intermediate has been characterized by an X-ray crystal structure determination. Further reaction of this imine with nitroethane leads to the macrocyclic complex $[CuL^8]^{2+}$, where the phenyl substituents on the six-membered chelate ring are found in cis positions.[9] This contrasts with the trans methyl groups found in the corresponding chelate rings of α-$[CuL^1]^{2+}$ and β-$[Cu(H_2L^2)]^{2+}$.

Similar monocyclic[31,32] and bicyclic[33,34] C-methylated fourteen-membered tetraazamacrocycles have been formed by nontemplate routes, but show different stereochemistries to those reported herein. The configurations of the methyl-substituted C atoms in α-$[CuL^1]^{2+}$ depend upon the direction of nucleophilic attack by the nitromethanate anion on the coordinated ethylimine precursor. That is, the disposition of the methyl groups is determined by kinetic factors, and the observed configuration of the methyl groups is not necessarily the most stable isomer. By contrast, the disposition of the pendent nitro groups in α-$[CuL^1]^{2+}$ is not fixed, because deprotonation of each nitro-substituted C atom, to give a planar nitronate anion as an intermediate, renders the C atom stereochemically labile. The absence of β-$[CuL^1]^{2+}$ or *cis*-$[CuL^1]^{2+}$ indicates that the α-isomer is the most stable.

(28) The *trans*-**V** configuration is only observed in six-coordinate complexes where the macrocycle folds and coordinates in a nonplanar conformation, leaving two vacant cis coordination sites.

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N-Donor Stereochemistry. Examples of the *trans*-**I** N-based isomeric form of a coordinated fourteen-membered macrocyclic secondary tetraamine are few,[35] and examples of the *trans*-**II** configuration are rarer still. These less common configurations are generally stabilized by N-alkylation, which slows the rate of N-based isomerization, thus allowing the complex to be trapped in a metastable form. The K_2CO_3/H_2O_2 method (also known as the modified Nef reaction[36]) is totally selective for the formation of *trans*-**II** $[CuL^3]^{2+}$ from α-$[CuL^1]^{2+}$. This type of reaction is generally employed in the conversion of secondary nitro groups to ketones, but in this case we have not been able to hydrolyze the intermediate oxime L^3 to the corresponding ketone. Under the basic conditions of the reaction (pH ∼ 10) it appears that the nitro-substituted C atoms of the parent complex are deprotonated and that the neutral species *trans*-**III** $[Cu(L^1\text{-}2H)]$ is formed initially but rapidly develops a deep blue color ($\lambda_{max} = 564$ nm) very similar to that of the complex *trans*-**II** $[CuL^3]^{2+}$. The EPR spectrum of $[Cu(L^1\text{-}2H)]$ also indicates the formation of a new compound with the appearance of peaks at similar positions to those found in the spectrum of *trans*-**II** $[CuL^3]^{2+}$. This spectroscopic evidence strongly suggests that N inversion from *trans*-**III** to *trans*-**II** $[Cu(L^1\text{-}2H)]$ occurs *before* reduction to the oxime. Deprotonation of a nitro-substituted C atom leads to a change in geometry from tetrahedral (nitroalkane) to trigonal-planar (nitronate anion). This type of geometry change has been identified in the recently reported X-ray crystal structure of a closely related nitronate-substituted macrocycle.[37] It appears that this tetrahedral to trigonal conversion at the apical nitro-substituted C atom, in conjunction with the steric effects of the adjacent methyl groups, forces an N inversion from *trans*-**III** to *trans*-**II** $[Cu(L^1\text{-}2H)]$. Inversion of one N-donor evidently relieves much of this strain. The deprotonated blue complex *trans*-**II** $[Cu(L^1\text{-}2H)]$ is not particularly stable with degradation of the ligand occurring on standing, but reduction to $[CuL^3]^{2+}$ affords a stable product as discussed below.

Electrochemistry of α-$[CuL^1]^{2+}$ indicates that reduction of the nitro groups occurs at a potential ca. 400 mV more negative than that of the metal center. Therefore, the irreversible $-NO_2 \rightarrow =NOH$ reduction of the putative *trans*-**II** $[Cu(L^1\text{-}2H)]$ under the conditions of the reaction must result in concurrent reduction of the metal center to form *trans*-**II** $[CuL^3]^+$ as an intermediate. Electrochemical reduction of the metal center in *trans*-**II** $[CuL^3]^{2+}$ has been shown to reversible, so reoxidation of the intermediate copper(I) complex must occur without significant rearrangement.

In contrast, the reaction of α-$[CuL^1]^{2+}$ with nitrite in weakly acidic solution produces the *trans*-**I** (purple) and *trans*-**II** (blue) isomers of $[CuL^3]^{2+}$ in approximately equal amounts. X-ray analysis and spectroscopy have confirmed the identity of the blue *trans*-**II** isomer. The configuration of the purple product has been assigned to that of the *trans*-**I** isomer. In the formation of *trans*-**I** $[CuL^3]^{2+}$ from the *trans*-**III** α-$[CuL^1]^{2+}$ parent, at least two N-donors must invert under the reaction conditions employed. Again, the redox potential of α-$[CuL^1]^{2+}$ requires that reduction of the metal center also occurs if the nitro groups are reduced. It is possible, but unlikely, that two sequential N inversions occur while the ligand remains coordinated to Cu^I, *i.e.* *trans*-**III** α-$[CuL^1]^+ \rightarrow$ *trans*-**II** $[CuL^3]^+ \rightarrow$ *trans*-**I** $[CuL^3]^+$. Moreover, *trans*-**II** $[CuL^3]^{2+}$ is more stable than *trans*-**I** $[CuL^3]^{2+}$, so unless these is a reversal in the stabilities of the Cu^I analogues the second N-inversion in this consecutive process should not be possible. The more likely explanation for the appearance of *trans*-**I** $[CuL^3]^{2+}$ is that complete dissociation of the labile Cu^I complex occurs under the more acidic conditions employed in the nitrosation reaction. Recomplexation and oxidation initially generates *trans*-**I** $[CuL^3]^{2+}$ as the kinetically favored product, which then partially isomerizes to yield a mixture of *trans*-**I** and *trans*-**II** $[CuL^3]^{2+}$. This isomerization reaction may be accelerated by the addition of a competing ligand (Cl^-). It is known that the *trans*-**I** isomer is favored in complexation reactions of N-alkylated fourteen-membered macrocycles such as L^9 where the metal enters the ring anti to the four N-alkyl groups. A similar mechanism is proposed here to explain the formation of *trans*-**I** $[CuL^3]^{2+}$.

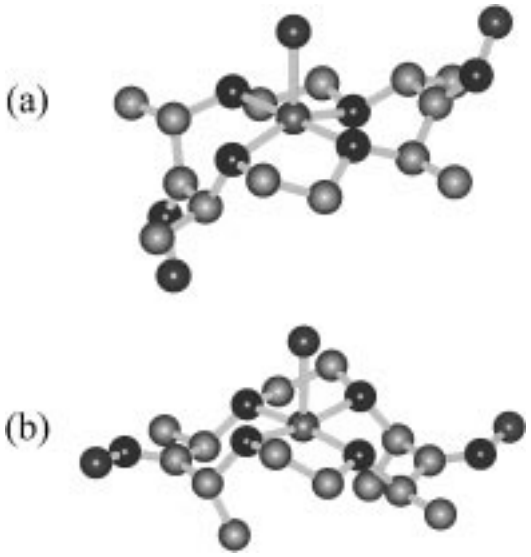

Figure 5. Molecular mechanics strain-minimized geometries of (a) *trans*-**II** $[Cu(L^3)(OH_2)]^{2+}$ (43.3 kJ mol^{-1}) and (b) *trans*-**I** $[Cu(L^3)(OH_2)]^{2+}$ (44.1 kJ mol^{-1}) (H atoms omitted for clarity).

The rationale for the observed reversible electrochemical behavior of the *trans*-**I** and *trans*-**II** $[CuL^3]^{2+}$ isomers lies in the distorted, nonplanar geometry of the CuN_4 group. It is thus easier for the ligand to adjust to the change in the size of the metal ion going from Cu^{II} to Cu^I then back again. The average Cu−N bond lengths in α-$[CuL^1]^{2+}$ are 2.010(5) Å. These distances increase significantly in *trans*-**II** $[Cu(L^3)Cl]^+$, ranging from 2.021(4) to 2.047(4) Å. More importantly, in *trans*-**II** $[Cu(L^3)Cl]^+$ the metal is displaced above the least-squares plane of the four N-donors by 0.27 Å, compared with the planar CuN_4 groups in α-$[CuL^1]^{2+}$ and β-$[Cu(H_2L^2)]^{4+}$. Molecular modeling of the *trans*-**II** and *trans*-**I** isomers of $[Cu(L^3)(OH_2)]^{2+}$ indicate that they should exhibit similar stability as their calculated strain energies are effectively the same (Figure 5). The calculated structure of *trans*-**II** $[Cu(L^3)(OH_2)]^{2+}$ reproduces the crystallographically observed structure (in the same conformation). The calculated strain-minimized structure of *trans*-**I** $[Cu(L^3)(OH_2)]^{2+}$ (Figure 5) leads to a distorted square-pyramidal structure. There are other possible conformations of these molecules, but the ones shown in Figure 5 represent the lowest energy and hence most important forms. It is likely that the actual structure of *trans*-**I** $[CuL^3]^{2+}$ is square pyramidal, as shown in Figure 1, as the conformation of the macrocyclic ring should inhibit approach by a sixth ligand in the remaining trans coordination site.

All previous examples of *trans*-**II** coordination of tetradentate coordinated tetraazamacrocycles have involved N-methylated tertiary amine ligands. We have been able to find only a limited

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number of such examples in the literature, including the complexes *trans*-**II** $[RuO(L^9)Cl]^+$ and *trans*-**II** $[Ru(L^9)(NCMe)(N_3)]^+$.[38,39] In the case of $[CuL^3]^{2+}$, a combination of the trigonal-planar geometry of the apical C atom and the adjacent methyl groups results in the normally stable *trans*-**III** geometry being destabilized relative to the less common *trans*-**II** configuration.

Conclusions

In this report, we have demonstrated that nitromethane and acetaldehyde may be employed successfully in metal-directed template reactions to form a new macrocyclic complex α-$[CuL^1]^{2+}$ both stereoselectively and in good yield. The appended methyl groups are not innocent and play an important role in blocking access to the axial coordination sites, at least in the solid state. In addition, the reactivity of the nitro-appended C-atoms has been demonstrated by both strong ($-NO_2 \rightarrow -NH_2$) and mild ($-NO_2 \rightarrow =NOH$) reduction to form stable complexes exhibiting unusual configurations of their coordinated N-donors.

Acknowledgment. Financial support from the University of Queensland is gratefully acknowledged. P.C.S. acknowledges the receipt of an F. G. Meade Scholarship.

Supporting Information Available: Crystallographic data in CIF format are available on the Internet only. Access and ordering information is given on any current masthead page.

IC971020D

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